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PHARMACEUTICAL COMPLIANCE AND ENFORCEMENT

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Ms. Reig conducts compliance training for life sciences companies and prepares and implements policies for lawful interactions with healthcare providers. She has extensive experience in drafting Standard Operating Procedures and Policies for corporate compliance programs, negotiating and drafting contracts, and advising on consulting arrangements with key opinion leaders. She has participated on Review Committees for both commercial and pre-commercial companies and advises on how to lawfully communicate about FDA-regulated products. Ms. Reig guides companies on how to minimize legal risk while achieving business objectives by ensuring compliance with laws, such as the Anti-Kickback and False Claims Acts.

Ms. Reig assists companies with their state and federal "Sunshine Act" obligations, and advises on aggregate spend, marketing disclosures, data mining, clinical trial disclosure, adherence to compliance codes, sales representative licensure, and manufacturing/distribution licensure.

Ms. Reig was previously recognized by the *New Jersey Law Journal* on its list of "40 Lawyers Under 40," which recognizes individuals who are viewed as future leaders of the New Jersey Bar. Ms. Reig is co-chair of the BioNJ Legal Compliance & Regulatory Advisory Committee, which she was instrumental in forming in 2008.

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Preface

I am privileged to introduce the 2018 edition of the PLI *Pharmaceutical Compliance and Enforcement Answer Book*. As first stated in the Preface to the 2014 edition, it has been our intention to present an overview of the enforcement and compliance environment relevant to the pharmaceutical industry in a different and somewhat unique manner as we analyze the overall legal, regulatory, and compliance framework that impacts every facet of the industry's activities. Continuing in this vein, the 2018 edition takes a holistic approach to define and analyze the rigorous, complex, and frequently overlapping requirements imposed by various federal and state governmental authorities (sometimes working in concert, sometimes working independently) and the role played by third parties in the private sector who collectively contribute to the totality of the current enforcement environment. As we have noted in each edition of the Answer Book, the one constant in the overall process has been continuing change.

To identify and address the requirements facing the industry, one must consider the three major forces that impact the practices and policies of the pharmaceutical manufacturer, from the laboratory through the completion of the life cycle of a prescription pharmaceutical. First and foremost, the provisions of the Food, Drug, and Cosmetic Act (FDCA) as enforced by the Food and Drug Administration (FDA)[1] provide the regulatory framework upon which all additional sources of enforcement, both public and private, are premised. The statutes and regulations have evolved over time, most frequently in response to unanticipated and negative developments impacting the public health (for example, the passage of the Kefauver Amendments in 1962 as a response to the thalidomide tragedy). These events provided the impetus to Congressional action that expanded FDA's authority over the industry and resulted in the imposition of new requirements on manufacturers, beginning from the earliest stages of the drug development process through post-approval commercialization. One of the most far-reaching regulatory developments came in 2007 with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA) which provided FDA with power to direct manufacturer conduct in areas that were previously beyond FDA's authority, including FDA-promulgated label changes, risk management procedures, and mandating specific distribution channels for marketed drugs. In addition, FDA has relied upon the FDCA to implement and enforce additional changes through such procedures as issuance of guidelines, on-site inspections, and both civil and criminal enforcement measures. Regulatory action implemented through issuance of draft guidance documents has become a more frequently utilized (and now criticized) procedure.

As noted in this edition, a more recent legislative initiative in the form of the 21st

Century Cures Act has introduced the promise of even greater changes to the drug regulatory process as Congress and FDA continue to modernize the requirements and pathways in the development and approval of pharmaceuticals. It remains to be seen what changes the implementing legislation and future FDA actions will bring to the pharmaceutical industry.

Of course, not all FDA-proposed rules are finalized. A significant development in the regulatory area was the release of a Proposed Rule from FDA—*Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products*.[2] The Proposed Rule would permit generic companies to incorporate newly discovered information into their product labeling prior to specific FDA authorization. The rule could have a profound impact on labeling both for generics and innovator companies, as well as impact product liability exposure for a new class of manufacturers. On December 4, 2015, the FDA postponed (for the second time) its schedule for finalizing the generic drug labeling changes contained in the 2013 draft guidance. The new date proposed in January 2016 extended the deadline yet again without any final action taken.

Another significant change may be developing as the DOJ has announced its intention to require the government agencies subject to its enforcement authority to utilize the stricter notice and comment requirements of the Administrative Procedure Act instead of continuing the guidance process. Since a major aspect of FDA oversight has been accomplished through the release of various guidance documents (some in draft form that are never finalized), it is likely that the industry's ability to rely on these guidances to revise their internal processes and procedures may in fact be adversely impacted.

Regulatory oversight by FDA is only one of the pillars of enforcement. The second arises from the compliance obligations imposed by federal and state agencies, most notably the U.S. Department of Justice (DOJ) in conjunction with the Office of the Inspector General (OIG) of the Department of Health and Human Services (HHS) as well as the various state attorneys general. Although much of the statutory framework had been in place for a longer period of time,[3] the issuance of compliance guidelines for pharmaceutical manufacturers by the OIG in 2003 is often seen as the beginning of a new period of rigorous enforcement of pharmaceutical commercialization activities that are considered violations of federal and state health reimbursement laws. Since then, the DOJ and the OIG have investigated, charged, and settled with pharmaceutical manufacturers for violations of the False Claims Act, the Anti-Kickback Statute, as well as price reporting statutes, resulting in significant monetary fines and reimbursements to government entities (several exceeding $2 billion and $3 billion dollars). Often, multiple states have instituted their own lawsuits in conjunction with federal actions, basing liability on various state laws including state False Claims Acts and consumer protection laws. In addition to the financial impact, the manufacturers have entered into stringent Corporate Integrity Agreements (CIAs) and Deferred Prosecution Agreements (DPAs) that impose processes and procedures affecting

every aspect of corporate conduct, including oversight of the review and approval of advertising and promotion, responding to requests from healthcare professionals for off-label, albeit scientifically accurate and balanced, medical information, and the conduct and supervision of the medical communication function (internal and field-based). Both governmental entities have imposed quasi-regulatory requirements on manufacturers[4] beyond those imposed by the FDA.

The often overlapping focus of enforcement initiatives by FDA and the DOJ/OIG isreflected in the Center for Drug Evaluation and Research (CDER) 2016 priorities issued by Janet Woodcock, M.D. that indicated CDER'sintention to "re-evaluate our regulation of drug advertising and promotion in light of current Jurisprudence around the 1st Amendment" following a series of reversals of FDA enforcement initiatives against manufacturers for off-label promotion. Recent cases, *Amarin Pharma Inc. v. FDA*,[5] as well as related issues and developments in this area and *Pacira Pharmaceuticals v. FDA*,[6] are discussed in considerable detail in the revised chapter 7 to this volume.

The extensively revised chapter 7, as well as the significantly updated chapter 6, focus on the intense legal, regulatory, and compliance activity surrounding the issue of the impact of the First Amendment on the promotional activities of pharmaceutical manufacturers as well as on the general question of appropriate dissemination of accurate and non-misleading medical and scientific information where formal FDA labeling approval has not been granted. The FDA convened a two-day conference in 2016, following a series of adverse appellate decisions in the Second Circuit, to focus on these issues and to obtain input from a range of stakeholders. FDA issued two draft guidance documents in January 2017—one regarding communication with payors and formulary committees and a second addressing communications by medical product manufacturers that are consistent with FDA labeling. In addition, a memorandum containing additional background regarding the agency's views on off-label enforcement and the First Amendment was also issued with a comment period extended to April 19, 2017. We anticipate additional activity in this area by FDA as well as by the OIG and the DOJ in the future.

Nevertheless, the industry has seen a reduction in the number and size of settlements reached between the OIG/DOJ and pharmaceutical companies, as noted in this year's update. The focus appears to have shifted from FCA and FDCA violations arising from off-label promotion of FDA-approved and marketed drugs to other areas of the FDA regulatory process such as actions taken by companies during the pre-approval period.

The third pillar of pharmaceutical enforcement is one frequently overlooked, that being product liability. Yet litigation not only presents financial burdens on the pharmaceutical manufacturer in the form of costs in discovery, attorneys' fees, and settlements and/or judgments, but presents challenges to the regulatory process in determining whether risk identification and management processes are sufficient to provide a scientifically rigorous

defense to a lawsuit alleging failure to warn or an inadequate warning. The debate over preemption for the pharmaceutical manufacturer, absent express preemption in the FDCA, has been engaged again with the Supreme Court having last addressed the issue in the *Wyeth v. Levine*[7] case. Given that the FDA authority to require additional and upgraded warnings under the risk management provisions of the FDAAA has yet to be addressed in the context of preemption, the issue is yet to be determined with finality.

Another litigation-related issue has arisen in the context of generic pharmaceutical manufacturers. In *Pliva, Inc. v. Mensing*,[8] a case involving liability on the part of a generic manufacturer, the Supreme Court found conflict preemption where federal law barred a generic company from unilaterally changing its label and state tort law, upheld liability for the failure to make such changes. It will be interesting to follow the course of the FDA Proposed Rule on extending the Changes Being Effected (CBE) provisions of the FDCA to generics and the potential impact on liability exposure of generics. The issue of the innovator versus generic liability remains contentious, not only as seen in the FDA draft guidance awaiting further action, but also in terms of the claims of generic manufacturers that innovators are using inappropriate means to prevent their ability to access risk management programs (REMS) approved by the FDA for innovator products. These continuing disputes can yet have implications for liability exposure for both innovator and generic manufacturers.

One important development has been observed in the continuing question of liability of innovator pharmaceutical companies for damages incurred following exposure to those companies' generic counterparts. While the majority of cases following the *Conte v. Wyeth*[9] decision have rejected innovator liability where only a generic form of the drug was administered, a series of cases continue to emerge embracing some form of such liability, the most recent issued by the Massachusetts Supreme Judicial Court imposing liability on an innovator manufacturer for injuries caused by a generic drug in *Rafferty v. Merck & Co.*[10]

In addition, Congress has continued to show interest in extending the provisions of CBE to generic manufacturers which would reduce judicial pressure to impose liability on innovators (where courts have been reluctant to deny an injured party recovery for injuries) but place a significant potential burden on generic manufacturers where none had existed previously.

The enforcement environment impacting the pharmaceutical industry remains in a continuing state of change. We hope this 2018 edition will serve to identify these changes and provide useful guidance on the issue of pharmaceutical industry enforcement to all those involved in this field, including manufacturers, academics, and law firms practicing in the area.

HOWARD L. DORFMAN

1. There are other federal agencies that represent additional sources of regulatory oversight nforcement, depending to a large extent on the nature of the drug and the therapeutic le, such as the Drug Enforcement Agency (DEA). This volume, while referencing these cies as the context dictates, will generally focus on the enforcement authority and activities e FDA.

2. 78 Fed. Reg. 67,985 (Nov. 13, 2013).

3. The federal False Claims Act, relied upon in conjunction with elements of the FDCA to cute pharmaceutical companies for off-label promotion, was passed during the Civil War to cute manufacturers of defective armaments supplied to Union forces.

4. One state required the settling pharmaceutical manufacturer to impose stricter dures in the form of having filed or intending to file a supplemental New Drug Application)A) before disseminating off-label medical literature discussing that unapproved indication. FDA Guidance on Dissemination of Off-Label Reprints does not contain that requirement.

5. Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

6. Pacira Pharm., Inc. v. FDA, 1:15-7055-RA (S.D.N.Y. 2015).

7. Wyeth v. Levine, 555 U.S. 555 (2009).

8. Pliva, Inc. v. Mensing, 131 S. Ct. 2567 (2011).

9. Conte v. Wyeth, 158 Cal. App. 4th 89 (2008).

10. Rafferty v. Merck & Co., ___N.E.3d___, 2018 WL 1354064 (Mass. 2018).

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Overview of the FDA Regulatory Process Pre- and Post-Approval and the 21st Century Cures Act

Howard L. Dorfman [1]

The U.S. Food and Drug Administration (FDA) is a federal government agency with broad jurisdiction that touches on products that American consumers purchase or use on an almost daily basis. With regard to its regulation of prescription drugs, FDA has one of the most powerful tools available to any government agency, so-called "pre-approval authority," which controls whether a drug can be marketed in this country.

In addition to pre-approval authority, FDA has a range of mechanisms to ensure compliance with the laws and regulations under its purview. This chapter outlines the regulatory and enforcement authority of FDA as it relates to prescription drugs and biologics, focusing on FDA's regulatory and enforcement authority during the pre-approval period as well as the mechanisms it has to regulate drugs after they have been allowed on the market, so-called "post-approval" regulation.

The chapter also includes an overview of the 21st Century Cures Act (the "Cures Act") and its potential impact on the current FDA regulatory process discussed at length in this chapter. The Cures Act is a major legislative initiative passed by both houses of Congress and signed into law by President Obama in December 2016. It was described by the U.S. House of Representatives Committee on Energy and Commerce as designed to expedite the discovery, development and delivery of novel medical treatments and potential cures while maintaining America's global leadership in biomedical innovation. In general, the act provides the various U.S. health authorities significant authority to support high-risk/high-reward research, incentivize competitions to advance biomedical research, and develop treatments for serious and debilitating diseases. Particular emphasis is placed on prioritizing efforts to address mental health and substance abuse (notably opioid misuse) as well as revising reimbursement policies.

Introductory Definitions

Q 1.1 What is FDA?

FDA "is a scientific, regulatory, and public health agency" charged with overseeing "most food products (other than meat and poultry), human and animal drugs, therapeutic agents of biological origin, medical devices, radiation-emitting products for consumer, medical, and occupational use, cosmetics, and animal feed."[2] FDA was created by the Federal Food and Drugs Act of 1906.[3] Its role was drastically expanded with the passage of the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938,[4] which granted the initial pre-approval authority for drugs based on safety. The 1962 Kefauver-Harris Amendments to the FDCA extended pre-approval authority to require a showing of a drug's efficacy prior to the drug's approval.[5]Though it has been located within a number of different departments over its lifespan, today FDA is a branch of the Department of Health and Human Services (DHHS).[6]

Q 1.2 What is the Federal Food, Drug, and Cosmetic Act?

The FDCA is a law passed by Congress in 1938 giving FDA the authority to oversee the safety of food, drugs, and cosmetics. Since 1938, the FDCA has been amended on numerous occasions, and its amendments have significantly broadened FDA's enforcement powers and authority. The FDCA sets out the processes and requirements for a new drug to be approved and brought to market in the United States.[7]

Q 1.3 What is a drug?

The FDCA defines the term "drug" as any substance that is recognized as a drug by an official compendium of medication,[8] is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention" of a disease or condition in a person, or is intended to affect the structure or function of any part of the body of a person.[9] A drug is not food. Any component of a substance that would meet the above definition of a drug is also considered a drug.[10] The key element of this definition is the "intended use" of the substance and not the particular physical characteristics of the substance. For example, if a particular substance is used as a shampoo simply to clean hair, then it is not a drug. If the manufacturer of that same substance, however, intends to market it to treat a skin condition, then that intended use makes the substance a drug, subject to pre-approval by FDA.

Q 1.4 What is a new drug?

A new drug is any drug, either innovator or generic, that is not yet generally recognized as being safe and effective for use under the conditions prescribed, recommended, or

suggested in the drug's label.[11] In effect, this applies to any new chemical entity that is intended to be used as a drug. A company must first seek and obtain FDA approval before introducing a new drug into interstate commerce.

Q 1.5 What is a biologic?

A biologic, or biological product, is any drug derived from a living organism, such as a vaccine, blood and blood component, tissue, protein, or gene therapy.[12] All biologics meet the drug definition, but not all drugs are biologics because drugs may be sourced from non-living substances.

Q 1.6 What is an IND?

An Investigational New Drug Application (IND) is an application to allow an unapproved drug to be shipped in interstate commerce for the purpose of conducting clinical trials.[13] An IND must be in effect before clinical trials are commenced.

Q 1.7 What is a clinical trial?

Any experiment in which a drug is administered or dispensed to human subjects is considered a clinical trial.[14]

Q 1.8 What is an IRB?

An Institutional Review Board (IRB) is "any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects."[15]

Q 1.9 What is an NDA?

A New Drug Application (NDA) is the vehicle through which a drug manufacturer presents a new drug for FDA approval. The purpose of an NDA is to allow FDA to determine if a drug is safe and effective for its proposed prescribed uses.[16]

Q 1.10 What is a BLA?

A Biologics License Application (BLA) is the vehicle through which the manufacturer of a biologic presents a new biologic for FDA approval.[17] The purpose of a BLA is to allow FDA to determine if a biologic is safe and effective for its proposed prescribed uses.

Q 1.11 What is an ANDA?

An Abbreviated New Drug Application (ANDA) is an application through which a drug manufacturer presents a generic drug for FDA approval.[18] The purpose of an ANDA is to allow FDA to determine if the generic drug is the same as a previously approved drug, a so-called reference listed drug.

Q 1.12 What is a 351(k) application?

Section 351(k) of the Public Health Service Act (PHSA)[19] creates an application through which a manufacturer presents a biosimilar product for FDA approval. The purpose of a 351(k) application is to allow FDA to determine if the biosimilar product is "highly similar" to a previously licensed biological product, a so-called reference product, such that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

Q 1.13 What is a 505(b)(2) application?

Section 505(b)(2) of the FDCA creates a special form of NDA, called a 505(b)(2) application.[20] "A 505(b)(2) application is one for which one or more of the investigations relied upon for approval '[was] not conducted by or for the application and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.'"[21] A 505(b)(2) application can thus rely upon either published literature (on clinical trials or animal studies) for which the applicant has no right of reference—that is, the manufacturer does not need to have conducted the study, or even to have the authority to use the study, in order to include it in the application. A 505(b)(2) application can also rely upon FDA's previous finding of safety and effectiveness for an approved drug.[22]

Q 1.14 What is a generic drug?

A generic drug is a drug that is identical to a previously approved drug (called the "reference listed drug") in dosage, form, safety, strength, route of administration, quality, performance characteristics, and intended use.[23] In addition, a generic drug's label must be identical to the label of the reference listed drug.

Q 1.15 What is a biosimilar product?

A biosimilar product is a biologic that is highly similar to a previously approved biologic, notwithstanding minor differences in clinically inactive components, in that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency. As of December 2015, FDA had approved only one biosimilar product for marketing in the United States.[24]

Q 1.16 How does the 21st Century Cures Act address drug development in relation to the current FDA procedures for pre- and post-approval FDA regulation?

The analysis of the Cures Act in this chapter will focus specifically on those provisions related to drug development. Included in the act's various provisions are sections addressing the expansion of the various types of evidence the agency will deem acceptable in its review of drug applications, the expansion of the use of non-traditional clinical trial designs, and

the increased reliance on various surrogate endpoints in the drug development process.

FDA's Enforcement Authority

Q 1.17 What is the source of FDA's enforcement authority with respect to drugs and biologics?

The FDCA and its implementing regulations granted FDA the authority to enforce laws and regulations pertaining to drugs and biologics, among other products. FDA is charged with administering more than forty-five other statutes in addition to the FDCA, and received authority to regulate biologics in 1972.[25] FDA's enforcement powers have expanded over time and now include oversight over a broad range of drug development, sales, and marketing activities, and the authority to take remedial action as needed.

Q 1.17.1 What is the source of FDA authority with respect to drugs pre-approval?

Since 1938, section 505 of the FDCA has required that all drugs be approved by FDA before they are introduced into interstate commerce.[26] This requirement is mirrored for biologics under section 351 of the Public Health Service Act (PHSA).[27] FDA's approval authority initially only went so far as to ensure that the drugs were safe for consumption. In 1962, the FDCA was amended to require, among other things, that any new drug demonstrate substantial evidence of a drug's efficacy for a marketed indication,[28] along with its safety.[29]

Q 1.17.2 What is the source of FDA authority with respect to drugs post-approval?

The FDCA authorizes FDA to prevent misbranding and adulteration of drugs, and to regulate the uses for which drugs are advertised.[30] Title IX of the 2007 Food and Drug Administration Amendments Act (FDAAA) expanded FDA's post-market authority beyond labeling and marketing, and empowered FDA, under certain circumstances, to require post-market studies and clinical trials, safety labeling changes, and a risk evaluation and mitigation strategy (REMS).[31]

A more detailed analysis of the REMS process appears in chapter 9.

Q 1.18 What is the rationale behind FDA enforcement?

FDA's application of its enforcement authority centers around three goals: ensuring drug safety, protecting research subjects, and promoting health. When it began, FDA's role in regulating drugs was simple: to ensure that drugs were safe to consume.[32]

Over time, however, FDA's role has expanded in scope and nature. Following the 1962 FDCA amendments that required FDA to establish rules governing clinical trials, FDA

added human subjects research protection to its objectives and has developed regulations accordingly.[33] More recently, FDA has adopted a more active role of promoting public health, and pursued objectives such as encouraging production of orphan drugs (for rare diseases)[34] and drugs for serious diseases.[35] To accomplish its various goals, FDA regulates the research and development of new drugs; ensures that drugs are safe and effective before allowing them on the market; advises industry on the effective design of clinical trials;[36] encourages industry to promote the development of drugs for rare or serious conditions; regulates the ways in which drugs are labeled and advertised; and monitors the facilities in which drugs are manufactured.

Pre-Approval Regulation

Q 1.19 What approval does FDA require for the permissible sale of innovator drugs?

The FDCA requires that every new drug sold in the United States first be approved by FDA.[37] FDA must approve all aspects of the drug, including its manufacture, chemical composition, and label. Only after all of these elements have been approved can a drug be marketed in the United States. It is illegal in the United States to sell an unapproved drug,[38] and to do so can result in criminal prosecutions under misdemeanor or felony charges.[39]

Q 1.20 How does a manufacturer obtain FDA approval to sell an innovator drug?

To obtain approval to sell an innovator drug a manufacturer must submit an NDA that sufficiently demonstrates that the new drug is both safe and effective in treating the disease or condition for which it is intended to be used.[40] The NDA is the vehicle through which a drug manufacturer presents information about the innovator drug, such as the data gained from laboratory and animal testing, clinical studies on humans, details about the drug's formulation, and the proposed label.[41] This involves providing data from well-documented research and clinical studies that inform the other information about the drug submitted in the NDA, such as the proposed label, the recommended dosages, and a summary of the drug's risks and benefits.[42] Once the NDA is submitted, FDA will review the application and make a determination about the drug's approval.[43]

Q 1.20.1 What is the research process involved in seeking approval for an innovator drug?

The process of developing a new drug is one of scientific discovery. The development of a new drug typically begins with scientists studying the cellular and genetic factors that play a role in a specific disease. Once these factors are identified, they are commonly referred to as "targets," and scientists can begin to search for molecules that have an effect on those targets. If the researchers uncover a molecule, or set of molecules, that appear to have the intended effect on the target(s), large numbers of related molecules generally are produced and tested to identify those that are most likely to be effective in treating the disease.[44] These molecules are then tested using *in vitro* testing models, which only require small (that is, non-commercial) amounts of the chemical compound.[45] If the *in vitro* tests are successful, the manufacturer will begin *in vivo* testing in animals to screen the drug candidates for pharmacological activity and acute toxicity (that is, whether the drug is likely to be safely administered in humans).[46]

To begin human testing of the new drug the manufacturer must submit an IND to FDA.[47] The prohibition in section 505 of the FDCA would otherwise make it illegal to transport an unapproved investigational drug in interstate commerce.[48] When an IND is in effect, however, this prohibition is waived, and a drug manufacturer may lawfully ship an unapproved investigational new drug in interstate commerce for the purpose of conducting clinical investigations of that drug.[49] FDA monitors INDs "to assure the safety and rights of the subjects" and to ensure "that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety."[50]

An IND will go into effect thirty days after it is submitted, unless FDA has questions or concerns regarding the proposed clinical trials, in which case FDA will place the IND on a clinical hold until the issues can be resolved.[51] Once an IND goes into effect and the manufacturer has obtained IRB approval for each proposed clinical trial (see question 1.20.3 below), the manufacturer may begin Phase 1 clinical testing, followed by Phase 2 and Phase 3 testing. Throughout the clinical trials, the manufacturer must make annual reports to FDA,[52] report safety information to FDA,[53] and update FDA on any adjustments to the study's protocols.[54] When the clinical trials are complete, the manufacturer may submit an NDA seeking final approval of the drug. The NDA must include detailed records of each study, including information on the drug's safety, effectiveness, and the way that the drug behaves in the body.[55]

Q 1.20.2 What are the phases of clinical testing that lead to approval?

There are three phases of clinical testing generally followed before a manufacturer submits an NDA to FDA for approval.

Phase 1 investigations are the initial clinical tests on humans.[56] Phase 1 clinical trials are conducted on a relatively small population of individuals—generally twenty to eighty subjects—for the primary purpose of determining how a drug behaves in humans.[57] Because the primary goal in Phase 1 studies is to determine a drug's general behavior, the test subjects do not need to have the condition or illness that the drug is designed to treat. A successful Phase 1 study will give the investigators sufficient data on the drug's effects, such that that they are able to design well-controlled, scientifically valid Phase 2 studies.[58] During Phase 1 studies, drugs are distributed in an environment in which the subjects can be carefully watched for adverse reactions.

If Phase 1 studies demonstrate that the drug being tested is safe enough to expose more human subjects to it, Phase 2 studies will commence. Phase 2 investigations are controlled clinical studies to "evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study."[59] In addition, Phase 2 studies are designed to determine what short-term side effects and risks are associated with a drug.[60] In other words, while Phase 1 studies are primarily to determine how a drug behaves in the body, Phase 2 studies focus on determining if the drug actually works for its intended therapeutic purpose, which is why Phase 2 trials sometimes are referred to as

"proof of concept" studies. Phase 2 studies usually include up to several hundred subjects.[61]

If effectiveness is shown in Phase 2, Phase 3 investigations will introduce the drug to new populations and environments.[62] FDA uses Phase 3 data on effectiveness and safety to evaluate the overall benefit-risk relationship of the drug being investigated and to provide an adequate basis for the drug's labeling.[63] Unlike the prior phases, Phase 3 studies will often include anywhere from several hundred to several thousand subjects.[64] Once Phase 3 testing is complete, a manufacturer can submit an NDA to FDA to have its drug approved for sale.

Q 1.20.3 When is IRB approval necessary?

The primary purpose of IRB approval and review is to "assure the protection of the rights and welfare of the human subjects."[65] Every clinical trial in the United States, including trials at all three phases of research discussed previously, needs advance approval from an IRB, as well as continuing IRB review.[66] An IRB must review the trial protocols, informed consent forms, subject recruitment procedures, written information that is to be provided to the subjects, the investigator's brochure (discussed in more detail in Q 1.20.4 below), available safety information, information on financial compensation offered to the subjects, qualifications of the investigators, and any other relevant data.[67] Based upon this information, the IRB has the power to approve, require modifications to, or disapprove all research activities that it oversees.[68] Once the IRB has approved a testing protocol, any amendments to that protocol must also receive IRB approval.[69] Failure to have an IRB provide initial and continuing review of a study can result in FDA deciding to ignore that study in considering an NDA.[70] And if FDA learns, after having approved a drug, that the clinical trials used to support that drug's approval were not subject to proper IRB review, FDA may withdraw its approval for that drug.[71]

Q 1.20.4 Who conducts the clinical trials?

A clinical trial's sponsor is the person "who takes responsibility for and initiates a clinical investigation."[72] A sponsor, however, is not required to conduct the investigation; it generally plays a more managerial role. If a manufacturer wishes to bring a drug to market, it must sponsor clinical trials on the drug. Thus, FDA permits a manufacturer to hire a Contract Research Organization (CRO) to oversee the clinical trials on the manufacturer's behalf.[73] The manufacturer can transfer any or all of its clinical trial-related obligations to the CRO.[74]

The sponsor (or CRO) typically hires an investigator, who is the "individual who actually conducts a clinical investigation (that is, under whose immediate direction the drug is administered or dispensed to the subject)."[75] In other words, while the sponsor funds and manages the study, the investigator is the person administering the study drug, taking data, and ensuring that the study is run correctly. The sponsor has responsibility for providing the investigator with an investigator's brochure, which is a document containing

information about the drug to be studied, such as its chemical makeup and pharmaceutical properties, as well as any information known about how the drug behaves in humans, and any known safety information.[76]

An individual may both initiate and conduct an investigation, in which case that individual is known as the sponsor-investigator.[77] A sponsor-investigator must follow the requirements applicable to both sponsors and investigators.[78]

Q 1.20.5 What are a sponsor's and investigator's responsibilities in conducting a clinical trial?

All clinical trials must be carried out in accordance with Good Clinical Practices (GCP), which impose both scientific and ethical requirements on those carrying out clinical trials.[79] GCP is the standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting to which clinical trials must adhere if they wish to be included as evidence of a drug's safety or effectiveness. GCP ensures that the data and reported results from a clinical study are credible and accurate, and that the rights of the test subjects are respected.[80] A sponsor must obtain appropriate informed consent from every test subject, which certifies that the subject understands the research, the potential risks and benefits of the study, and is participating in the study voluntarily.[81] Informed consent must be documented in writing and kept on file.[82]

In addition to the IRB and informed consent requirements noted above, a study's sponsor is required to monitor continuously any ongoing investigations to assure that the investigators are complying with the investigational protocols.[83] The sponsor periodically must review the data concerning the drug's safety coming from the investigation and report that data to FDA.[84] Failure to report safety data to FDA, to adhere to the investigational protocols, or to comply with ethics requirements can result in FDA's placing the trial on clinical hold.[85] If a study is placed on clinical hold, it cannot recruit additional subjects, and existing subjects must be taken off the investigational drug.[86] Investigations may only resume after the sponsor corrects the deficiency(ies) that resulted in the clinical hold, and FDA has given the sponsor permission.[87] Serious or repeated violations of FDA's regulations concerning clinical trials can result in FDA terminating the IND, in which case the sponsor must end all clinical investigations conducted under that IND and the studies will not be able to be used to support an NDA.[88]

The sponsor must keep detailed records of the handling of the investigational drugs,[89] as well as any compensation paid to the investigators.[90] All of these records must be maintained for two years *after* the NDA is approved, or, if the NDA is not approved, for two years after the investigations ceased.[91] Annual reports must also be furnished to FDA, as failure to do so can, in some cases, result in FDA terminating the IND.[92]

Investigators are responsible for ensuring that the investigation is conducted according to the investigational plan, as well as any applicable regulations.[93] In addition, investigators are required to keep records of the disposition of the investigational drug, as well as detailed

case histories on each test subject for the same period of time.[94] They must also ensure that the investigational drug is administered only to the study's subjects.[95] The investigators, like all those involved in conducting clinical trials, are also charged with ensuring that the rights and welfare of human subjects are protected, and so the investigator must also ensure that informed consent has been received from all subjects, and that there is adequate IRB review.[96]

Q 1.20.6 What registration requirements apply to clinical trials?

The Food and Drug Administration Modernization Act of 1997 (FDAMA) created clinicaltrials.gov, a registry of clinical trials run by the National Institutes of Health (NIH).[97] When the registry was first created, however, most privately run clinical trials were not required to participate, and so many companies did not register their trials. In 2007, the FDAAA changed this and imposed a requirement that many more clinical trials be registered with the clinicaltrials.gov website.[98] Now, all controlled, clinical investigations (other than Phase 1 investigations) of a product subject to FDA regulation must be reported to clinicaltrials.gov.[99] The reports must include descriptive information, such as the study's design and goals; recruitment information on the types of individuals being sought for the study; location and contact information; and administrative information, such as the protocol identification number.[100] The information must then be updated with reports on adverse reactions and study outcomes.[101] Clinical trial results will be made public on the website when they either form the primary basis for an efficacy claim, or are conducted post-approval. As with other clinical trial-related obligations, a drug manufacturer can delegate trial registration to a CRO. Failure to timely submit data to the website can result in civil monetary penalties.[102] A timeline of clinicaltrials.gov's development is included on the next page.

TABLE 1-1

History of the Clinical Trial Registry[103]

1997	FDAMA requires that NIH and FDA create a publicly accessible database of clinical trials. The law requires that the database include information on clinical trials run by the federal government, and on privately funded clinical trials for experimental treatments for patients with serious or life-threatening disease or conditions.
2000	The first version of clinicaltrials.gov is made available to the public.
2007	FDAAA expands the requirements for registration with clinicaltrials.gov. All clinical investigations, other than Phase 1 studies, are required to be registered.
2010	Clinicaltrials.gov begins accommodating summary information on results and adverse effects.

2011	FDA requires that informed consent documents include a statement that clinical trial information will be entered into the database.
2012	Clinicaltrials.gov to expand and further enhance its ability to accommodate the submission of summary results data.

Q 1.20.7 What are the standards of approval for an NDA?

For FDA to approve an NDA, it must find that:

- Upon the basis of the information submitted in the NDA, and all other information available on the drug, FDA has sufficient information to determine that the drug is safe for use under the conditions prescribed;[104]
- There is *substantial evidence*, based on the data submitted as part of the NDA, along with all other information available, that the drug will have the effect it purports to have under the conditions of use prescribed;[105]
- The methods used in, and the facilities used for, the manufacture, processing, and packing of the drug are adequate to preserve its identity, strength, quality, and purity—as established by pre-approval inspection of the manufacturing facility;[106]
- The NDA contains the necessary patent information;[107] and
- The proposed label is neither false nor misleading.[108]

Even if all of those conditions are met, however, there are circumstances in which FDA will not approve an NDA.[109] For instance, if the clinical studies were not conducted according to FDA's ethics requirements[110] or the applicant denies admission to an FDA inspector,[111] then the application may also be denied.

Q 1.20.8 What is the "substantial evidence" standard?

Substantial evidence means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[112]

In 1997, Congress amended the FDCA to clarify that substantial evidence can consist of a single "adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation)," if FDA determines that the evidence is "sufficient to establish effectiveness."[113] Independent substantiation of a study's results is preferred, and substantial evidence normally consists of more than one adequate and well-controlled study.[114]

According to FDA regulations, an adequate and well-controlled study is one that:

- Has clear and well-defined protocols;
- Permits a valid comparison with a control to provide a quantitative assessment of a drug's effect;
- Provides adequate assurance that the study's subjects have the disease or condition being studied;
- Is designed to minimize bias with respect to variables such as age and sex, as well as with respect to the subjects, observers, and analysts; uses a reliable and well-defined method of assessment; and
- Contains an analysis adequate to assess the effects of the drug.[115]

Q 1.20.9 How does the Cures Act seek to expand the type of data that may be submitted in support of pharmaceutical development?

The Cures Act is one of the most significant and far-reaching modifications of the FDA drug approval process. It is designed to expedite the process by which new drugs and new indications for existing pharmaceuticals are developed and approved by the agency. For example, under certain conditions, the Cures Act permits companies to provide data summaries and real-world evidence including observational studies, insurance claims data, patient input, and anecdotal data in place of or in support of clinical trial results.

One of the most significant changes to the development process for prescription drugs relates to the FDA's plan for development of a guidance required under Title III of the act relating to Patient-Focused Drug Development. The statute expressly requires the agency to develop one or more guidances over a period of five years addressing the appropriate process for the collection of patient experience data and the use of that information in the drug development process.[116]

Patient experience data refers to the identification and systematic collection of data by any person or entity (including but not necessarily limited to the patients themselves, caregivers, family members, patient advocacy organizations disease research foundations, researchers and pharmaceutical manufacturers). In addition to identifying potential sources, the data would be intended to provide information about patients' experiences and the impact of the disease or condition as well as patient's preferences with respect to treatment of the disease or condition.[117]

Q 1.20.10 What are fast track, breakthrough therapy, accelerated approval, and priority review?

FDA has recognized that for drugs designed to treat serious illness and fill an unmet medical need, there is a strong interest in getting those drugs to the people that need them as quickly as possible. To that end, FDA has developed four programs: fast track, breakthrough therapy, accelerated approval, and priority review.[118] Each must be specifically requested by the NDA applicant.[119]

Fast track is a process for which a drug can qualify if it treats a serious disease or condition for which there is no current therapy, or if it treats a serious disease and has an advantage over extant therapies, such as superior effectiveness or reduced side effects.[120] Once a drug is put on the fast track, FDA will meet with the manufacturer frequently to ensure that the clinical studies are well designed and will gather the appropriate data, helping to ensure that there are no hold-ups in the approval process.[121] In addition, a drug that has been fast tracked can receive rolling review of its NDA, which means that FDA will review completed sections of the NDA as they become available rather than waiting for the completed application. Drugs that qualify for fast tracking may also qualify for accelerated approval and/or priority review.[122]

Breakthrough therapy designation applies to drugs that treat a serious or life-threatening disease or condition and where preliminary clinical evidence indicates that the drug "may have substantial improvement on at least one clinically significant endpoint over available therap[ies]."[123] Drugs that qualify for breakthrough therapy designation receive all of the benefits of fast tracking, as well as additional FDA guidance and organizational involvement in the continued development of the drug, including more involved interaction with FDA senior management and experienced review staff.[124] Breakthrough therapy designation can be submitted for multiple indications of the same drug, though separate applications are required.[125]

Accelerated approval is another option for getting drugs designed to treat a serious disease to market more quickly, namely when there is an unmet medical need. If a drug for a serious disease could take years to demonstrate effectiveness, the accelerated approval process allows the drug's manufacturer to propose a surrogate or an intermediate endpoint that shows the drug is likely to have its intended clinical effects. If FDA accepts a surrogate endpoint, then clinical trials need only show that the drug is able to reach the surrogate endpoint.[126]

For instance, if a drug is designed to help cancer patients live longer, the surrogate endpoint could be demonstrating that the drug causes tumor shrinkage. This is because tumor shrinkage can be measured more quickly than determining if a patient's lifespan has increased.[127] If FDA accepts an intermediate endpoint, then clinical trials need to show a therapeutic effect, such as an effect on mortality or irreversible morbidity.[128] If a drug is approved for marketing pursuant to accelerated approval, the manufacturer will need to conduct Phase 4 testing to determine that the drug does have the desired effect and to verify the predicted effect or clinical benefit, but in the meantime the drug can be marketed and can reach those whom it is intended to help.[129]

Priority review expedites FDA's extensive NDA review process, which often takes ten or more months.[130] If a drug qualifies for priority review, FDA will allocate additional resources to the drug's review process with the goal of approving the drug for sale in the United States within six months.[131]

Q 1.20.11 Under what circumstances is a 505(b)(2) application

appropriate?

A 505(b)(2) application can either be used to seek approval of a new chemical entity (a new drug), or of changes to a previously approved drug.[132] Often, a 505(b)(2) application is used where a manufacturer is seeking approval of a drug product that represents a modification of a listed drug, and for which clinical investigations are essential to the approval.[133] Thus, according to FDA, a manufacturer may use a 505(b)(2) application to change a drug's:

- Dosage Form—"such as a change from a solid oral dosage form to a transdermal patch";[134]
- Strength—for a change to a lower or higher strength;
- Route of administration—such as a change from intravenous administration to intrathecal administration;
- Formulation—for a change in the quality or quantity of the inactive ingredients in a drug;
- Dosing regimen—such as a change from administering twice daily to once daily;
- Indication—to get approval for the drug to treat an indication for which it was not previously indicated; or
- Active ingredient—for either the change of the, or one of the, active ingredients in a drug.[135]

A 505(b)(2) application might also be used for a new drug that is a combination product consisting of active ingredients, each of which has previously been found safe and effective by FDA.[136]

Q 1.21 What approval does FDA require for the sale of generic drugs?

All drugs, whether they are innovators or generics, must be approved by FDA.[137] However, because generic drugs are meant to be identical to drugs that have already been approved, the manufacturer of a generic drug does not need to prove independently that the generic drug is safe and effective. Instead, the generic drug manufacturer merely needs to prove that the generic drug meets the requirements of an ANDA.[138]

Q 1.22 How does a manufacturer obtain FDA approval to sell a generic drug?

The ANDA process was added to the FDCA as a component of the Hatch-Waxman Amendments to the FDCA in 1984, in an effort to spur the development of generic drugs.[139] To obtain approval to sell a generic drug, a manufacturer must submit an ANDA, which shows that the generic drug and the reference listed drug[140] have the same active ingredient or ingredients;[141] label;[142] route of administration, dosage form, and

strength.[143] The two drugs also must be bioequivalent, meaning that they have the same bioavailability[144]—in other words, the rate and extent to which the two drugs' active ingredients are absorbed and get to the point in the body at which they work must be the same.[145] In addition to showing that the drugs behave in the same manner, the generic manufacturer must show that the producer of the reference listed drug is no longer entitled to any period of exclusivity, be it via patent or a statutorily created period.[146] An ANDA cannot be used to present clinical trial data to FDA, other than data on bioavailability and bioequivalence. If other clinical trial data is necessary for the drug's approval, the applicant should submit either an NDA or a 505(b)(2) application.[147]

Q 1.23 How does a manufacturer obtain FDA approval to sell a biologic?

Biologics are subject to very similar regulations as other drugs; however, biologics generally are reviewed by the Center for Biologics Evaluation and Research (CBER),[148] and they are approved through BLAs rather than via NDAs.[149] Much like an NDA, a BLA must include information on how a product is manufactured, data from pre-clinical and clinical studies, and proposed labeling.[150] Once a BLA has been approved for a product, the biologic's manufacturer has a license to sell that product in the United States.

Q 1.23.1 How does a manufacturer obtain FDA approval to sell a biosimilar product?

The Biologics Price Competition and Innovation Act, enacted in 2010 as part of overall healthcare reform in the Patient Protection and Affordable Health Care Act, authorizes FDA to approve biological products through an abbreviated regulatory pathway that does not require such products to undergo full clinical testing.[151] This abbreviated pathway is analogous to the ANDA process that has been in place for generic drug products under the Hatch-Waxman Amendments since 1984. FDA is authorized to approve biosimilar products via so-called 351(k) applications based on, among other things: analytic studies which show that the product is "highly similar" to an innovator or "reference product" that was approved based on full clinical studies; animal toxicology studies; and one or more human studies that assess immunogenicity, pharmacokinetics, or pharmacodynamics. FDA may waive these requirements, and others, in connection with its review of an application.

Q 1.24 How does FDA communicate its approval decisions?

When FDA determines that a drug meets the statutory standards for safety and effectiveness, it sends the applicant an approval letter.[152] The approval becomes effective on the date the approval letter is issued, unless the approval is for a generic drug where the reference listed drug is still entitled to exclusivity, in which case the approval will have a delayed effective date.[153] An approval letter grants to a manufacturer the right to sell its drug, but may also include requirements for post-marketing activities if FDA believes that such activities are necessary.[154] For instance, if FDA has specific safety concerns, it can

require the manufacturer to undertake post-market studies, or implement a REMS.[155] In addition, FDA may attempt to persuade a manufacturer to commit to Phase 4 clinical trials before FDA will approve a drug.[156] FDA can also require that certain labeling changes be made to the drug before FDA approves it for sale on the market.[157]

If FDA does not approve an application it will send the applicant a Complete Response Letter, which includes a description of the application's deficiencies, a review of the data, and, when possible, recommendations for actions the applicant should take to obtain approval.[158]

Post-Approval Regulation

Q 1.25 What post-approval acts can FDA require a manufacturer to undertake?

Previously, FDA's formal authority to require manufacturers to conduct studies after a product's approval was, in most circumstances, very limited. However, in 2007, the FDAAA's amendments to the FDCA expanded FDA's ability to require post-marketing activities on the part of the manufacturer.[159] For instance, if, prior to approval, there are serious known risks or data indicating there may be serious risks, FDA can require a post-approval study.[160] In addition, FDA can require post-approval studies for already-approved products if it becomes aware of new safety information.[161] The manufacturer must submit plans and timetables for completing these studies, and it is required to provide FDA with periodic updates.[162] FDA can also require that changes be made to the drug's labeling based upon new safety information.[163]

In addition, if a drug presents unusual risks, and FDA believes that certain steps are necessary to ensure that the drug's benefits outweigh those risks, FDA may require a manufacturer to implement a REMS.[164] As amended, sections 505 and 505-1 of the FDCA authorize FDA to require a REMS as part of the approval for any NDA, ANDA, or BLA, consistent with FDA's determination that such a strategy is necessary to ensure that the drug or biologic will be used safely and appropriately.[165] Should FDA find that it is necessary, FDA can also require the implementation of a REMS for a drug that has already been approved.[166] A REMS might require, among other things, that a drug include special medication guides or package inserts, that a manufacturer disseminate information explaining the safety protocols, or that a drug be dispensed only in certain locations or by individuals with certain training.[167] A REMS must periodically be evaluated, and a timetable for submissions of the assessments must be included as part of the REMS.[168] A manufacturer's failure to comply with either of the post-marketing study or REMS conditions will result in FDA considering the drug misbranded.[169]

Q 1.26 When does FDA reconsider or withdraw approval of a drug?

FDA's monitoring of a new drug does not cease with a drug's approval. Rather, FDA requires that all manufacturers investigate adverse events that are associated with their drugs, and submit reports on adverse events to FDA.[170] A company must also submit a field report to FDA if it believes any of its products have been mislabeled or contaminated.[171] In 2008, FDA expanded its monitoring of adverse events pursuant to a mandate in the FDAAA requiring FDA to establish an active surveillance system for monitoring drugs on the market. FDA launched the Sentinel Initiative, a long-term FDA

effort to create a national electronic system for monitoring product safety.[172] Though the Sentinel Initiative is still in its infancy, with FDA initiating the Mini-Sentinel pilot program to test concepts, its intended purpose is to draw existing automated healthcare data from multiple sources so that FDA can look for patterns and actively monitor the safety of medical products in real-time.[173]

In certain circumstances, FDA will withdraw its approval of a drug. If FDA learns, either through the adverse event reporting system or through other new evidence that was unavailable at the time of a drug's approval, that an approved drug is unsafe for use or ineffective for its prescribed use, or that the drug poses an imminent hazard to the public health, FDA *must* withdraw its approval for the drug.[174] FDA must also withdraw its approval if it learns that a drug's application contained an untrue statement of material fact.[175]

In other situations, FDA has discretion over whether or not to withdraw a drug. It may exercise this discretion if a manufacturer fails to maintain the appropriate records; the labeling of the drug is false or misleading; FDA learns that any of the clinical studies used to support the NDA or ANDA were not conducted according to appropriate ethical standards; or if certain other regulations are violated.[176] In the event of either mandatory or discretionary withdrawal of a drug, the drug's manufacturer is entitled to a hearing on the proposed withdrawal. If the approval for a drug is withdrawn, the drug may no longer be sold within the United States. Only in cases of an imminent threat to public health can FDA bypass the hearing process and withdraw the drug immediately.

Q 1.27 How does FDA regulate manufacturing practices?

FDA requires that all drugs be manufactured according to current Good Manufacturing Practices (cGMP), including those intended for import into the United States.[177] These standards exist to ensure that drugs on the market are not adulterated, and that they contain the proper amounts of their active ingredients. To ensure that manufacturers are complying with cGMP regulations, FDA undertakes regular inspections of facilities used to manufacture or store drugs.[178] In advance or in lieu of an inspection, FDA may require manufacturers to provide records or other information that would otherwise have been made available during a facility inspection.[179] Failure to observe cGMPs can result in FDA deeming a drug adulterated without FDA having to find evidence of actual contamination.[180] Distribution of an adulterated drug is illegal under the FDCA, and may lead to civil enforcement action or criminal prosecution as discussed below.

Once FDA has inspected a facility, if the inspector observes indications that drugs or biologics have been adulterated, held, packaged, or prepared under conditions in which the drug or biologic may have been adulterated, the investigator will issue a Form 483 to the company's management.[181] In response to a Form 483, a recipient company should provide FDA with a corrective action plan to address the observations noted and to thereafter implement the corrective action plan to address those observations, as well as any objectionable conditions not cited in the Form 483.[182]

While a Form 483 is not a final FDA determination of whether a violation of the FDCA has occurred, it will be considered along with the accompanying evidence, documentation, and any company response when FDA determines whether to take additional steps to address any observed findings.[183]

FDA's inspection authority was expanded under Title VII of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA).[184] FDASIA requires an increased amount of information for the registration of domestic or foreign drug manufacturers and expands the circumstances under which a drug will be deemed to be adulterated to include instances where the owner or operator of any factory, warehouse, or establishment that manufactures, processes, packages or holds a drug has delayed, denied or limited an inspection, or has refused to permit entry or inspection.[185]

Q 1.28 What drug-related communications does FDA regulate?

FDA regulates all promotional communications related to prescription drugs. This covers a drug's label and labeling, as well as any advertising for the drug. However, FDA does not regulate scientific exchange,[186] which may take the form of responses to unsolicited requests for information,[187] support for continuing medical education, reporting of scientific results, market research, or meetings with investigators and consultants.[188]Communications that are not made by or affiliated with a drug's manufacturer are also not regulated by FDA.[189]

Q 1.28.1 What is a drug's labeling?

A drug's label is "a display of written, printed, or graphic matter upon the immediate container of any article";[190] in other words, it is what is printed *on* the packaging. Labeling, however, is much more expansive, and is defined in the FDCA as "all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such an article."[191]The U.S. Supreme Court has interpreted this definition broadly, holding that labeling "is not restricted to labels that are on or in the article or package that is transported," but can include any material meant to "supplement or explain" the labels included with the drug, and thus that mailings sent separately from a drug could still constitute labeling.[192]

FDA has embraced this broad definition by defining labeling as "[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the 'Physicians Desk Reference') for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor."[193]

Q 1.28.2 What standards and prohibitions apply to labeling?

As part of the new drug approval process, FDA reviews a drug's proposed label to ensure that the label appropriately lists a drug's intended usage, dosage regimen, and potential side-effects, among other things.[194] Once the label is approved it *must* be included with the drug when it is sold; otherwise, the drug will be considered misbranded.[195] Because the label is often extensive, it usually takes the form of an insert in the drug packaging.[196] Any materials that are considered to be labeling (such as letters to physicians promoting the drug) must be consistent with the label and, with few exceptions, must include a full copy of the label.[197] A drug will be considered misbranded if its label or labeling deviates from the approved form, contains any false or misleading statements, or states or suggests that the drug should be used to treat any condition other than that for which it was approved. Distribution of a misbranded drug is prohibited by the FDCA, and can result in civil enforcement action[198] or criminal prosecution.[199] FDA can also require that changes be made to a drug's label if FDA becomes aware of new information concerning the drug's safety.[200]

Q 1.28.3 What is a drug's advertising?

Labeling and advertising are both considered promotional activities subject to FDA jurisdiction, but they are not the same activity.[201] Labeling is material distributed directly by the drug manufacturer, or on its behalf, intended to promote a specific drug; whereas, advertising is material attributable to a drug manufacturer, but distributed via a third-party medium intended to promote a specific drug. For instance, product promotions created by the manufacturer that appear in print media, on television, or on third-party websites all constitute advertising.[202]

Q 1.28.4 What standards and prohibitions apply to advertisements?

All prescription drug advertising must be consistent with the information on the drug's label. Unlike the label, however, an advertisement needs to contain only a brief summary of the product's side effects, contraindications, and effectiveness.[203] Certain other information, such as a drug's ingredients, at least one example of its dosage, and the drug's proper name (as opposed to the name used for marketing), must be included in the advertising as well.[204] Drug advertisements must not be false or misleading, and must present the benefits of the drug fairly balanced with its risks.[205] An advertisement may not make a claim of superiority over another drug or treatment, either directly or by implication, unless the statement was approved as part of a drug's labeling, or is supported by substantial evidence derived from adequate studies.[206] Moreover, a drug's advertising cannot recommend or suggest that the drug be used for any purpose that is not on the label that was accepted as part of the drug's approved NDA.[207] As previously noted, the advertising restrictions do not apply to scientific exchange.[208]

In 2012, FDA issued draft guidance, which it has not issued in final form yet, describing how it intends to implement the review of certain direct-to-consumer prescription drug television advertisements, including submission to FDA for review forty-five days prior to dissemination and an obligation to make changes to or include additional information in advertisements based on FDA's recommendations.[209] The guidance shows a risk-based approach to review, with several proposed categories of prescription drugs and other advertisements that would be subject to pre-dissemination review.[210] Also included in the guidance are the requirements for submission and the various consequences of violating the review requirements.[211]

Q 1.28.5 How does FDA regulate drug promotion?

FDA's regulations on advertisements and promotional materials are enforced through pre-release advisory comments that FDA may make on a draft promotional campaign, as well as through monitoring of advertisements that are in the market. FDA requires that all advertisements and promotional labeling for a drug product be submitted to FDA at the time of their publication or dissemination via FDA Form 2253.[212] These materials, however, are merely kept on file; FDA does not require most advertisements to be pre-approved.[213] The Office of Prescription Drug Promotion (OPDP), which is charged with enforcing the advertising regulations, will offer advisory comments on draft promotions and marketing materials if such comments are requested.[214] Additionally, in an effort to step up its enforcement of regulations on advertising, FDA has begun the Truthful Prescription Drug Advertising and Promotion Program (Bad Ad Program), which encourages healthcare providers to report to OPDP any false or misleading advertising.[215]

If FDA believes a company's promotional activities violate the FDCA, it can take informal agency action by issuing an Untitled or Warning Letter to request that the company cease and desist its prohibited activities.[216] The Untitled Letter generally is reserved for initial violations or activities that do not pose a significant safety risk.[217] The Warning Letter is a more graduated response generally applied to repeat violations or activities that may create a safety risk.[218] In addition to a cease and desist request, the Warning Letter generally asks for the creation and implementation of a corrective action plan.[219] Untitled and Warning Letters are made available to the public on FDA's website, and are frequently published in the trade press and other business sources, potentially creating significant negative publicity for the recipient.[220] A manufacturer is not required to comply with an Untitled or Warning Letter, though most generally do accede to FDA's requests. And while FDA typically issues a Warning Letter before turning to formal enforcement actions, FDA has taken the position that it is *not* required to do so.[221]

Q 1.28.6 What is off-label promotion?

Off-label promotion is the promotion of a drug for a use other than that for which it was approved by FDA.[222] According to FDA, "[a]n approved drug that is marketed for an

unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.'"[223] Off-label promotion can take many forms, such as claims made in print advertisements, in television advertisements, or in statements made by a manufacturer's agents, including contracted physician speakers. Scientific exchange, as discussed previously, is not subject to the prohibitions against off-label promotion. In recent years, prosecution of off-label promotion has continued to increase and has led to the collection of billions of dollars in criminal and civil settlements.[224] However, recent court decisions have addressed whether FDA can regulate the dissemination of truthful, non-misleading information, including off-label information, consistent with the First Amendment. There is a detailed discussion of these recent decisions in chapter 5 below.

Q 1.29 What are FDA's formal enforcement tools?

FDA may take a number of formal enforcement actions. If FDA believes that a particular product or batch of a product is adulterated, misbranded, or otherwise in violation of the FDCA, FDA can request that a U.S. Attorney's Office seize those products.[225] If FDA believes that a company is operating in a way that significantly deviates from the FDCA and the company has persisted in such conduct after FDA notified the company of the violations, FDA can also ask the Department of Justice (DOJ) to seek an injunction against the company.[226] If FDA secures an injunction, the manufacturer must cease manufacturing its products, and will be permitted to resume manufacturing only once it has taken the remedial measures prescribed by FDA.[227]

In addition to the civil remedies discussed above, distribution of adulterated or misbranded drugs can result in criminal prosecutions, either for a misdemeanor or a felony, depending on the context.[228] Conviction for a misdemeanor violation of the FDCA does not require that an individual have had the intent to violate the act, or even the knowledge that the act was being violated.[229] A felony prosecution, on the other hand, requires a showing that the defendant either committed the violation with intent to defraud or mislead, or that the defendant is a repeated violator.[230] If a person is convicted of certain felonies or misdemeanors related to drug products FDA has the authority to prohibit that individual or a corporation affiliated with that person from participating in certain aspects of the drug industry (referred to as "debarment").[231]

FDA Regulation Generally

Q 1.30 How does FDA communicate its enforcement policies and priorities, as well as guidance on compliance?

FDA has traditionally communicated its enforcement priorities through a variety of methods, including, among other means, preambles to regulations, advisory opinions, press announcements, statements to the media, direct contact with manufacturers, and other guidance documents. FDA also communicates its enforcement policies through its website as well as through compliance guides for industry, such as the *Manual of Compliance Policy Guides* and the *FDA Regulatory Procedures Manual*.[232] In addition, FDA's *Weekly Enforcement Report* publicizes all enforcement actions FDA has taken in a given week, including the reasons the actions were taken and the products affected, while the annual enforcement story provides information on the enforcement activities taken that year.[233] All of these resources are accessible and available to the public at www.fda.gov. Further information can also be gained from Freedom of Information Act (FOIA) requests.[234]

As part of a broader, government-wide push to increase transparency, FDA implemented the "Food and Drug Administration Transparency Initiative" with the goal of increasing public and industry awareness of FDA activities.[235] As part of the initiative, FDA has created a new "FDA Basics" website for consumers.[236] FDA has also issued several reports containing draft policies and disclosing information about FDA-regulated companies and products, and increasing the transparency of FDA operations and decision-making.[237] In addition, FDA released a draft policy for increasing access to its compliance and enforcement data.[238] FDA has also opened a web portal to facilitate more transparent communication with the public and drug industry about its enforcement and compliance-related activities.[239]

Q 1.31 What FDA divisions perform enforcement activities?

The FDA Commissioner is ultimately responsible for assuring compliance with laws and regulations enforced by FDA, and has the power to participate in all regulatory decisions.[240] In practice, however, most enforcement activities are implemented by the various divisions within FDA. FDA is divided into six product-related centers, two of which, CDER and CBER regulate drugs and biologics. The Office of Regulatory Affairs (ORA) serves as the lead office for all field activities and is primarily responsible for conducting inspections, collecting and analyzing samples, initiating enforcement actions, and conducting follow-up actions to assure industry compliance.[241] ORA has regional and district offices, each of which typically contains an inspection unit, a laboratory unit (for performing analyses), and a compliance branch (for performing district-level enforcement activities).[242]

In addition to ORA, the Office of Compliance, Enforcement, and Criminal Investigations (OCI) acts as the law-enforcement arm of FDA. OCI investigates alleged criminal violations of the laws governing foods, drugs, and cosmetics. OCI deals directly with violations of Prescription Drug Marketing Act,[243] off-label promotion of FDA-approved drugs, and fraud in NDAs.[244] OCI has grown markedly since its creation in 1992; OCI's budget has grown from about $19 million in 1999, to about $41 million in 2008,[245] and the number of arrests and convictions has grown from roughly 100 of each in 1996 to over 330 arrests and over 260 convictions in 2012,[246] and, in 2013, the most recent period for which OCI has reported these statistics, to 303 drug-related arrests and 273 drug-related convictions with fines, restitutions, and other monetary penalties exceeding $2.3 billion.[247]

Q 1.32 When does FDA collaborate with other agencies to meet enforcement objectives?

FDA works with DHHS, DHHS's Office of Inspector General (OIG), the Department of Defense (DOD), DOJ, and the Federal Trade Commission (FTC), the Securities and Exchange Commission (SEC), as well as with certain states and state attorneys general, for conducting investigations and enforcement actions. While FDA has the primary authority to enforce the FDCA, FDA has partnered with these other agencies in light of their universal emphasis on protecting the consumer and fighting fraud in the healthcare system, as well as to bolster its enforcement authority. As FDA lacks the power to bring lawsuits on its own behalf, in exercising some of its enforcement powers (that is, seizure, injunction and certain criminal proceedings) it must refer matters to DOJ or the appropriate U.S. Attorney's Office for prosecution.[248]

The 21st Century Cures Act and Its Potential Impact on the FDA Regulatory Process

Q 1.33 How does the 21st Century Cures Act seek to accelerate the pace of drug discovery and development by expanding the type of data to be included in the overall research process?[249]

Under discussion for a number of years, the Cures Act takes the initial steps to develop the process to be followed by FDA and drug companies in utilizing "Patient Experience Data" as a component of both drug development and approval. The data is broadly defined as data designed to provide information as to a patient's personal experiences with a disease or condition, which would include both the impact on the patient's life as well as the patient's reaction to and preference for the particular treatment or therapy utilized. The Cures Act requires the FDA to draft and issue various guidance documents over the next five years to provide details regarding the methodologies to be used in the collection and assessment of patient experience data and to detail how FDA intends to utilize such data in the review and approval process.

The Cures Act is one of the most significant and far-reaching modifications of the FDA drug approval process. It is designed to expedite the process by which new drugs and new indications for existing pharmaceuticals are developed and approved by the agency. For example, under certain conditions, the Cures Act permits companies to provide data summaries and real-world evidence including observational studies, insurance claims data, patient input, and anecdotal data in place of or in support of clinical trial results.

One of the most significant changes to the development process for prescription drugs relates to the FDA's plan for development of a guidance required under Title III of the act relating to Patient-Focused Drug Development. The statute expressly requires the agency to develop one or more guidances over a period of five years addressing the appropriate process for the collection of patient experience data and the use of that information in the drug development process.

Patient experience data would relate to the systematic collection of data by any person or entity (including but not necessarily limited to the patients themselves, caregivers, family members, patient advocacy organizations disease research foundations, researchers and pharmaceutical manufacturers. In addition to identifying potential sources, the data would be intended to provide information about patients' experiences and the impact of the disease or condition as well as patient's preferences with respect to treatment of the disease or condition.

Q 1.34 How are various drug development tools addressed in the Cures Act?

In seeking to further one of its primary goals of modernizing the clinical trial process

relied upon in the drug review and approval process, the act sets out a process for qualifying drug development tools,[250] which may be utilized by sponsors to support their various applications including INDs, NDAs, and BLAs. These various tools, such as the use of biomarkers and surrogate endpoints, have been discussed and utilized, albeit on a somewhat limited basis. The Cures Act provides an impetus to their broader adoption by FDA.

Q 1.35 How will acceptable clinical trial designs change under the Cures Act?

The act requires FDA to address the matter of novel clinical trial designs[251] in a series of guidance documents focusing on the type and qualifying process for novel types of clinical trial design. In particular, FDA is expected to clearly articulate how novel clinical trial designs would help satisfy the agency's existing substantial evidence standards as well as define the types of data to be submitted by sponsors for review, and develop a process for interaction between FDA and sponsors to expedite understanding and utilization of the novel trial designs.

Q 1.36 What role will "real-world evidence" assume under the Cures Act?

Clearly one of the most contentious aspects of the act is the section detailing the potential role of "real-world evidence."[252] The Cures Act requires FDA to establish a process and issue guidance documents to facilitate the collection, utilization and reliance of real-world evidence (as distinguished from data collected in various clinical trials) to assist in the regulatory review and approval function where a sponsor is seeking approval of a new indication for a previously NDA-approved drug or to satisfy post-approval study commitments. In this context, real world evidence would constitute data relative to the use, risks and/or benefits of a drug "derived from sources other than randomized clinical trials," heretofore deemed the "gold standard" for evaluation of a drug seeking approval. The data itself could be derived from various sources, including patient registries, post-approval spontaneous surveillance reports, and observational studies. The FDA is required to issue draft guidance within five years that would clearly articulate the precise circumstances under which sponsors could utilize such data as well as the appropriate standards to be followed in the actual collection and analysis of the real-world evidence for filing with the agency. The Cures Act clearly states that the guidance on the use of real-world evidence will have no impact on FDA's existing authority and requirements for initial NDAs and BLAs for initial approval prior to commercialization or on any post-approval study or additional traditional clinical trials. In light of the significant changes expected by this provision of the act, it is likely that significant debate and possible revisions may result.

Q 1.37 What is the definition and scope of a "qualified data summary"?[253]

The Cures Act allows the agency to rely upon a "qualified data summary" as the basis for review and approval of a *supplemental* application for a drug or a biologic for specific and

limited indications. qualified data summary refers to a summary of various clinical data that establishes the safety and effectiveness of the drug or biologic for a "qualified indication," defined under the act as an indication that FDA deems appropriate for reliance on a summary of clinical data. The focus and anticipated benefit of this provision would be to grant FDA wider latitude in establishing the quantum of evidence necessary to support approval of an expanded indication and obviate the need for a full clinical trial.

Q 1.38 How does the Cures Act address the issue of "expanded access"?

Although the act does not specifically mandate any significant changes to the existing concept of "expanded access,"[254] it does require increased dissemination of information by manufacturers as to the existence and qualifications for patient use of the expanded access policy. Sponsors would be required to post such information as the company's contact information, procedures to follow to file a request for consideration, as well as the manufacturer's criteria for consideration and acceptance into the expanded access policy. In addition, the act would require posting such information on www.clinicaltrials.gov for certain studies.[255]

Q 1.39 What are some forthcoming developments related to the Cures Act?

There are a number of statutory deadlines imposed on the FDA under the Cures Act. These deadlines relate to issuance of various guidance documents, detailed implementation plans and processes in addition to holding public meetings to obtain additional input regarding next steps in finalizing the provisions of the Cures Act. These requirements include development of the draft guidance on patient-focused drug development, issuance of reports on such topics as regenerative advanced therapies, and scheduling public meetings on such matters as development of novel clinical trial designs.

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1. An earlier version of this chapter, entitled FDA Enforcement Pre- and Post-Approval, uthored by Al Cacozza with additional contributions from Lauren E. Foster Wu and rt S. Shapiro. Revisions and additional analysis to address the impact of the 21st Century s Act appear in this revised chapter.
2. JOHN P. SWANN, U.S. FOOD AND DRUG ADMINISTRATION, FDA'S GINS (1998), www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm ɔted from George Kurian, ed., *A Historical Guide to the U.S. Government* (New York: rd University Press, 1998)) [hereinafter SWANN].
3. Pub. L. No. 59-384, codified at 21 U.S.C. § 1-15 (1934), repealed by 21 U.S.C.)(a) (1938).
4. Pub. L. No. 75-717, codified at 21 U.S.C. §§ 301 *et seq.* (1938).
5. FDCA Amendments, Pub. L. No. 87-781 (1962); SWANN, *supra* note 1.
6. SWANN, *supra* note 1.
7. *See* 21 U.S.C. § 505 (2013).
8. The official compendia of medications are "the official [U.S.] Pharmacopoeia, official

oeopathic Pharmacopoeia of the [U.S.], official National Formulary, or any supplement to f them." 21 U.S.C. § 321(j). The U.S. Pharmacopeia—National Formulary is a book of ards for medications. It contains information (called monographs) on drug substances and urations, and sets FDA-enforceable quality standards for drugs, as well as for dietary lements and excipients. *See* U.S. PHARMACOPOEIA, USP-NF—An OVERVIEW, .usp.org/USPNF/.

9. "The term 'drug' means (A) articles recognized in the official [U.S.] Pharmacopoeia, al Homoeopathic Pharmacopoeia of the [U.S.], or official National Formulary, or any lement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, nent, or prevention of disease in man or other animals; and (C) articles (other than food) ded to affect the structure or any function of the body of man or other animals; and (D) es intended for use as a component of any article specified in clause (A), (B), or (C)." 21 C. § 321(g)(1) (2013).

10. *Id.*

11. "The term 'new drug' means—

> Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to the enactment of this Act [enacted June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or
>
> Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

21 U.S.C. § 321(p) (2013).

12. Biologics include "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood onent or derivative, allergenic product, protein (except any chemically synthesized eptide) or analogous product, or arsphenamine or derivative of arsphenamine (or any other ent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease ndition of human beings." 42 U.S.C. § 262(i) (2013); *see also* 21 C.F.R. § 600.3(h) (2013).

13. 21 C.F.R. § 312.1(a) (2013).

14. 21 C.F.R. § 312.3(b).

15. 21 C.F.R. § 56.102(g).

16. U.S. FOOD AND DRUG ADMINISTRATION, NEW DRUG APPLICATION A),

.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/Appr
pplications/NewDrugApplicationNDA/default.htm.

17. 21 C.F.R. § 601.2(a) (2013).

18. *See* 21 U.S.C. § 355(j) (2013).

19. 42 U.S.C. § 262(k) (2013).

20. *See* 21 U.S.C. § 355(b)(2).

21. U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY:
ICATIONS COVERED BY SECTION 505(B)(2)—DRAFT GUIDANCE (Oct. 1999)
inafter 505(b)(2) DRAFT GUIDANCE], at 2,
.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07
.pdf (quoting 21 U.S.C. § 355(b)(2) (1999)).

22. 505(b)(2) DRAFT GUIDANCE, *supra* note 20, at 2–3; *see also* 21 C.F.R. § 314.3(b)
l) ("Right of reference or use means the authority to rely upon, and otherwise use, an
tigation for the purpose of obtaining approval of an application, including the ability to
available the underlying raw data from the investigation for FDA audit, if necessary.").

23. *See* U.S. FOOD AND DRUG ADMINISTRATION, GENERIC DRUGS:
STIONS AND ANSWERS,
.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm.

24. News Release, FDA, FDA Approves First Biosimilar Product Zarxio (Mar. 6, 2015),
.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm.

25. As adopted in 1938, the FDCA gave FDA the authority to oversee the safety of only
drugs and cosmetics. At that time biologics were regulated by the National Institutes of
th.

26. 21 U.S.C. § 355 (2011); U.S. FOOD AND DRUG ADMINISTRATION,
NIFICANT DATES IN U.S. FOOD AND DRUG LAW HISTORY,
.fda.gov/aboutfda/whatwedo/history/milestones/ucm128305.htm.

27. 42 U.S.C. § 262 (2013).

28. An indication is a particular symptom of a disease or condition, or a disease or condition
FDA approves drugs only for those indications for which they have been proven effective.

29. FDCA Amendments, Pub. L. No. 87-781 (1962). These amendments, known as the
ıver-Harris Amendments, also expanded FDA's enforcement powers to restrict drug
tising of approved indications for drugs and to inspect drug manufacturing facilities.

30. 21 U.S.C. § 331 (2013).

31. 21 U.S.C. § 355(p); *see also* Pub. L. No. 110-85 (2007).

32. Michelle Meadows, *Promoting Safe Drugs for 100 Years*, FDA CONSUMER MAG.
–Feb. 2006),
.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDACon
r/ucm093787.htm [hereinafter Meadows].

33. *Id.* FDA issued regulations to require independent committee review of proposed
rch; these regulations developed from the "Common Rule" (*i.e.*, the Federal Policy for the
ction of Human Subjects), which regulates research supported or regulated by seventeen

al agencies. *See* 21 C.F.R. § 50 (2013).

34. An orphan drug is a "drug intended for use in a rare disease or condition." 21 C.F.R. 5.3(b)(10) (2013). The Orphan Drug Act was passed to incentivize manufacturers to op orphan drugs by offering tax credits and marketing incentives to the sponsor of the uct that qualifies as an orphan drug. *See* Pub. L. No. 97-414 (1983); U.S. FOOD AND G ADMINISTRATION, DESIGNATING AN ORPHAN PRODUCT: DRUGS AND LOGICS, .fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrph oductDesignation/default.htm.

35. *See* Meadows, *supra* note 31 (describing the push to develop orphan and generic drugs).

36. *See, e.g.*, 21 C.F.R. 312.41(b) (2013), stating that on request, FDA "will provide advice ecific matters relating to an [Investigational New Drug Application]. Examples of such e may include advice on the adequacy of technical data to support an investigational plan, e design of a clinical trial, and on whether proposed investigations are likely to produce the and information that is needed to meet requirements for a marketing application."

37. *See* 21 U.S.C. §§ 331(d), 355(a) (2013).

38. 21 U.S.C. § 331.

39. 21 U.S.C. § 333; *see also* ARTHUR N. LEVINE, FDA ENFORCEMENT MANUAL mpson 2013) [hereinafter ENFORCEMENT MANUAL], at tab 1300, ¶¶ 1311–12.

40. *See* 21 C.F.R. § 314.2 (2013).

41. For a full description of what is required in an NDA, see 21 C.F.R. § 314.50.

42. *See id.*

43. 21 U.S.C. § 355(c) (2013); 21 C.F.R. § 314.100(a) (2013).

44. U.S. FOOD AND DRUG ADMINISTRATION—CTR. FOR DRUG LUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, INVESTIGATORS, REVIEWERS: EXPLORATORY IND STUDIES, at 2 (Jan. 2006), .fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07 .pdf.

45. *Id. In vitro* testing refers to tests performed outside of a living organism, whereas *in vivo* g refers to tests performed on/in living beings.

46. *Id.*; *see also* U.S. FOOD AND DRUG ADMINISTRATION, INVESTIGATIONAL 7 DRUG APPLICATION, .fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/Appr pplications/InvestigationalNewDrugINDApplication/default.htm. If non-clinical animal es are to be used in the ultimate NDA and are essential to demonstrating that the drug is or use in humans, the studies must be conducted according to FDA's guidelines on good atory practice for nonclinical laboratory studies, or FDA will refuse to approve the cation. *See* 21 C.F.R. § 314.125(b)(15). For FDA's good laboratory practice for nonclinical atory studies regulations, see 21 C.F.R. §§ 58 *et seq.* (2013).

47. 21 C.F.R. § 312.20 (2013).

48. 21 U.S.C. § 355(a) (2013).

49. 21 C.F.R. § 312.1(a) (2013); *see also* 21 U.S.C. § 355(i)(1) (2013).

50. 21 C.F.R. § 312.22(a) (2011).

51. 21 C.F.R. § 312.40(b)(1). "A clinical hold is an order issued by FDA to the sponsor to a proposed clinical investigation or to suspend an ongoing investigation." 21 C.F.R. 2.42(a). When a proposed study is placed on clinical hold, subjects may not be given the tigational drug. *Id.* When an ongoing study is placed on clinical hold, no new subjects may cruited to the study, and existing subjects should be taken off the investigational drug unless nued administration is permitted by FDA in the interest of patient safety. *Id.*

52. 21 C.F.R. § 312.33.

53. 21 C.F.R. § 312.32.

54. 21 C.F.R. § 312.23. A protocol is a document that describes the way in which a clinical s to be conducted. It should include a description of the trial's objective(s), design, odology, and organization. In essence, it tells someone why and how a study is being done. nvestigators follow the protocol in running a study, and any changes to a study must be through protocol amendments. 21 C.F.R. § 312.23(a)(6).

55. *See* 21 C.F.R. § 314.50.

56. *See* 21 C.F.R. § 312.21(a).

57. *Id.* Per FDA regulations, the studies are designed to "determine the metabolism and nacologic actions of the drug in humans, the side effects associated with increasing doses, if possible, to gain early evidence on effectiveness." *Id.* These studies also examine the onship between the drug's structure and its activities, as well as its mechanism of action in ans. *Id.* Phase 1 studies can also be studies in which "investigational drugs are used as rch tools to explore biological phenomena or disease processes." *Id.*

58. *Id.*

59. 21 C.F.R. § 312.21(b).

60. *Id.*

61. *Id.*

62. 21 C.F.R. § 312.21(c).

63. *Id.*

64. *Id.*

65. 21 C.F.R. § 56.102(g).

66. *See* 21 C.F.R. §§ 56.103(a), 312.23(a)(1)(iv); *see also* 21 C.F.R. § 312.53(c)(vi)(d); U.S. D AND DRUG ADMINISTRATION, UNDERSTANDING CLINICAL TRIALS, //clinicaltrials.gov/ct2/info/understand. Among other things, FDA regulations require that ND include a commitment that an IRB "will be responsible for the initial and continuing w and approval of each of the studies in the proposed clinical investigation and that the tigator will report to the IRB proposed changes in the research activity." 21 C.F.R. 2.23(a)(1)(iv) (2013). Per this requirement, the IRB and the investigator's reporting to the must comply with applicable FDA regulations.

67. U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY: E6 OD CLINICAL PRACTICE: CONSOLIDATED GUIDANCE, at 10 (Apr. 1996),

.fda.gov/downloads/regulatoryinformation/guidances/ucm129515.pdf [hereinafter GOOD NICAL PRACTICE].

68. *See* 21 C.F.R. § 56.109(a) (2013).

69. *See* 21 C.F.R. § 312.30(a), (b). The role of the IRB is to ensure that appropriate med consent is received, review and approve all research, and ensure that the research is ucted ethically. 21 C.F.R. § 56.111. Careful adherence to these guidelines is necessary, ıse FDA will not approve any drug whose NDA relies upon a study that violated either the med consent or IRB requirements. *See* 21 C.F.R. § 314.125(b)(16).

70. *See* 21 C.F.R. § 56.103(b).

71. *See* 21 C.F.R. § 314.150(b)(8).

72. *Id.* 21 C.F.R. § 312.3(b).

73. *See* 21 C.F.R. § 312.52.

74. *Id.*

75. *Id.* 21 C.F.R. § 312.3(b).

76. *Id.* 21 C.F.R. § 312.23(a)(5).

77. *Id.* 21 C.F.R. § 312.3(b).

78. *Id.*

79. *See* U.S. FOOD AND DRUG ADMINISTRATION, RUNNING CLINICAL ALS, www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm;)D CLINICAL PRACTICE, *supra* notes 66, at 4.

80. GOOD CLINICAL PRACTICE, *supra* notes 66, at 9.

81. 21 C.F.R. § 50.25 (2013); *see also* 21 C.F.R. § 312.53(c)(vi)(d). For Informed Consent ırements, see 21 C.F.R. § 50.20. There are ethical limits to the studies that can be ucted. For instance, if the risks associated with a potential new drug far outweigh the ĭits, and cannot be controlled for in the study, or if a study would require exposing "healthy ın volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or ar substance[s]," FDA will not allow the study to be carried out. *See* 21 C.F.R. § 314.600; *so* 21 C.F.R. § 312.42 (imposing clinical holds on, among other things, studies in which ıan subjects are or would be exposed to an unreasonable or significant risk of illness or y").

82. 21 C.F.R. § 50.27.

83. 21 C.F.R. § 312.56.

84. 21 C.F.R. § 312.56(b), (c). Should the manufacturer uncover problems with how the al trial is being run, the manufacturer must either fix the problems or shut down the study. study drug is found to create a significant or unreasonable risk, the manufacturer must ntinue the investigations immediately. If the study is shut down for either of these reasons, ıanufacturer must inform the study's IRB and FDA. 21 C.F.R. § 312.56(d).

85. 21 C.F.R. § 312.42.

86. 21 C.F.R. § 312.42(a).

87. 21 C.F.R. § 312.42.

88. 21 C.F.R. § 312.44(a), (b)(vii), (b)(ix).

89. The manufacturer must keep records of the "receipt, shipment, or other disposition of ıvestigational drug," including "the name of the investigator to whom the drug is shipped, he date, quantity, and batch or code mark of each such shipment." 21 C.F.R. § 312.57(a).

90. *See* 21 C.F.R. § 312.57(b); *see also* 21 C.F.R. § 54.4.

91. 21 C.F.R. § 312.57(c).

92. 21 C.F.R. §§ 312.33, 312.44(b)(viii).

93. 21 C.F.R. § 312.60.

94. *See* 21 C.F.R. § 312.62.

95. 21 C.F.R. § 312.61.

96. *See* 21 C.F.R. §§ 312.60, 312.66.

97. *See* CLINICALTRIALS.GOV, U.S. NATIONAL INSTITUTES OF HEALTH, KGROUND,http://clinicaltrials.gov/ct2/info/about.

98. *See id.*

99. *See* CLINICALTRIALS.GOV, U.S. NATIONAL INSTITUTES OF HEALTH, TORY, POLICIES, AND LAWS,http://clinicaltrials.gov/ct2/about-site/history.

100. *See* CLINICALTRIALS.GOV, U.S. NATIONAL INSTITUTES OF HEALTH, TOCOL DATA ELEMENT DEFINITIONS, //prsinfo.clinicaltrials.gov/definitions.html; CLINICALTRIALS.GOV, U.S. NATIONAL TITUTES OF HEALTH, HELPFUL HINTS, //prsinfo.clinicaltrials.gov/ResultsExamples.pdf.

101. *See* Clinicaltrials.gov, U.S. NATIONAL INSTITUTES OF HEALTH, PROTOCOL 'A ELEMENT DEFINITIONS, http://prsinfo.clinicaltrials.gov/definitions.htm.

102. ENFORCEMENT MANUAL, *supra* note 38, at tab 1000, ¶ 1060.

103. *See* Informed Consent Elements, 76 Fed. Reg. 256 (Jan. 4, 2011); U.S. FOOD AND IG ADMINISTRATION, GUIDANCE FOR INDUSTRY: INFORMATION GRAM ON CLINICAL TRIALS FOR SERIOUS AND LIFE-THREATENING ASES AND CONDITIONS (Mar. 2002), .fda.gov/downloads/RegulatoryInformation/Guidances/ucm126838.pdf; NATIONAL ARY OF MEDICINE, CONGRESSIONAL JUSTIFICATION FY2014, .nlm.nih.gov/about/2014CJ.html.

104. 21 U.S.C. § 355(d) (2013).

105. 21 U.S.C. § 355(d)(5).

106. 21 U.S.C. § 355(d)(3).

107. 21 U.S.C. § 355(d)(6).

108. 21 U.S.C. § 355(d)(7).

109. *See* 21 C.F.R. § 314.125 (2013).

110. *See* 21 C.F.R. § 314.125(b)(16).

111. 21 C.F.R. § 314.125(b)(12).

112. 21 U.S.C. § 355(d) (2013).

113. *See* Pub. L. No. 105-115, § 115(a) (1997); 21 U.S.C. § 355(d) (2011).

114. *See* 21 U.S.C. § 355(d) (2013); U.S. FOOD AND DRUG ADMINISTRATION,

DANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF
ECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS, at 4–5 (May
),
.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07
.pdf.

115. *See* 21 C.F.R. § 314.126(b) (2013).

116. FDA, PLAN FOR ISSUANCE OF PATIENT-FOCUSED DRUG DEVELOPMENT
DANCE UNDER 21ST CENTURY CURES ACT TITLE III SECTION 3002 (May
), https://www.fda.gov/downloads/forindustry/…/prescriptiondruguserfee/ucm563618.

117. *Id.*

118. *See* U.S. FOOD AND DRUG ADMINISTRATION, FAST TRACK,
AKTHROUGH THERAPY, ACCELERATED APPROVAL, AND PRIORITY
IEW,
.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNew
apies/ucm128291.htm [hereinafter FDA, FAST TRACK].

119. *Id.*

120. *Id.*

121. *Id.*

122. *Id.*

123. *See* FDA, FAST TRACK, *supra* note 117. *See also* U.S. FOOD AND DRUG
MINISTRATION, FAQS ON BREAKTHROUGH THERAPIES,
.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/Sig
ntAmendmentstotheFDCAct/FDASIA/ucm341027.htm [hereinafter FDA,
AKTHROUGH THERAPIES]. Additional guidance can be found at U.S. FOOD AND
G ADMINISTRATION, GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS
SERIOUS CONDITIONS—DRUGS AND BIOLOGICS—DRAFT GUIDANCE
2013),
.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm35
.pdf.

124. *See* FDA, BREAKTHROUGH THERAPIES, *supra* note 122.

125. *See id.*

126. 21 C.F.R. § 314.510 (2013).

127. *See* FDA, FAST TRACK, *supra* note 117.

128. *Id.*

129. *See* 21 C.F.R. § 314.510 (2013).

130. *See* FDA, FAST TRACK, SUPRA note 117.

131. *Id.* Although beyond the scope of this chapter, FDA issued a draft guidance in 2017 on
reakthrough Devices Program discussing the policies and procedures the agency intends to
op to implement that part of the Cures Act intended to expedite the development,
ment, review and approval of medical devices intended to treat life-threatening or
ersible and debilitating diseases and medical conditions.

132. *See* 505(b)(2) DRAFT GUIDANCE, *supra* note 20, at 3.
133. 21 C.F.R. § 314.54(a) (2013).
134. *See* 505(b)(2) DRAFT GUIDANCE, *supra* note 20, at 4–5.
135. *See id.*
136. *Id.* at 5. The active ingredient or ingredients in a drug are those components of the drug have a direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease ndition, or that affect the structure or any function of the human body.
137. *See* 21 U.S.C. § 355(a) (2013).
138. *See* 21 C.F.R. § 314.92(a) (2013).
139. *See* Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug lopment Process*, 54 FOOD & DRUG L.J. 187, 189 (1999). The Hatch-Waxman Act ed the modern system of generic drugs by creating the ANDA, and by ensuring that new are entitled to a period of exclusivity. *See id.*
140. "Reference listed drug means the listed drug identified by FDA as the drug product upon an applicant relies in seeking approval of its abbreviated application." 21 C.F.R. 4.3(b) (2013). Reference listed drugs are typically found in the *Approved Drug Products with apeutic Equivalence Evaluations*, also known as the Orange Book.
141. 21 U.S.C. § 355(j)(2)(A)(ii) (2013).
142. 21 U.S.C. § 355(j)(2)(A)(v).
143. 21 U.S.C. § 355(j)(2)(A)(iii).
144. 21 U.S.C. § 355(j)(2)(A)(iv).
145. "Bioavailability means the rate and extent to which the active ingredient or active moiety orbed from a drug product and becomes available at the site of action. For drug products are not intended to be absorbed into the bloodstream, bioavailability may be assessed by urements intended to reflect the rate and extent to which the active ingredient or active ty becomes available at the site of action." 21 C.F.R. § 320.1(a) (2013).
146. *See* 21 U.S.C. § 355(j)(2)(vii) (2013).
147. *See* 505(b)(2) DRAFT GUIDANCE, *supra* note 20, at 3–4.
148. *About the Center for Biologics Evaluation and Research*, U.S. FOOD AND DRUG MINISTRATION, .fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/default.h
149. *See* 21 C.F.R. § 601.2(a) (2013).
150. *Biologics License Applications (BLA) Process*, U.S. FOOD AND DRUG MINISTRATION, .fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicatio AProcess/default.htm.
151. *See* 42 U.S.C. § 262(k) (2013).
152. 21 C.F.R. § 314.105(a) (2013).
153. *Id.* § 314.107.
154. *See* 21 U.S.C. § 355(o), (p) (2013).

155. For a full description of conditions that can be placed upon a drug's approval, see *infra* 25.

156. *See* 21 C.F.R. § 312.85 (2012).

157. 21 C.F.R. § 314.105(b).

158. 21 C.F.R. §§ 314.110, 601.3.

159. Pub. L. No. 110-85 § 909(a) (2007).

160. 21 U.S.C. § 355(o)(3) (2013).

161. *Id.*

162. *Id.*

163. 21 U.S.C. § 355(o)(4).

164. 21 U.S.C. §§ 355(p), 355-1(a); LENA Y. CHOE, U.S. FOOD AND DRUG MINISTRATION, RISK EVALUATION AND MITIGATION STRATEGIES, .fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyProg/PharmacyStudentExperientialProgramCDER/ucm276838.pdf. Templates for REMS are ıble through the FDA's website. *See* U.S. FOOD AND DRUG ADMINISTRATION, TMARKET DRUG SAFETY INFORMATION FOR PATIENTS AND PROVIDERS, .fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/defa:m.

165. 21 U.S.C. § 355(p) (2013).

166. 21 U.S.C. § 355-1(a)(2).

167. *See* 21 U.S.C. § 355-1(e). A REMS may (but is not required to) include: a Medication e (highlighting important safety information to be distributed by pharmacists to patients ving the drug); a Patient Package Insert; a Communication Plan (for healthcare ssionals, which describes the safe and appropriate use of the drug or biologic); Elements to e Safe Use (EASU) (highly controlled systems or requirements used to enforce the ɔpriate use of a drug or biologic and are most commonly used to mitigate specific serious when other items included in the REMS are not sufficient to mitigate risks); and an ementation Plan (describing how certain EASUs will be implemented). *See id.*

168. *See* 21 U.S.C. § 355-1(d). Assessments must occur eighteen months, three years and years after the strategy is approved.

169. 21 U.S.C. § 352(y), (z).

170. Serious adverse events must be reported within fifteen days, but quarterly reports of all se events must also be submitted for three years post-approval and then at annual intervals. 1 C.F.R. § 314.80 (2013).

171. 21 C.F.R. § 314.81.

172. U.S. FOOD AND DRUG ADMINISTRATION, FDA'S SENTINEL INITIATIVE—KGROUND, www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm.

173. *Id.*

174. 21 C.F.R. § 314.150(a) (2013).

175. *Id.*

176. 21 C.F.R. § 314.150(b).

177. U.S. FOOD AND DRUG ADMINISTRATION, FACTS ABOUT CURRENT
)D MANUFACTURING PRACTICES,
.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm
inafter FDA, FACTS ABOUT CURRENT GOOD MANUFACTURING PRACTICES].
urrent regulations on cGMPs, see 21 C.F.R. § 211 (2013). cGMPs were expanded under
012 Food and Drug Administration Safety and Innovation Act (FDASIA), which amended
DCA, to include quality oversight and additional controls for the manufacture and supply
›f drugs. *See generally* Pub. L. No. 112-144 (2012).

178. *See* FDA, FACTS ABOUT CURRENT GOOD MANUFACTURING PRACTICES, note 176.

179. *See* FDASIA §§ 700 *et seq*.

180. ENFORCEMENT MANUAL, *supra* note 38, at tab 1600, ¶ 1610.

181. *See* U.S. FOOD AND DRUG ADMINISTRATION, FDA FORM 483
QUENTLY ASKED QUESTIONS,
.fda.gov/ICECI/EnforcementActions/ucm256377.htm.

182. *Id.*

183. *Id.*

184. FDASIA §§ 700 *et seq*.

185. FDASIA § 707(a).

186. *See, e.g.*, 21 C.F.R. § 312.7 (2013) (banning promotion of an investigational new drug
e or effective, but noting that "[t]his provision is not intended to restrict the full exchange
entific information concerning the drug, including dissemination of scientific findings in
tific or lay media."). Further clarification may be forthcoming as FDA requested public
nents by March of 2012, on the concept of scientific exchange generally as well as industry
ıt on a number of topics, such as the distinction between scientific exchange and
ıotion, and the relevance of speakers and audience, quality of data, and type of drug or
e being discussed in determining whether a particular communication is properly
dered promotion or scientific exchange. *See* Communications and Activities Related to Off-
l Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for
mation and Comments, 76 Fed. Reg. 81,508 (Dec. 28, 2011).

187. U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY:
'ONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION
UT PRESCRIPTION DRUGS AND MEDICAL DEVICES—DRAFT GUIDANCE
. 2011),
.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm28
.pdf.

188. *See id.; see also* Guidance for Industry: Industry Supported Scientific and Educational
ities, 62 Fed. Reg. 64,094–95 (Dec. 3, 1997).

189. *See* 62 Fed. Reg. at 64,094.

190. 21 U.S.C. § 321(k) (2013).

191. 21 U.S.C. § 321(m).

192. Kordel v. United States, 335 U.S. 345, 349–50 (1948).

193. *See* 21 C.F.R. § 202.1(*l*)(2) (2013).

194. 21 C.F.R. § 314.50(c)(2)(i); *see also* 21 C.F.R. § 208. Drugs that have been approved June 30, 2001, have more extensive labeling requirements than older drugs. For a full iption of labeling requirements, see 21 C.F.R. § 201.56(b), (e); 21 C.F.R. § 201.57.

195. 21 U.S.C. § 352 (2013).

196. U.S. FOOD AND DRUG ADMINISTRATION, AN INTRODUCTION TO THE ROVED FDA PRESCRIPTION DRUG LABELING—TRANSCRIPT, .fda.gov/Training/ForHealthProfessionals/ucm090801.htm.

197. *See* 21 C.F.R. § 201.56 (2013). Certain exceptions limit the information required to be ded in so-called "reminder labeling." *See* 21 C.F.R. § 201.100(f).

198. Potential civil enforcement actions include seizures, injunctions, and debarment. *See* 21 C. §§ 331(a), 332, 334, 335a (2013).

199. 21 U.S.C. §§ 331(a), 333.

200. 21 U.S.C. § 355(o)(4).

201. *See* 21 C.F.R. § 201 (2013) (labeling regulations); 21 C.F.R. § 202 (advertising ations).

202. *See* 21 C.F.R. § 202.1(l)(1); *see also* U.S. FOOD AND DRUG ADMINISTRATION, IG ADVERTISING: A GLOSSARY OF TERMS, .fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.ht oting that "advertisements generally appear in: Print periodicals, such as journals, zines, and newspapers, [and] broadcast media, such as television and radio, as well as igh telephone systems," while promotional labeling "differs from advertising in the way it is buted" and can consist of "brochures and booklets; mailed materials, including letters to nts; videotapes; [and] refrigerator magnets, cups, and other giveaways that show a drug's :.").

203. 21 U.S.C. § 352(n) (2013).

204. 21 C.F.R. § 202.1 (2013).

205. 21 C.F.R. § 202.1(e)(5).

206. 21 C.F.R. § 202.1(e)(6)(ii).

207. 21 C.F.R. § 202.1(e)(4).

208. *See, e.g.*, 21 C.F.R. § 312.7 (banning promotion of an investigational new drug as safe or ive, but noting that "[t]his provision is not intended to restrict the full exchange of tific information concerning the drug, including dissemination of scientific findings in tific or lay media.").

209. U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY: ECT-TO-CONSUMER TELEVISION ADVERTISEMENTS—FDAAA DTC EVISION AD PRE-DISSEMINATION REVIEW PROGRAM—DRAFT GUIDANCE . 2011), .fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm29 .pdf.

210. *Id.*

211. *Id.*

212. U.S. FOOD AND DRUG ADMINISTRATION, OPDP FORM FDA-2253 MISSIONS, .fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090 ıtm.

213. 21 C.F.R. § 202.1(j) (2013) (describing the conditions in which prior approval is sary).

214. 21 C.F.R. § 202.1(j)(4); U.S. FOOD AND DRUG ADMINISTRATION, UESTS FOR ADVISORY COMMENT ON PROMOTIONAL MATERIALS OTHER N PROPOSED DTC TV ADS, .fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090 ıtm; U.S. FOOD AND DRUG ADMINISTRATION, THE OFFICE OF SCRIPTION DRUG PROMOTION, .fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

215. U.S. FOOD AND DRUG ADMINISTRATION, KEY POINTS OF THE BAD AD GRAM, .fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketing rtisingandCommunications/ucm211498.htm.

216. *See* 21 U.S.C. § 336 (2013) (authorizing FDA to issue Untitled and Warning Letters).

217. *See* ENFORCEMENT MANUAL, *supra* note 38, at tab 400, ¶ 400.

218. *See id.*

219. *Id.* at tab 500, ¶ 510.

220. *Id.* at tab 400, ¶ 401; U.S. FOOD AND DRUG ADMINISTRATION, WARNING TERS, www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.

221. *See* Margaret A. Hamburg, M.D., Commissioner of U.S. FOOD AND DRUG MINISTRATION, Remarks at the Food and Drug Law Institute: Effective Enforcement Benefits to Public Health (Aug. 6, 2009), .fda.gov/NewsEvents/Speeches/ucm175983.htm (indicating that FDA will be ending its y of issuing multiple Warning Letters before taking action, and that it may take formal n before a Warning Letter is issued in the case of serious violations).

222. 21 C.F.R. §§ 201.100, 201.128 (2013).

223. U.S. FOOD AND DRUG ADMINISTRATION, GOOD REPRINT PRACTICES THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR NTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF ROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (Jan. 2009), .fda.gov/RegulatoryInformation/Guidances/ucm125126.htm (citing 21 U.S.C. § 352(f))); 21 C.F.R. § 201.100(c)(1) (2009)).

224. *See Factbox: Drugmakers' Big Settlements for* Off-Label *Promotion*, REUTERS (Nov. 23,), www.reuters.com/article/2011/11/23/us-doj-merck-fb-idUSTRE7AM0FA20111123.

225. 21 U.S.C. § 334 (2013); ENFORCEMENT MANUAL, *supra* note 38, at tab 1100,

)0. The company receives no formal notice before its products are seized, and has no right
ıearing. Once the products have been seized, they will be condemned and destroyed unless
ɔmpany begins the judicial process to defend them.

226. 21 U.S.C. § 332 (2013); ENFORCEMENT MANUAL, *supra* note 38, at tab 1200,
)0. If the situation presents an immediate threat to public health, FDA may seek a
orary restraining order, and will otherwise seek a permanent injunction. *Id.* at tab 1200,
)1. The corrective measures required by the injunction are often very costly, and serve as a
ıs to ensure that the noted problems will not recur. *Id.*

227. ENFORCEMENT MANUAL, *supra* note 38, at tab 1200, ¶ 1201.

228. 21 U.S.C. §§ 331(a), 333(a), 333(c) (2013).

229. 21 U.S.C. § 333(a)(1).

230. 21 U.S.C. § 333(a)(2).

231. 21 U.S.C. § 335a ("FDCA Debarment"). FDA keeps an up-to-date debarment list,
shes a notice in the *Federal Register* each time a person is debarred, and discloses debarment
mation under FOIA requests. *See* U.S. FOOD AND DRUG ADMINISTRATION, FAQS
DEBARMENTS/DISQUALIFICATIONS,
.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm176043.htm. As of May 2013,
had debarred over 120 individuals convicted of crimes related to drug products, but no
ɔrations. U.S. FOOD AND DRUG ADMINISTRATION, FDA DEBARMENT LIST
JG PRODUCT APPLICATIONS),
.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm. Debarment can be
specific term (for permissive debarment actions) or for a lifetime (for mandatory debarment
ns), though debarees may apply to terminate their debarment if they substantially assist in
ıvestigation or prosecution of others in drug-related cases and can demonstrate
ɔilitation. 21 U.S.C. § 335a (2013). Typical types of activities that have resulted in
ːment include submitting false data to FDA, lying to FDA investigators, paying or
ɔting bribes, and selling prescription drug samples. Tamar Nordenberg, *Inside FDA: Barring*
'e from the Drug Industry, FDA CONSUMER MAG. (Mar. 1997),
.fda.gov/ICECI/EnforcementActions/FDADebarmentList/ucm139627.htm. Under certain
mstances a debarment action may be subject to judicial review. *See* FDCA Debarment.

232. ENFORCEMENT MANUAL, *supra* note 38, at tab 200, ¶ 281.

233. *Id.* at tab 200, ¶ 281. For enforcement reports, see U.S. FOOD AND DRUG
IINISTRATION, ENFORCEMENT REPORTS,
.fda.gov/Safety/Recalls/EnforcementReports/default.htm.

234. ENFORCEMENT MANUAL, *supra* note 38, at tab 200, ¶ 282.

235. U.S. FOOD AND DRUG ADMINISTRATION, FDA TRANSPARENCY
'IATIVE, www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm
inafter FDA TRANSPARENCY INITIATIVE].

236. *Id.*; U.S. FOOD AND DRUG ADMINISTRATION, FDA BASICS,
.fda.gov/aboutfda/Transparency/Basics/ucm2021108.htm.

237. FDA TRANSPARENCY INITIATIVE, *supra* note 234.

238. U.S. FOOD AND DRUG ADMINISTRATION, DRAFT PROPOSALS FOR LIC COMMENT TO INCREASE TRANSPARENCY BY PROMOTING GREATER ESS TO THE AGENCY'S COMPLIANCE AND ENFORCEMENT DATA, .fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm273809.htm.

239. U.S. FOOD AND DRUG ADMINISTRATION, ENFORCEMENT ACTIONS, .fda.gov/ICECI/EnforcementActions/default.htm.

240. ENFORCEMENT MANUAL, *supra* note 38, at tab 200, ¶ 250.

241. U.S. FOOD AND DRUG ADMINISTRATION, ABOUT THE OFFICE OF ULATORY AFFAIRS, .fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ ılt.htm.

242. ENFORCEMENT MANUAL, *supra* note 38, at tab 200, ¶¶ 220–26.

243. Pub. L. No. 100-293 (1987).

244. U.S. FOOD AND DRUG ADMINISTRATION, WHAT OCI INVESTIGATES, .fda.gov/ICECI/CriminalInvestigations/ucm123062.htm.

245. ENFORCEMENT MANUAL, *supra* note 38, at tab 200, ¶ 243.

246. *Id.* The number of arrests and convictions reached a high in FY 2007, with 496 arrests 344 convictions. *Id.* The numbers lessened somewhat in FY 2008 to 386 arrests and 369 ictions, with a similar number of convictions the following year. *Id.* However, the arrest and iction rate dropped significantly in FY 2010 and 2011. *Id.*

247. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FY 2015 FOOD) DRUG ADMINISTRATION, JUSTIFICATION OF ESTIMATES FOR ROPRIATIONS COMMITTEES, at 44, .fda.gov/downloads/aboutfda/reportsmanualsforms/reports/budgetreports/ucm388309.pdf.

248. ENFORCEMENT MANUAL, *supra* note 38, at tab 200, ¶ 271.

249. 21st Century Cures Act, Pub. L. No. 114-255, §§ 3001–3004 (2016).

250. *Id.* § 3011.

251. *Id.* § 3021.

252. *Id.* § 3022.

253. *Id. § 3031.*

254. *Id.* § 3032.

255. 42 U.S.C. § 282(j)(2)(A)(ii)(II)(gg).

FDA Enforcement—Facility Inspections

Alena C. Galante & Michael F. Ruggio

This chapter provides an overview of FDA terminology and the basics of facility inspection. Questions are presented from the company perspective with regard to what can be refused, questioned, and stated. Since most companies are global, foreign inspections are mentioned.

FDA Inspection Basics

Q 2.1 What does FDA inspect?

FDA inspects manufacturers or processors of Food and Drug Administration (FDA)-regulated products to verify that they comply with relevant regulations. Those inspected include:

- vaccine and drug manufacturers;
- blood banks;
- food processing facilities;
- dairy farms; and
- animal feed processors.

FDA also inspects:

- facilities that conduct studies in people (clinical trials);
- laboratories that conduct studies in animals or microorganisms when these studies are used to apply for FDA approval of a medical product;
- foreign manufacturing and processing sites for FDA-regulated products that are sold in the United States; and
- imported products at the border.[1]

Q 2.2 When does/can FDA inspect an establishment/firm/company?

FDA inspects manufacturers or processors of FDA-regulated products after an application is submitted to FDA for a new product; when a facility is due for a "routine" inspection or as a follow-up to a previous inspection (for example, typically once every two years); or to investi-gate a specific problem that came to FDA's attention. As mentioned above, inspections include foreign manufacturing or processing sites for FDA-regulated products that are sold in the United States.

Q 2.3 What are the types of inspection?

FDA conducts a pre-approval inspection of a facility and the drug manufacturing process in order for the company to market the new product. FDA conducts a routine or general inspection to ensure that manufacturing facilities remain in compliance with federal regulations. FDA conducts a "for-cause" inspection to investigate a problem that was brought to the attention of FDA.

Q 2.4 Can the company refuse an inspection?

Yes. A company can refuse an inspection or access to any area or record, but the company needs to recognize that in order to manufacture drugs for distribution in the United States (ignoring vitamins and nutritionals, which are considered foods and subject to different rules), a company must hold a license. That license is predicated on conformance to the Federal Food, Drug, and Cosmetic Act (FDCA), and, more specifically, Title 21, Part 211 of the Code of Federal Regulation, which is FDA's mandate to inspect. If the company refuses an inspection, FDA has the right to terminate the license, which is a more drastic measure than recall, seizure, and injunction—all of which permit the company some measure of operational capability. If the company were to refuse access to an inspector, FDA can get a court order and force their way into the facility, accompanied by U.S. Marshals, to see what they wish to.

The Inspection

Q 2.5 How should an onsite inspector visit be handled?

The company should have standard operating procedures (SOPs) on handling FDA inspections. The SOPs shall address the notification of key company employees when an inspector arrives at the door. The SOPs shall also address who will and how to interact with the inspector(s) as well as the responsibilities of these key personnel, so that employees who are designated to host and accompany FDA inspectors shall be knowledgeable about site operations and how to appropriately work with regulatory authorities. The site manager is usually designated as the recipient of the inspection notice.

A designated location, such as a conference room near the building entrance, shall be identified. Inspector(s) typically remain in the designated conference room, except for personal breaks and if they request a tour of the facility. The inspector(s) may be consulted on the proper protocol for them when it comes to providing drinks, snacks, or meals. Typically, FDA inspectors prefer to purchase their own drinks, snacks, or meals, and may even want to do so offsite.

The SOPs on handling inspections shall also identify processes for obtaining requested information, recording and tracking of requested documents and copies, documenting inspection activities each day and distribution of this information, and follow-up and response procedures once the inspection concludes. The SOPs shall also identify site activities that are permitted and suspended during the inspection time period.

Q 2.6 Who does FDA see—Legal, Quality, or Management?

At the beginning of the inspection, FDA typically requests an overview of the site and asks for organization charts. They may request to speak with anyone in the organization, but usually leave it up to the company to identify the expert who can best answer the inspector's questions. It is typical for Quality Assurance to host FDA inspection, and for representatives of Validation, Quality Control, Production, Engineering, and any other departments that are involved with manufacturing of product to participate as required in the inspection process. Ultimately, the appropriate company representative will depend on the reason for the inspection and the inspector's path of questions.

Q 2.7 What documentation is subject to inspection?

Documentation subject to inspection includes any record that FDA is entitled to have access to or copies of under the FDCA. Typically, this is documentation that supports the product's life cycle (for example, production records, product stability studies, packaging material studies, analytical methods, equipment qualification studies, etc.). However, FDA authority does not include access to certain information such as product formulas,

shipment lists, codes, etc., unless specifically required by law.

Q 2.7.1 How should a company handle an inspector request to review records that are not subject to inspection?

The company should ask the inspector to provide the specific reference in the law that lists the record in question. If the inspector cannot provide the reference, then the company can refuse. The inspector will make note of the refusal.

Q 2.8 Does the company have to provide deviations, change controls, complaints, and rejected batches in an electronic format rather than just paper?

There is no requirement for the format of copies to be provided to FDA nor any guidance that states records must be provided in both paper *and* electronic format. However, if data exists as electronic data, then FDA may request a copy.

Q 2.8.1 Does the company have to grant FDA access to "live" demos of their systems?

FDA should not personally access a company's electronic records, databases, or source/raw data during the course of the inspection. The integrity of the data must be maintained and unauthorized changes must be prevented. FDA is required to verify that the data is original and authenticate the copy they receive, so FDA may observe an employee accessing the database/system that contains the requested information and the action of copying the data.

Q 2.9 If there are specific requirements in site SOPs (no cosmetics, for instance) to which inspectors are unwilling to conform, can access be denied to those areas?

Yes. The inspectors must comply with specific requirements, such as gowning procedures in order to enter production areas. The company should ensure that the appropriate escort, training, clothing, lockers, etc., are available to assist the inspectors.

Q 2.9.1 If an inspector comes to the site during non-business hours, is the company obligated to bring in the appropriate personnel?

The company has the option to refuse the inspector. Make certain to explain the reason for the refusal; the inspector is required to document the refusal. The company also has the option to allow the inspector on site during non-business hours, and it is at the company's discretion whether or not to bring in certain personnel. The company can better determine its options if it knows the inspector's reasons for coming during non-business hours and the line of questioning involved.

Q 2.10 How should a company handle an inspector whose questions are outside the scope of the inspection?

If an inspector begins to ask questions outside the scope of the inspection, which is noted on Form FDA 482, Notice of Inspection upon arrival, the company may point that out to the inspector and refuse to answer.

Q 2.10.1 If an adversarial relationship develops during an inspection, is there an opportunity to replace the inspector?

The company should do its best to diffuse the situation and proceed with diplomacy, honesty, and tact. However, should a situation escalate to the point where the inspection process is impeded, the company can request to stop for the day. The company may contact the inspector's supervisor and report the situation. The supervisor will advise on how the inspection will proceed.

Q 2.10.2 Does a company have the right to refuse permission to take photographs during an inspection?

The general consensus has long been that a company could deny an FDA inspector the right to take photographs of their facility absent a warrant documenting the need for such access. Although FDA has long expressed the opinion that the provisions of section 704 of the FDCA[2] provided agency inspectors with the right to take photographs as part of the inspection process, few if any challenges were made in the face of a refusal by companies.

The passage of the FDA Safety and Innovation Act (FDASIA) in 2012 authorized FDA to issue a guidance as to what constitutes a refusal to allow an inspection, thus subjecting the company to criminal sanctions under section 301(f).[3] A draft guidance was finally issued in July 2013 (made final in 2014) that specifically addresses the issue and clearly states that photographs are an integral part of an FDA inspection "because they present an accurate picture of facility conditions."

To date, there have been no legal challenges either by companies or FDA. An argument could be made that where the conditions of the site are not an issue (for example, reviewing internal documents to determine if filings with the agency were made in a timely manner), taking photographs may be considered unnecessary and beyond the scope of the inspection process.

Post-Inspection

Q 2.11 What are the possible results of an inspection?

A *Form FDA 482* is the Notice of Inspection that is delivered at the time of arrival on site. It states the intent of the inspection (for example, general inspection, pre-approval inspection for a new product, etc.).

Following the inspection, if there are any deviations found from the regulations, FDA issues a *Form FDA 483* to the company. This form lists the specific non-conformances to current Good Manufacturing Practices (cGMPs) and the details of the documentation reviewed that drew them to their conclusion. A response to the 483 is expected from the company. The response should address each observation by providing an explanation, corrective actions to be taken, and a timeline for those corrective actions, or by asking for clarification. If the company disagrees with the observation, then the company should state so and provide the justification. A timely response to the Form FDA 483 is a good idea to prevent, in some cases, the issuance of a Warning Letter.

A *Warning Letter* may be issued to a company that is in violation of regulations and may warrant enforcement action. The intent of the Warning Letter is to provide the company the opportunity to take voluntary and prompt corrective action to avoid any enforcement action by FDA, such as withholding product approval or shutting down a plant.

If no action is taken by the company or FDA is not satisfied with the proposed action, then the company may be put under the order of a *consent decree*. A consent decree legally forces the company to bring its products, processes, and/or facilities into compliance with regulations under the supervision of FDA. A consent decree often requires the company to hire a third-party expert to thoroughly audit its facilities and internal procedures, and assist with the implementation of new procedures and controls.

Q 2.11.1 If the company disagrees with an observation, or believes it is incorrectly stated, what are the company's options?

The inspectors should discuss all observations with the company management as they are observed, or on a daily basis, to minimize surprises, errors, and misunderstandings when the Form FDA 483 is issued. This discussion should include those observations that may be written on the Form FDA 483 and those that will only be discussed with management during the closeout meeting. The company may use this opportunity to ask questions about the observations, request clarification, and inform the inspection team what corrections have been or will be made during the inspection process. Inspectors are encouraged to verify the company's completed corrective actions as long as the verification does not unreasonably extend the duration of the inspection.

Once the Form FDA 483 is issued, the company must respond. The company may request clarification, criticize 483 items, disagree with the 483, or raise other questions or

issues. In these cases, the FDA District Office will evaluate the company's information and send the District's conclusion to the company. A copy shall also be sent to the official establishment file.

Q 2.12 Why are U.S. firms inspected without notice?

Pre-announcement of an inspection is only given to those estab-lishments that meet specific criteria and, using clearly described criteria, is done at the discretion of the inspecting office. The pre-announcement should be no less than five days in advance of the inspection. The company is expected to meet the expectations of having the appropriate personnel and records available for the inspection.

The following types of inspections are applicable for pre-announcement: pre-market inspections (such as 501(k) Premarket Notification and Premarket Approval (PMA)); foreign inspections; and Quality System/GMP inspections for biennial routine inspections, initial inspections of new facilities, or newly registered companies; and initial inspections under new management and/or ownership. The criteria used to determine applicability is (1) non-violative Quality System/GMP inspection histories; and (2) to remain eligible for pre-announced inspections, companies must have a history of having individuals and/or documents identified in previous pre-announced inspections reasonably available at time of the inspection.

Non-FDA Regulations

Q 2.13 If an inspector has seen a certain practice in one company does he/she have the right to mandate adoption to others?

FDA inspects to ensure compliance with existing and approved regulations. If there are practices observed in other previously inspected companies that FDA believes have resulted in raising the bar for the industry, then FDA may inform the current company of the better practices and suggest that it follow suit. This is a difficult position for the company to be in if it feels that it is complying with regulations and using an acceptable method or process. It should be noted that it is important for a company to participate in industry meetings and discussions as they pertain to new practices and regulations. There is nothing stopping FDA from withholding product approval if, for example, it has reason to believe that the company is not doing all that it can to be in alignment with current standards.

Foreign Complaints

Q 2.14 Can FDA enforce compliance on a company for issues/complaints that did not originate in the United States?

Yes. For example, FDA can enforce Food Additive Regulations or Biological Product Deviation Reports complaints on a U.S. company even if the origination of the complaint was from a foreign jurisdiction.

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1. U.S. FOOD AND DRUG ADMINISTRATION, ABOUT FDA, .fda.gov/AboutFDA/Transparency/basics/ucm194888.htm.
2. 21 U.S.C. § 374(a)(1)(B).
3. 21 U.S.C. § 331(f).

483s and Warning Letters

Daniel A. Kracov

This chapter provides an overview of two documents central to Food and Drug Administration (FDA or the "Agency") regulation and enforcement—the Form FDA 483 and the Warning Letter. These documents are FDA's front line tools for addressing observations of violations by firms in manufacturing, safety reporting, clinical research, promotion, and other regulated activities. A primary regulatory objective of regulated firms should be to achieve sustained compliance in their efforts to research, develop, manufacture and sell products. Nonetheless, even the most diligent firm may at one point face FDA observations or allegations of violations. Thus, it is essential to understand the nature of the 483 and Warning Letter, the processes associated with these regulatory tools, and effective strategies for responding to these challenges in a manner that balances responsiveness and advocacy to preserve legitimate rights, achieve closure without further enforcement activities, and instill FDA confidence in the firm generally.

Form FDA 483

FDA Inspections

Q 3.1 What is an FDA inspection?

The Food and Drug Administration has broad authority to conduct inspections of regulated facilities. FDA investigators "are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein."[1] FDA's Investigations Operations Manual defines an inspection as a "careful, critical, official examination of a facility to determine its compliance with the laws administered by FDA. Inspections may be used to obtain evidence to support legal action when violations are found . . ."[2] There are various reasons for FDA inspections, including prior to the approval of a product, routine inspections (which are typically biennial, but subject to risk prioritization due to FDA resource constraints), in follow up to complaints or a recall, for the purpose of gathering data on a company or industry, or to verify compliance with enforcement-related commitments.

Q 3.2 Are FDA inspections subject to prior notification?

No. There is no requirement of prior notice, and typically there is no voluntary notice by the Agency, although such notice may be provided prior to a foreign inspection due to logistical issues. Typically, the investigators merely arrive at the establishment and present their credentials and a Form FDA 482, which is the Notice of Inspection, to a top management official at the establishment.

Form FDA 483 Basics

Q 3.3 What is an FDA Form 483?

An FDA Form 483 ("483") is a form that provides FDA's observations from an inspection. It was created in 1953 pursuant to an amendment to the Federal Food, Drug, and Cosmetic Act (FDCA), section 704(b), which provides:

> Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or

> agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, tobacco product, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

The objective of this provision was to ensure that firms were provided prior notice of potential FDA action by ensuring that the receiving firm was aware of FDA's inspectional findings that could result in regulatory action. In general, a 483 provides a list, often quite detailed, of FDA inspectional observations—objectionable conditions and practices—that indicate what the investigators believe are violations of the FDCA. FDA views the 483 as playing both an educational and enforcement role. The document fulfills the requirements of FDCA section 704(b) by providing notice of potential violations that could result in enforcement action, but also educates the inspected firm as to issues that should be corrected and developing FDA interpretations of statutory requirements (*e.g.*, the Agency's views as to a particular aspect of current good manufacturing practices or good clinical practices).

Q 3.4 Are FDA observations in a 483 necessarily violations?

No. The 483 documents and communicates concerns regarding objectionable conditions that are observed during inspections. The form specifically states that it ". . . lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance." The Agency considers the 483, along with a written report called an Establishment Inspection Report (EIR), all evidence collected on-site, and any responses from the company, and then determines what further action, if any, is appropriate.

Q 3.5 When will my firm receive a 483?

If an inspection results in observations of objectionable conditions or practices that indicate violations, a 483 is issued at the end of the inspection, often in a "close out" meeting at which the FDA investigators may either read or summarize the observations to responsible representatives of the inspected establishment.

Q 3.6 What are the elements of a 483?

A 483 has the following elements:

- The header identifies the FDA office that performed the inspection, the date(s) of the inspection, the name and address of the facility that was inspected, the name and title of the individual to whom the 483 is issued (usually the most responsible individual physically present in the facility), provides a brief description of the type

of facility, and notes the facility's FDA Establishment Identification (FEI) number.

- The observations section begins with a disclaimer:

  > "This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above."

  The 483 then lists each observation, which should be ranked in order of significance.

  Medical device-related 483s may be annotated with one or more of the following, which may be added during the final discussion with the firm's management:

  1. Reported corrected, not verified.
  2. Corrected and verified.
  3. Promised to correct (may be appended with "by xxx date" or "within xxxx days or months").
  4. Under consideration.

- Signatures and Date of Issuance

  This section includes the investigator names, printed and signed, and the date of issuance.

- The converse side of the 483 states:

  "The observations of objectionable conditions and practices listed on the front of this form are reported:

  1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
  2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration."

A software program known as Turbo EIR, loaded on laptop computers assigned to certain investigators, is intended to standardize inspectional documents. When utilized, for each 483 observation, Turbo EIR calls for the inspection team to choose a "canned" citation, then describe the details of the situation. Each "canned" citation contains a paraphrase of the underlying authority. Not all 483s and EIRs (see below) are generated in Turbo EIR as

some are manually prepared and not available in this format.

Avoiding, Correcting, and Annotating 483 Observations

Q 3.7 What should be done to avoid observations in a 483?

The first step is listening carefully during the inspection and attempting to address issues as they arise. Companies should take comprehensive notes of all statements and requests made by FDA investigators, all documents requested by FDA should be quickly reviewed and copied, and the impact of such requests and statements should be evaluated on an ongoing basis during the inspection. If an issue that arises has been dealt with, that fact and supporting information should be brought to the attention of the investigator as soon as possible, with the objective of keeping the observation out of the 483. If the issue nonetheless is found in the 483, the investigator should be reminded that the issue was corrected prior to or during the inspection, probed as to whether the correction was sufficient, and asked to remove the observation from the 483 or, failing that, note the fact of the correction in the 483, or at a minimum, in the EIR.

Q 3.8 What should be done at a close-out meeting?

Again, carefully listen to each observation. To the extent there are issues to be corrected or clarified that may warrant removal or modifications to 483 observations, this is a final opportunity to do so before the 483 is issued. Verbal responses should be provided, and to the extent deficiencies that were identified in the inspection have been corrected, those steps should be brought to the attention of the investigator, along with supportive documents if possible. Similarly, if the characterization of a particular issue is simply wrong —*e.g.*, a standard operating procedure that purportedly was not followed was in fact followed—those mistakes should be highlighted for the investigator. However, a response at a close-out meeting does not obviate a full written response to each and every observation that ends up in the 483.

It is FDA policy that investigators should offer to "annotate" the 483 for all medical device inspections, and the district office has discretion to annotate the FDA 483s in other program areas. A decision to annotate the 483 is voluntary on the part of the inspected establishment. Such annotations are succinct comments about the status of the FDA 483 item that can be made after each observation, at the end of each page of the FDA 483, or at the bottom of the last page of the FDA 483 prior to the investigator's signature. If the establishment has promised and/or completed a corrective action to an 483 observation prior to the completion of the inspection, the 483 should be annotated with one or more of the following comments, as appropriate: (1) reported corrected, not verified; (2) corrected and verified; (3) promised to correct (by [ ] date); (4) under consideration. An establishment's stated objections to any given observation, or to the 483 as a whole, will not be annotated on the 483.

It is important to note that a response at a close-out meeting, or an annotation, does not

obviate a full written response to each and every observation that ends up in the 483.

Responding to a 483

Q 3.9 How quickly should we respond to a 483?

Typically within fifteen business days, if at all possible, even if the response must be supplemented. In 2009, FDA initiated a program to establish a time frame for the submission of post-inspection responses to 483s for FDA's consideration in deciding whether to issue a Warning Letter.[3] The Agency will not ordinarily delay the issuance of a Warning Letter in order to review a response to a 483 that is received more than fifteen business days after the 483 was issued. If FDA receives a response to a 483 within fifteen business days after the 483 was issued, it will conduct a detailed review of the response before determining whether to issue a Warning Letter. If FDA issues a Warning Letter after reviewing a firm's timely response, the Warning Letter will recognize receipt of the response to the 483 and reply as to the apparent adequacy of the firm's corrective actions. If FDA receives a response more than fifteen business days after the 483 was issued, it does not routinely include a response regarding the firm's corrective actions in the Warning Letter, and the 483 response will be evaluated along with any other written material provided in response to the Warning Letter. A firm's response to a Warning Letter may reference any of the firm's earlier responses.

Q 3.10 Who should be involved in preparing a 483 response?

A critical aspect to a successful 483 response is the formation of an appropriate team. The team should be multi-disciplinary, including experts in the areas to be addressed in the 483 response, quality and regulatory leadership for the facility who are empowered to either make decisions about approaches to the response and associated commitments (or can quickly obtain such decisions from senior management), and individuals with superior writing and project management skills who can frame the response in a clear and organized manner, keep the team on task and within the time frame, and compile the necessary documentation.

Q 3.11 Can we sue the Food and Drug Administration in response to a 483?

Except in highly unusual situations in which FDA has taken other actions indicative of "final agency action" under the Administrative Procedure Act, such actions are generally unsuccessful because a 483 merely constitutes inspectional observations rather than a final Agency determination that violations have occurred.

Q 3.12 What are the elements of a good 483 response?

First, those receiving the 483 should carefully study and attempt to fully understand the nature, scope and significance of the observations.

Second, with respect to most observations, the significance of the observations should be

acknowledged and a detailed response should be provided. In the written response, each observation should be repeated, and below the observation the company should directly address the observation, point-by-point. Corrections that have been made should be detailed, with supporting information appended. To the extent an investigation or correction is in process or planned, describe the ongoing or planned efforts in detail, and provide a realistic timeline for completion.

Special attention should be given to issues that indicate an FDA concern regarding an overall "system" within a company, *e.g.*, is the Agency concerned about the integrity or compliance of the quality system as a whole, or a particular sub-system? Typically, efforts should be made to address FDA's concerns through managerial review and a systemic corrective and preventive action (CAPA) plan.

483 observations are often merely examples of problems identified in the inspection that signal a broader concern with a particular process or quality subsystem. It is generally insufficient to address the specific finding and that finding only. Rather, FDA is often seeking a broader action—a review or investigation—in which the company determines the root cause of the problem and addresses all similar violations that may have resulted. The objective is to show FDA that you have "fixed the problem" in the broadest sense. Thus, the elements of such a response typically include:

- A detailed description of the investigation into the root cause of the problem identified, including a logical flow indicating the alternative root causes that were investigated and ruled out, and the support for the conclusion that a particular root cause needs to be addressed to correct the observation. Companies should have an appropriate SOP for investigations in place, but if not a written plan for the investigation should be developed and the development of an SOP for investigations may be appropriate to cite as part of the corrective actions. Root causes can be complex, ranging from issues associated with SOPs, to inadequate management oversight, to faulty testing procedures, to supplier specifications. If a root cause cannot be determined, it is often appropriate to bring in third-party expert resources to help identify the root cause or validate the company's findings that the root cause was indeterminate and—at a minimum—narrowed down to a range of potential causes that can be addressed with specificity.
- Once a root cause is determined, a CAPA plan should be developed. Such CAPAs can vary widely in scope and intensity, from the shut-down of a facility to a minor adjustment in a policy or procedure and associated training. In all cases, the CAPA should be adequate to address the observation in a thorough manner, both with specificity and systemically, with well-defined actions that can be monitored and audited both during implementation and on a sustained basis. All of this should be laid out in a clear and detailed manner, with attached documentation (*e.g.*, the new SOP that has been developed and implemented) and a timeline providing actions completed to date and planned. It is generally insufficient to merely state that an action has been taken—attaching documentation confirms that the action

actually occurred.

It is typically good practice to summarize the response at the beginning, and then provide an overall summary of the action plan and timeline at the end. Although the action plan should reflect an acknowledgment of the urgency of the matter, companies should not overpromise. The response should be realistic, and timelines based upon a careful assessment, after consultation with the stakeholders responsible for the implementation of the actions (and often outside consultants), of what can be achieved. FDA will use such timelines to hold the company—and in certain cases its personnel—accountable.

If the quality of a product is at issue, if possible the response should seek to provide evidence to reassure FDA that public safety is not impacted, and immediate action—such as a recall or enforcement such as a seizure or injunction—is not warranted.

The response should be professional in tone and transparent. Absent a gross error on the part of FDA, and very strong legal and scientific positions, adopting an aggressive tone in a 483 response rarely serves a good purpose, and will only antagonize the Agency. A clear and forceful presentation of strong facts and, where appropriate, sound legal arguments—backed up by good science and understanding of the relevant regulatory requirements—will typically have a much bigger impact.

In all cases, the response should be factually accurate. Each assertion in a 483 response should be probed for accuracy and whether the documentation to support the assertion is available and can be appended.

Q 3.13 What if I don't understand an observation in a 483?

It is often the case that a particular observation in a 483 is cryptic: what exactly is the nature of the issue raised by FDA, and is it an isolated concern or a matter of general applicability that should be addressed in a systemic manner? First, internal review is necessary—is the company compliant with its own procedures and applicable legal requirements in the area cited? What can we deduce about the Agency's intent? If the issue remains unclear, it is appropriate to contact the investigator or District Office to attempt to attain clarity. If such clarity is not forthcoming, it is typically best to attempt to address both the particular violation cited as well as place the response in the context of an overall attempt to rectify any systemic issues for which the violation may be merely emblematic. For example, if FDA cites a particular instance of the improper handling of an out-of-specification (OOS) result, a review of that particular event as well as the company's overall approach to OOS results is warranted, with the response conveying the nature and scope of that review and both the specific and systemic CAPAs.

Q 3.14 When is it appropriate to address personnel issues in a 483 response?

Typically, 483 responses reference particular systems, processes or practices, rather than individual failings. Nonetheless, at times an observation may clearly indicate that FDA believes that particular individuals are lacking in qualifications or integrity, contributing to

violations of legal requirements. In such cases, it is appropriate to address specific changes in personnel by title, noting the qualifications of new personnel (or a plan to seek new personnel with appropriate enhancements in management oversight or even third-party (*e.g.*, consulting) involvement pending a more complete resolution of the issue).

Q 3.15 Should a 483 response note that the company has brought in outside expert resources to assist in addressing one or more observations?

This is often a good practice, and the involvement of the experts (typically consultants with specialized expertise in the relevant field) can be integrated into the response as appropriate—that is, their role in assisting the company in evaluating the root cause of a particular problem, or in providing oversight and training with respect to an improved process. The involvement of the third-party should be substantive, however, and not overstated. It will not be helpful if the reference to consulting assistance is determined to be "window dressing" for a fundamentally inadequate response.

Q 3.16 Who should sign a response to a 483?

A 483 response is typically signed by the head of the unit of the company being inspected, or the head of quality or regulatory, as appropriate to the nature of the inspection (that is, a manufacturing inspection versus a pharmacovigilance or bioresearch monitoring inspection). If the 483 alleges violations that indicate an FDA concern regarding the company's broader practices or management generally, it is typically best to elevate the level of response to a more senior company official, signaling that the company takes the matter seriously, recognizes the broader nature of the Agency's concerns, and is addressing the issues from an enterprise perspective.

Q 3.17 To whom should the 483 response be sent?

Typically, a 483 response should be sent to the Director of the FDA District Office that conducted the inspection (or multiple Directors if more than one office was involved in a concurrent inspection of multiple facilities) with copies to the investigators who conducted the inspection. If an inspection was initiated by headquarters rather than a District Office, *e.g.*, directed by the Office of Compliance at an FDA Center, the response should be directed to that office. The company should consider copying other FDA personnel if it knows they were involved in inspectional decision making, such as an expert at the District or headquarters level, or the reviewer of an application that spurred a pre-approval inspection.

Q 3.18 Should proprietary information be included in a 483 response?

Although trade secret and proprietary commercial and financial information should be protected from release under the Freedom of Information Act (FOIA), mistakes are sometimes made in the release of inspectional documents (or they may become public through other investigations or litigation), and companies should attempt to balance the

needs of an effective response with the unnecessary provision of proprietary information in a sensitive document. To support a claim to an exemption from release under FOIA, confidential information should be prominently marked as Confidential—Contains Trade Secret/Confidential Commercial Information, or the equivalent.

If information is redacted from documents submitted, that fact should be noted for FDA. Alternatively, if the company wants to anticipate potential release of the documents by FOIA, it should consider providing a redacted version of the response that it would be comfortable with being made public—subject to the proviso that such a redaction may facilitate FOIA review and speed release.

Meeting with FDA

Q 3.19 Should we try to meet with FDA after receiving a 483?

Depending upon the nature of the 483 observations, it may be worthwhile to contact the District Office and request a meeting to discuss the 483 response and reinforce the firm's commitment to compliance. However, such requests are often declined due to tight resources and schedules, or a belief by the Agency that the 483 response should provide the necessary information for evaluation or corrections, and a meeting would be more appropriate after a Warning Letter or other enforcement decision is made.

Dispute Resolution

Q 3.20 What are the mechanisms for dispute resolution around 483s and Warning Letters?

There are various mechanisms for seeking the resolution of a dispute relating to an inspection. First, issues relating an inspection can be elevated by asking for review at each successive supervisory level in the District Office or headquarters, up to the Commissioner's office.[4] In some cases, if legal or procedural issues are critical to a resolution, it may be appropriate to seek the involvement of the Office of Chief Counsel. Moreover, FDA, and each product center, has an Ombudsman that is specifically tasked with, *inter alia*, addressing disputes and complaints regarding interactions with regulated industry related to interactions with field offices, including inspection and compliance issues.

If a human or animal drug/biologic cGMP issue is scientific or technical in nature, and more informal dispute resolution efforts are not productive, FDA guidance also provides a formal process for elevating such issues during or after an inspection, including—if warranted—a dispute resolution panel at the Commissioner's office level.[5]

Establishment Inspection Reports

Q 3.21 What is an Establishment Inspection Report?

Following an inspection, FDA investigators prepare a written report, known as the Establishment Inspection Report (EIR). The EIR may include the following elements, although the report may be abbreviated to essentially a summary if there are no violative conditions.

- Summary of Findings
- Administrative Data
- History
- Interstate Commerce
- Jurisdiction (products manufactured or distributed)
- Labeling
- Individual responsibility and persons interviewed
- Training program
- Manufacturing and Design Operations
- Manufacturing Codes
- Complaints
- Recall Procedures
- Objectionable conditions and management's response
- Supporting evidence and relevance
- Discussion with management
- Refusals
- Additional information
- Exhibits and attachments

Q 3.22 How do I obtain a copy of an EIR for an inspection of my facility?

It is FDA policy to provide a copy of the narrative portion of the EIR to the management of the facility when FDA determines that the inspection is closed, that is, no enforcement action will be taken. Companies can inquire as to the status of the EIR with the District Office or other FDA office handling the inspection.

Q 3.23 Are 483s and EIRs available to the public under the Freedom of Information Act?

Yes, such documents may be released under FDA's FOIA regulations, found at 21 C.F.R. Part 20. Information not protected by a FOIA exemption may be released once the inspection is closed out by the Agency. Such exemptions protect, *inter alia*, against the

release of trade secret and commercial or financial information that is privileged or confidential, as well as information reasonably expected to interfere with enforcement proceedings.

To a considerable extent, the availability of 483s and EIRs under FOIA provides a public record of FDA's developing views as to the interpretation of relevant regulatory requirements, and cGMPs in particular. In essence, repeated citations of issues in 483s typically indicate FDA's views as to what is "current" in cGMPs. However, an isolated observation in a 483 is not necessarily indicative of "current" GMPs in that the particular observation may have simply been wrong—the views and judgments of one set of investigators may have been successfully rebutted in the response to the 483.

Warning Letters

Warning Letter Basics

Q 3.24 What is a Warning Letter?

Warning Letters are letters from FDA that serve several purposes. First, a Warning Letter "give[s] individuals and firms an opportunity to take voluntary and prompt corrective action before [FDA] initiates an enforcement action."[6] Second, Warning Letters are "issued to achieve voluntary compliance and to establish prior notice."[7] This approach is "based on the expectation that most individuals and firms will voluntarily comply with the law" and also serves to conserve the Agency's scarce resources. Under FDA policy, Warning Letters should be issued only for "violations of regulatory significance" or "those violations that may lead to enforcement action if not promptly and adequately corrected."[8] Such a letter indicates that FDA's concerns go beyond the specific investigator's observations and are shared by compliance personnel at the district or center level. Although a Warning Letter should be taken very seriously, and certainly constitutes a threat of enforcement action, from FDA's legal perspective it is "informal and advisory."[9] In other words, a Warning Letter "communicates the agency's position on a matter, but it does not commit FDA to taking enforcement action."[10]

Q 3.24.1 What is an Untitled Letter?

An "Untitled Letter cites violations that do not meet the threshold of regulatory significance for a Warning Letter."[11] In other words, it is a lower level of communication that signals FDA concern regarding what it believes may be a violation, often minor in nature. It can be distinguished from a Warning Letter as follows:

- The letter is not titled.
- It does not include a statement that FDA will advise other federal agencies of the issuance of the letter so that they may take this information into account when considering the awarding of contracts.
- It does not include a warning statement that failure to take prompt correction may result in enforcement action.
- It does not evoke a mandated district follow-up.
- The letter requests (rather than requires) a written response from the firm within a reasonable amount of time (*e.g.*, "Please respond within thirty days") (unless more specific instructions are provided in a relevant compliance program).

Q 3.25 Must FDA send a Warning Letter before taking enforcement action?

No. A Warning Letter is not a prerequisite to enforcement action. FDA does maintain a "prior notice" policy that generally favors providing a warning before taking enforcement action in order to achieve voluntary compliance, conserve resources, and strengthen its legal position if it later decides to take such action. However, with certain exceptions, FDA generally "has no legal obligation to warn firms or individuals that they, their practices, or their products are in violation of the law prior to taking formal enforcement action."[12] The Agency considers the following factors in "evaluating the adequacy of prior notice (prior warning):

1. The conduct, condition, practice, or product violates the laws enforced by FDA.
2. The notice (warning) adequately identified the violative conduct, condition, practice or product. (Note: Similar violations do not need separate prior notices, for example, separate prior notices are not necessary for each unapproved new drug shipped.)
3. Notice (warning) was provided to the firm and the most responsible individuals.
4. The firm was afforded a reasonable amount of time to implement corrections. Corrections may include halting shipments, recalling product in violation, or changing procedures and controls.
5. [The Agency will] [c]onsider if situations have occurred that may affect the adequacy of prior notice, such as a change in ownership or responsible management. For example, consider what is known by the new management, and if the 'firm' received notice."[13]

Q 3.26 What factors increase the likelihood of a Warning Letter?

In general, FDA personnel with the authority to issue a Warning Letter (that is, district directors and center or other officials) consider the following:

- Evidence shows that a firm, product, and/or individual is in violation of the law or regulations and that failure to achieve adequate and prompt correction may result in agency consideration of an enforcement action;
- The violation(s) are determined to be of regulatory significance, and the issuance of a Warning Letter is appropriate and consistent with agency policy, as described in Compliance Policy Guides or elsewhere; and,
- There is a reasonable expectation that the responsible firm and persons will take prompt corrective action.

However, if the Agency is aware of ongoing or promised corrective actions, the following factors are considered:

- "The firm's compliance history, *e.g.*, a history of serious violations, or failure to prevent the recurrence of violations;
- The nature of the violation, *e.g.*, a violation that the firm was aware of (was evident or discovered) but failed to correct;
- The risk associated with the product and the impact of the violations on such risk;
- The overall adequacy of the firm's corrective action and whether the corrective action addresses the specific violations, related violations, related products or facilities, and contains provisions for monitoring and review to ensure effectiveness and prevent recurrence;
- Whether documentation of the corrective action was provided to enable the agency to undertake an informed evaluation;
- Whether the timeframe for the corrective action is appropriate and whether actual progress has been made in accordance with the timeframe; and,
- Whether the corrective action taken ensures sustained compliance with the law or regulations."[14]

As a general matter, a Warning Letter will not be issued if FDA concludes that a firm's corrective actions are adequate and that the violations that would have supported the letter have been corrected. However, a response letter may be sent to the firm reflecting the Agency's decision to rely on the firm's actions and/or promises, and may include a statement that should it later observe that these or similar violations have not been corrected, enforcement action may be taken without further notice. In such cases, the Agency will verify the completeness and effectiveness of the corrective action during the next inspection, which may be expedited.

District offices generally will not recommend a Warning Letter as a follow-up to a preapproval inspection (PAI) for pending drug or device applications if no other FDA-regulated products are marketed by the company. However, the application may be put on "compliance hold" pending resolution of the inspectional issues, and typically a re-inspection will occur.

Q 3.27 How quickly will a Warning Letter be issued after issuance of a 483?

To ensure the relevance of the evidence, the Agency strives to issue Warning Letters within four months from the appropriate reference date (that is, the date of sample analysis, or the date of evidence collection).

Q 3.28 Can a firm sue FDA in response to a Warning Letter?

Such actions are generally unsuccessful because the courts typically deem an FDA Warning Letter to be a "tentative or interlocutory action" rather than "final agency action," as defined under the Administrative Procedure Act.[15] Recently the U.S. Court of Appeals for the D.C. Circuit, in *Holistic Candlers & Consumer v. FDA*[16], ruled that Warning Letters

—even combined with statements on the FDA website and in a meeting adverse to the Appellant's position—"do not mark the consummation of FDA's decision making" and "do not represent final agency action subject to judicial review." However, at times courts have been willing to consider the collateral impact of Warning Letters in this analysis, including the impact on constitutional rights, financial factors, public perception, government contracts, and actions by product liability or consumer class action plaintiffs.[17] Thus, it is not out of the question to consider going to court on the basis of a Warning Letter—but only in the appropriate case in which significant legal rather than factual issues are at stake and pre-enforcement action by the Agency will have an irreversible impact. Even in such scenarios, a successful suit is an uphill battle.

Q 3.29 What is the process for issuing a Warning Letter?

Within fifteen working days after completion of the inspection, or, if applicable, sample analysis, the district office should submit a Warning Letter recommendation to the appropriate reviewing office for concurrence. The FDA Compliance Management System (CMS) is used for electronic submission of Warning Letter recommendations from district offices. All recommendations by the district offices use CMS for submitting the proposed Warning Letter, the 483 supporting alleged violations, the EIR, and any written response by the firm. Then, within fifteen working days after receipt of the Warning Letter recommendation, the relevant center should review the Warning Letter and notify the district office of its decision. If the Warning Letter is disapproved, the center will notify the district office of its decision within fifteen days of receipt, and issue a memorandum stating its reasons for disapproval within thirty days, or as soon after that as possible. If the Warning Letter is approved, the center will forward its approval memo and the proposed Warning Letter, as appropriate, for further review and concurrence.

The district compliance officer (or, the center consumer safety officer, if the Warning Letter was center-initiated) assigned to the Warning Letter monitors the progress of the case through the Agency review process to its conclusion (that is, voluntary compliance or enforcement action).

Center concurrence is required prior to issuing Warning Letters in certain areas, or Warning Letters may be issued directly by the Center. Exhibit 4-1 to Chapter 4 of the Agency Regulatory Procedures Manual provides detailed "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. The Exhibit provides, in part, that the following Center reviews are required:

1. All Centers
    a. All labeling violations—except where specific guidance has been provided (*e.g.*, Compliance Programs, Compliance Policy Guides, and Drug Health Fraud Bulletins);
    b. Computer application and software violations;

c. Bioresearch Monitoring Program violations; and

d. Product advertising violations.

Note: Only Centers issue Warning Letters for violations associated with product advertising, OTC drug monographs, and the Bioresearch Monitoring Program.

2. Center for Drug Evaluation and Research (CDER)

a. New drug charges—including unapproved changes in processes or formulations and recommendations to withhold approvals of applications or supplements;

b. Adverse drug experience reporting violations;

c. Novel and unusual tamper-evident packaging violations;

d. Prescription Drug Marketing Act violations;

e. Investigational drug use violations;

f. cGMP charges involving active pharmaceutical ingredients and other drug component manufacturing deficiencies;

g. cGMP charges involving all dosage forms, including medical gases;

h. cGMP charges involving inspections of facilities for therapeutic biologic products regulated by CDER;

i. Pharmacy compounding issues; and

j. Violations related to required postmarketing studies and clinical trials.

3. Center for Biologics Evaluation and Research (CBER)

a. Donor re-entry violations (*e.g.*, HBsAg, anti-HIV-1);

b. Violations relating to drug CGMP[18];

c. Violative inspections of federal government agencies;

d. Violative inspections of Team Biologics (Core Team) facilities for biologic products regulated by CBER;

e. Viral marker test run deficiencies[19];

f. Violations in areas where specific guidance has not been provided[20];

g. Violations relating to HIV and HCV lookback; and

h. Violative inspections of manufacturers of human cell, tissue, and cellular and tissue-based products (HCT/Ps).

4. Center for Devices and Radiological Health (CDRH)

a. All 21 U.S.C. § 352(j) "dangerous to health" violations;

b. Medical device reporting violations which cite failure to report malfunctions as defined in 21 C.F.R. 803.3(n). Center medical and technical expertise is necessary for these evaluations;

c. Restricted device violations;

d. Radiation Control for Health and Safety Act violations—except for sunlamp products and x-ray assemblers;

e. Violation of requirements for post market surveillance studies;

f. Any violation of device tracking regulations other than failure of the firm to implement any form of a tracking system;

g. All suspected violations of the user reporting regulations;

h. Failure to submit a premarket notification (510(k)) or Premarket Approval Application (PMA);

i. Failure to submit a 510(k) or a PMA supplement for a significant modification(s) and/or the addition of a new intended use(s) to a previously cleared or approved device;

j. All violations arising from pre-approval PMA inspections including supplements to a previously approved PMA application; and

k. Mammography Quality Standards Act (MQSA) violations in the following situations, unless superseded by a relevant Compliance Program or other directive:

   i. Where numerous Level 2 or 3 inspection findings were observed, but no single noncompliance constitutes a Level 1 or repeat Level 2 inspection finding; or

   ii Any situations not specifically identified as a Level 1 noncompliance or repeat Level 2 noncompliance.

5. Center for Veterinary Medicine (CVM)

   a. Product approval violations;

   b. Tissue residue violations involving meat and poultry where no tolerance has been established, extra-label use is documented, and/or those which involve the use of compounded drugs or other drug adulteration;

   c. Tissue residue violations involving aquacultured seafood, and other animal-derived products;

   d. Feed contaminant violations where no tolerance has been established;

   e. Adverse drug reaction reporting violations;

   f. Low acid canned pet food violations requiring technical review; and

g. CGMP violations for medicated feed (21 C.F.R. Part 225), Type A Medicated Articles (21 C.F.R. Part 226), and dosage form drugs (21 C.F.R. Part 211].

Submit complete recommendation package (recommendation, EIR, CRs, all exhibits, and other supporting documents).

6. Center for Food Safety and Applied Nutrition (CFSAN)

All violations not covered by direct reference authority, in a compliance policy guide, or compliance program. These include, but are not limited to, the following examples:

a. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue;

b. Pesticide and chemical contamination violations not covered by direct reference authority;

c. Dietary supplements, medical foods, and infant formulas, including dietary supplements CGMPs;

d. Low acid canned (LACF) and acidified foods (AF) violations;

e. Food and color additive violations;

f. Actions involving environmental microbial contamination

g. Seafood HACCP violations not covered by direct reference authority in the Compliance Program;

h. All situations involving violations of section 402 (a)(4) of the Food, Drug & Cosmetic Act, including deviations from CGMP regulations for foods, low acid and acidified canned foods, bottled water and any other CGMP regulation concerning CFSAN issues, *e.g.*, dietary supplements;

i. Mycotoxins;

j. Animal drugs in foods (aquaculture chemotherapeutic agents);

k. Food standards;

l. Cosmetics; and

m. Egg rule (21 C.F.R. 118) violations.

In addition, Centers should issue Warning Letters, not Untitled Letters, for promotional activities if the nature of the activity is such that the center would support further regulatory action. The Center should alert the district office of the violation and ask that they bring the promotional activity to the attention of the firm on the next scheduled visit. If the district inspection reveals additional problems, this violation may be included as part of their regulatory action plan. If the problem is urgent the district could request a meeting

with the firm to discuss the violations.

For issues in a Warning Letter that require review by more than one Center, a designation of "Lead Center" will be made at the earliest possible opportunity. The lead center is responsible for communication with the other involved Center(s), the district, and the Office of Chief Counsel, and shepherding the Warning Letter through the review process, including the review and incorporation of comments as appropriate from the other involved entities. Prior to submission of the Warning Letter recommendation, the district should communicate with each Center and identify which Center will serve as the lead. The recommendation should identify the Lead Center and the other involved Center(s). The recommendation should be sent electronically via CMS to the Lead Center, and the lead center will create a consult task to the other reviewing Center(s). The Centers should conduct concurrent (not sequential) reviews.

If the district did not identify the need for multiple reviews prior to submission of the recommendation, the Center receiving the recommendation should communicate with the district and the other involved center(s) to appropriately designate the Lead Center. The district should then promptly send a copy of the recommendation to the other involved Center(s).

Although prior legal review of regulatory letters (Warning and Untitled Letters) by the Agency's Office of Chief Counsel was required in the past, at present, the OCC review provisions in these procedures apply only to Warning and Untitled Letters as described below (section numbers refer to the FDAC):

CFSAN

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.
2. Warning Letters involving medical foods.
3. Warning Letters involving section 502(f)(1) drug misbranding charges.
4. Warning Letters involving section 403(a) false or misleading food labeling.
5. Warning Letters involving section 403(r)(1)(A) (unauthorized nutrient content claim) or section 403(r)(1)(B) (unauthorized health claims) charges.
6. Warning Letters for dietary supplements with a new drug charge based in whole or in part on promotional use of scientific studies to market the product for disease uses.
7. Warning Letters with violations of the general cGMP regulations.
8. Warning and Untitled Letters with violations of the dietary supplement cGMP regulations.
9. Warning Letters with adulteration and/or misbranding charges related to cosmetics.

In addition, cyber letters (letters resulting from websites promoting dietary supplements with drug claims) will be reviewed under an audit review program, with OCC reviewing every tenth letter.

CDRH

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.
2. Advertising/promotion Warning/Untitled letters.
3. Warning/Untitled Letters with unapproved device charges under section 501(f)(1)(B) if the firm contests that the product is a device or any other Warning/Untitled Letter in which the firm contests that the product is a device.
4. Warning/Untitled Letters with section 502(a) charge—labeling of the device is false or misleading.
5. Warning/Untitled Letters with section 502(j) charge—device is dangerous to health when used in the manner or with the frequency or duration prescribed, recommended or suggested in the labeling thereof.
6. Warning/Untitled Letters with section 502(o) charge—notice/information of modification of the device not provided to FDA.
7. Warning/Untitled Letters with section 502(o) charge—notice/information of new intended use of the device not provided to FDA.
8. Warning/Untitled Letters with section 502(t)(3)—firm has failed or refused to comply with a requirement under section 522.
9. Warning and Untitled Letters involving bioresearch monitoring not covered by a December 8, 2005 agreement between OCC and CDRH's Office of Compliance.

CVM

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.
2. Warning Letters involving bioresearch monitoring.
3. Warning Letters with violations of 21 C.F.R. 589.2000 (ruminant feed ban) and/or 21 C.F.R. 589.2001 (new animal feed ban).
4. Warning and Untitled Letters involving advertising and promotion.
5. Warning Letters with section 502(a) false or misleading labeling drug misbranding charges.
6. Warning Letters related to turtles.

7. Warning and Untitled Letters involving new animal drug compounding.

CBER

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.
2. Warning Letters and notice of initiation of disqualification proceedings and opportunity to explain (NIDPOEs), or involving clinical investigators and IRBs.
3. Warning Letters involving advertising or promotion, except for those involving only straightforward omission of risk (*e.g.*, no risk information whatsoever).
4. Warning and Untitled Letters involving product jurisdiction.
5. Warning and Untitled Letters involving unregistered or unlicensed blood banks.

CDER

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.
2. Warning Letters involving clinical investigators and IRBs.
3. Warning Letters involving advertising or promotion, except for those involving only straightforward omission of risk (*e.g.*, no risk information whatsoever).
4. Warning and Untitled Letters involving compounding.
5. Warning and Untitled Letters involving unapproved new drugs, except health fraud, over-the-counter drugs subject to final monographs, and Warning Letters that contain both GMP and unapproved new drug charges.

Office of Regulatory Affairs

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.

When OCC review is required, the time frame for review is fifteen working days from receipt of the supportive packet of materials. If OCC does not respond to Direct Reference Warning Letters and those issued pursuant to foreign inspections within this time frame, the district or Center can presume concurrence and may send the letter out without additional input. All other categories of letters requiring OCC review await an OCC decision prior to being issued. For all categories of Warning Letters receiving a decision by OCC, OCC will either concur, concur with changes, not concur with written reasons, or flag the letter because it raises significant issues and questions (*e.g.*, jurisdictional issues or insufficient evidentiary support).

The period for OCC review officially begins once OCC has received the full packet of

materials that serve as support for the agency's issuance of the Warning Letter.

Q 3.30 What are the elements of a Warning Letter?

Although Warning Letters vary somewhat in form, style, and content, the elements listed below are common to Warning Letters:

- A clear title at the top: "WARNING LETTER."
- They are sent in a manner intended to ensure overnight delivery and receipt of delivery (*e.g.*, return receipt requested, FedEx) is documented.
- The Warning Letter is generally addressed to the highest known official in the corporation that includes the facility that was inspected, and a copy is sent to the highest known official at the facility that was inspected.
- The dates of the inspection and a description of the violative condition, practice, or product are set out in brief but sufficient detail.
- Citation of the section of the law and, where applicable, the regulation violated.
- Appropriate acknowledgment of corrections promised during the inspection, or annotated on the 483, or provided to the district in a written response.
- A request for correction and a written response within a specific period of time after the date of receipt of the letter, usually fifteen working days.
- At the district's discretion, the recipient may be offered an opportunity to discuss the letter with district officials or, when appropriate, with center officials.
- A warning statement that failure to achieve prompt correction may result in enforcement action without further notice. Examples of such actions may be cited. The letter will not include a commitment to take enforcement action.
- A statement in drug Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) about the implications for the award of federal contracts and, if cGMP violations are cited, a statement regarding the potential impact on requests for approval of export certificates and drug applications.
- A statement in drug Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) that: "Federal agencies are advised of all Warning Letters about devices so that they may take this information into account when considering the award of contracts."
- If cGMP violations are cited, a statement regarding the potential impact on requests for approval of export certificates and drug applications. For device Warning Letters that include cGMP violations: "Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been

corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected."

- Instructions, as appropriate, that the response include:
    - each step that has been or will be taken to completely correct the current violations and to prevent similar violations;
    - the time within which correction will be completed;
    - any reason the corrective action has not been completed within the response time; and,
    - any documentation necessary to show that correction has been achieved.
- A designated district or center official to whom the response should be addressed.

Impact of a Warning Letter

Q 3.31 What impact does a Warning Letter have on a company's government contracts?

Other federal agencies are informed about certain Warning Letters issued by FDA so they may consider this information when awarding government contracts. This will at times require follow up by the inspected firm to address the issues raised in the letter, and those issues, if material, could result in a suspension or termination of government contracting relationships.

Q 3.32 How quickly should we respond to a Warning Letter?

Typically, the first step is to contact the district office or center and let them know that the Warning Letter has been received, and arrive at a timeline for a response. A fifteen-business-day response period is the norm—most Warning Letters specify that "[w]ithin fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation." However, at times FDA will agree to additional time to permit a comprehensive response. If not, every effort should be made to respond to the Warning Letter within the fifteen-business-day period—to the extent additional, longer term measures must be taken, the firm's plans can be detailed in the response, including specific timelines for completion and reports to the Agency on status. Depending upon the nature and complexity of the Warning Letter, a meeting with FDA may be requested, which, if agreed to by the Agency, provides an opportunity for the firm to present plans, seek clarifications, explain or object to various findings, and develop a common understanding as to a comprehensive response.

Q 3.33 What is an appropriate Warning Letter response?

As with a 483 response, a Warning Letter response should address each alleged violation in the Warning Letter with specificity, building on the 483 response but also fully addressing any gaps between the attempted resolution of the issue at the 483 level and the findings and factors spurring the FDA decision to send the Warning Letter. These gaps may be provided in the Warning Letter text, but if not they must be divined from interactions with the Agency and/or critical self-examination of the issues through further investigation and testing by the firm. Detailed findings as to root causes and plans for CAPAs should be laid out in detail, with associated documentation and firm commitments to expeditious, achievable timelines for completion. It is particularly important to assure FDA that any systemic issues have been fully addressed in a sustainable manner, and to demonstrate that there is no public health concern relating to product quality (or that such risks have been appropriately contained). As with a 483 response, attention should be paid to the potential for disclosure of trade secret or confidential information, and proper marking of documents.

The Warning Letter usually provides to whom the response should be sent, although it is typically appropriate to send a copy to the sender of the letter (*e.g.*, the district director), as well as other key FDA personnel involved in the inspectional issues at the field/district or center levels.

Q 3.34 Who should sign a response to a Warning Letter?

A Warning Letter is typically addressed to the most senior company official responsible for the registered establishment, *e.g.*, the chief executive officer. Although a direct response from the addressee may be appropriate to convey the seriousness of the firm's commitment to its response and compliance generally, many firms prefer that the response be sent by another high-level company official with direct responsibility for the establishment or functions associated with the allegedly violative conditions (*e.g.*, the head of quality or regulatory affairs). This will depend upon the nature of the Warning Letter issues, but in any case the response should convey that the firm as a whole, including its senior leadership, is fully committed to compliance.

Q 3.35 Are Warning Letters available to the public? What about the recipient's responses?

Yes. Warning Letters are redacted for FOIA-exempt information and posted on the FDA website, typically two to four weeks after issuance.

FDA Receipt of a Warning Letter Response

Q 3.36 What does FDA do when it receives a response to a Warning Letter?

The issuing district or center will evaluate the response to the Warning Letter. If the response is inadequate, or if no response is received, the district or center will begin follow-up action as necessary to achieve correction. The district or center that issued the Warning

Letter will acknowledge, in writing, receipt of Warning Letter responses.

If the response appears adequate, the district or center will verify that commitments have been fulfilled and that correction has been achieved, and will notify other appropriate FDA units. Usually, verifying that corrections have been implemented will involve a follow-up inspection, typically conducted after the promised date of completion of the corrections.

Q 3.37 What is a "close-out" letter?

A Warning Letter close-out letter ("close-out letter") indicates that the violative issues and conditions identified by FDA have been resolved. Such a letter will not be issued based on representations that some action will or has been taken. Rather, the corrective actions must actually have been made and verified by FDA.

Specifically, the district or center that issued the Warning Letter will issue a close-out letter if the violations in the Warning Letter have been adequately addressed, and the following conditions have been met:

- The firm replied to the Warning Letter with sufficient information to demonstrate that any listed violations have been adequately corrected; or
- A follow-up inspection shows that implementation of the corrective actions was adequate, or, based on other verified, appropriate and reliable information, FDA determines that the follow-up inspection is not needed; and
- The follow-up inspection (or other appropriate and reliable information) does not reveal other significant violations.[21]

Districts or centers should issue close-out letters within a total of sixty-five working days of having the necessary information upon which to make a decision.

A close-out letter does not relieve the recipient from the responsibility of taking all necessary steps to assure compliance. If a subsequent inspection reveals problems with the adequacy or sustainability of the corrections that were taken in response to the Warning Letter, that would be considered a serious finding, and FDA may take enforcement action without further notice.

FDA posts a notice on http://www.fda.gov/foi/warning.htm when a close-out letter is issued.

The text of a close-out letter is typically as follows:

FEI: _____

[DATE]

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

CEO
Acme Company

ADDRESS

Dear _____:

The Food and Drug Administration has completed an evaluation of your firm's corrective actions in response to our Warning Letter [NUMBER] dated [DATE]. Based on our evaluation, it appears that you have adequately addressed the violations contained in this Warning Letter. Future FDA inspections and regulatory activities will further assess the adequacy and sustainability of these corrections.

This letter does not relieve you or your firm from the responsibility of taking all necessary steps to assure sustained compliance with the Federal Food, Drug, and Cosmetic Act and its implementing regulations or with other relevant legal authority. The Agency expects you and your firm to maintain compliance and will continue to monitor your state of compliance. This letter will not preclude any future regulatory action should violations be observed during a subsequent inspection or through other means.

Sincerely,

/s/

[NAME]
Compliance Officer
[LOCATION] District

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1. FDCA § 704 (21 U.S.C. § 374).
2. Investigations Operations Manual 2017 section 5.1.2 ://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf).
3. 74 Fed. Reg. 40,211 (Aug. 11, 2009).
4. 21 C.F.R. § 10.75.
5. Guidance for Industry: Formal Dispute Resolution: Scientific and Technical Issues ed to Pharmaceutical CGMP (Jan. 2006) ://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances M070279.pdf).
6. Regulatory Procedures Manual Section 4-1-1 ://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htr
7. *Id.*
8. *Id.*
9. *Id.*
10. *Id.*
11. Regulatory Procedures Manual section 4-2-1 ://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176871.htr

12. *Id.* section 10-2-2,
.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179537.htm.
latory Procedures Manual Section 10-2-2
://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179537.htr

13. *Id.* section 10-2-3,
.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179537.htm.
latory Procedures Manual Section 10-2-3
://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179537.htr

14. Regulatory Procedures Manual section 4-1-3
://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htr

15. *See, e.g.*, Regenerative Scis., Inc. v. FDA, 2010 WL 1258010 (D. Colo. Mar. 26, 2010);
:ing-Plough Healthcare Prods., Inc. v. Schwarz Pharma, Inc., 547 F. Supp. 2d 939, 946–47
. Wis. 2008); Clinical Reference Lab., Inc. v. Sullivan, 791 F. Supp. 1499, 1501, 1503 (D.
1992).

16. Holistic Candlers & Consumers Ass'n v. Food & Drug Admin., 664 F.3d 940 (D.C.
2012) *cert. denied,* 133 S. Ct. 497 (2012).

17. *See, e.g.*, Farm-to-Consumer Legal Def. Fund v. Sebelius, 734 F. Supp. 2d 668, 696–698
). Iowa 2010).

18. CBER concurrence is required for Warning Letters involving deviations from Part 211
ıre not associated with provisions in Part 606, such as 21 C.F.R. § 211.68(b) or 211.113.

19. The districts no longer need center concurrence regarding viral marker testing violations.
ever, center concurrence is required for Warning Letters based on invalidation of viral
er test run deficiencies since center guidance on this issue is relatively recent.

20. "Violations in areas where specific guidance has not been provided: In these situations,
ıcourage the programs to contact the Division of Case Management (DCM) in CBER's
e of Compliance and Biologics Quality (OCBQ) before recommending a Warning Letter
ɛ center."

21. Regulatory Procedures Manual Section 4-1-8
://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htr

FDA Regulations and Enforcement Actions Relative to Oversight of Advertising and Promotion

Michael A. Swit[1]

The media available for advertising and promoting pharmaceutical products regulated by the Food and Drug Administration (FDA) expanded quickly over the last fifteen years. The extensive use of social media such as Facebook and Twitter as forms of drug product promotion and communication was unknown only a few years ago. While FDA regulations covering traditional forms of print and electronic media, that is, newspapers and television, are relatively straightforward, the application of the rules and principles to new forms of media requires caution, care, and common sense. The rapid evolution of media channels has outpaced the regulatory framework for addressing each, although FDA has taken measures to adapt to these new media. This chapter reviews the overarching principles and regulations that FDA applies to the oversight of the marketing and promotion of pharmaceutical products. The ever-changing forms of media introduce a level of uncertainty about the boundary between allowed and prohibited activity.

FDA Responsibility for Oversight of Advertising and Promotion

Q 4.1 What centers within FDA are responsible for oversight of the advertising and promotion of FDA-regulated medical products?

The Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiologic Health (CDRH).

Within CDER, the Office of Prescription Drug Promotion (OPDP), formerly the Division of Drug Marketing, Advertising and Communications (DDMAC), has oversight responsibility for drug promotion. Within CBER, the Advertising and Promotional Labeling Branch (APLB), has oversight for biologics. Within CDRH, the Office of Compliance (OC) has oversight of the promotion of medical devices, but, unlike CDER and CBER, CDRH lacks an office or division devoted to overseeing device advertising and promotion.

Q 4.2 What are the responsibilities of these centers?

All of these offices focus on protecting the public health by seeking to assure that products are labeled properly, and that the information contained in promotional materials is truthful, balanced, and accurate. Each office is engaged in reviewing promotional materials, monitoring their use and engaging in enforcement actions and educational programs to achieve these goals with respect to labeling and promotional information disseminated by regulated industry to healthcare professionals and consumers. These offices generally review advertising and promotional labeling to ensure the information within is not false or misleading and is consistent with not only applicable laws and regulations, but also the labeling approved/cleared by FDA for the product. The office reviewers provide written comments to submitted promotional materials, review complaints alleging promotional materials violate applicable laws and regulations, evaluate the potential for lack of clarity in labeling and promotional materials, initiate enforcement actions, monitor promotional exhibits and activities at medical meetings and conventions, and liaise between their offices and other FDA divisions with respect to promotional issues.[2]

Controlling Statutes and Regulations

Controlling Law

Q 4.3 What statutes and regulations control pharmaceutical marketing and promotion?

The content of prescription drug labels and promotional material is overseen by FDA through the Food, Drug, and Cosmetic Act (FDCA) and the FDCA's implementing regulations.[3] FDA also regulates the content of labels for over-the-counter drugs, dietary supplements, medical devices, and cosmetics. Advertising for most over-the-counter drugs, most medical devices, and cosmetics, however, is regulated by the Federal Trade Commission (FTC) through the Federal Trade Commission Act.[4] In addition to regulations governing the content of promotional material, there are regulations that govern how and when prescription drug and prescription biologic advertising and promotional material must be submitted to FDA.[5]

FDA Authority Over Prescription Drug-Related Promotional Material

Q 4.4 What information in prescription drug-related promotional material does FDA control?

In general, regardless of the type of promotional material, the FDCA and its regulations control product naming as well as the placement, size, and prominence of both proprietary (brand) and established (generic) names for drugs.[6] FDA also requires that promotional material include additional information about the prescription drug's use, benefits, effectiveness, risks, and contraindications.[7] Further, the statutes and regulations set out prohibited content, such as the inclusion of non-approved uses for drugs and unsupported claims, and require that the advertisement not be false or misleading.[8] The regulations control both written content of promotional material as well as images used in the material. The extent of the required information is determined by the type of promotional material and the medium used to disseminate the material.

Q 4.5 Are promotional materials required to be pre-approved by FDA?

In general, pre-approval of promotional material by FDA for already approved prescription drugs is not typically required regardless of whether the material is intended for medical professionals or is directed to consumers. FDA does, however, require that promotional material, including promotional labeling, be submitted to FDA.[9] Although the FDCA includes provisions for FDA to require that television advertisements for a drug be submitted no later than forty-five days before the dissemination of the television

advertisement, those provisions have not been implemented.[10] FDA permits companies to voluntarily submit advertisements for pre-approval.

Q 4.6 When must promotional materials be submitted to FDA?

Holders of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), and antibiotic applications must submit samples of "mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of the initial dissemination of the labeling and at the time of the initial publication of the advertisement for a prescription drug product."[11] Form FDA 2253 must accompany each submission.[12]

Q 4.6.1 Are there exceptions to the time of submission of promotional materials to FDA?

Yes. Manufacturers of pre-1938 products and products that are declared "not new drugs" are generally exempt from the requirement that promotional material be submitted to FDA.[13] In addition, new drugs or new indications being considered for accelerated approval for serious or life threatening conditions, also known as "Subpart H drugs," and for new drugs when human efficacy studies are not ethical or feasible, applicants must submit for pre-approval promotional labeling and advertisements that are intended for dissemination or publication within 120 days of approval of the drug. After the first 120 days after market approval, promotional materials for these drugs must be submitted at least thirty days before "the intended time of initial dissemination of the labeling or initial publication of the advertisement."[14] FDA has recognized that, with respect to advertising/promotion on the Internet, having to submit web-based promotional materials at time of dissemination presents logistical challenges and is not always needed.[15]

Q 4.7 How does FDA evaluate whether promotional material is in violation of the FDCA and its regulations?

While there are many ways in which promotional material may violate the controlling law, common violations include failing to achieve the "fair balance" requirement by downplaying or omitting risk information; using misleading images or graphics, including a representation or suggestion of an unapproved use; misstating or misusing the results of studies; and suggesting that a drug is more effective than demonstrated by the scientific evidence.[16]

Section 502 of the FDCA and its implementing regulations delineate when a drug or medical device is misbranded. This statutory section and its regulations include general guidance on the how drugs and devices should be packaged, labeled, and advertised.[17] Pursuant to section 502(n), when evaluating whether promotional material is misleading, FDA assesses both the explicit language of the promotional material as well as implications or suggestions made by the design and images used in the material and omissions of

relevant information. In particular, FDA looks to determine whether the material contains false information, lacks fair balance of material, and whether the material makes unsupported claims.[18] The implementing drug advertising regulations found at 21 C.F.R. § 202.1 set out additional details on what constitutes or what may constitute false, lacking in fair balance, or otherwise misleading promotional material.

FDA Treatment of Different Types of Prescription Drug Promotional Material

Q 4.8 How does FDA treat different types of promotional material for prescription drugs?

The FDCA and its regulations contain explicit rules for the content of promotional material, based in part upon the type of promotional material at issue and the medium for disseminating that material. FDA differentiates between the following categories of promotional material:

- Professional label and labeling
- Promotional labeling
- Product claim advertisements
- Reminder advertisements
- Help-seeking advertisements[19]

Q 4.9 What is the difference between the professional label and promotional labeling?

FDA has separate regulations governing the content and appearance of the professional labeling that is placed on a drug or its packaging.[20] Label content is subject to the content requirements set out in section 502 of the FDCA as well as the related regulations.[21] FDA regulates the on-product labeling and product packaging of both prescription and over-the-counter drugs.[22] The controlling regulations set out general requirements for prescription drugs and non-prescription drugs and, in some cases, provide labeling requirements for specific drugs.

"Promotional labeling" is treated as advertisement and is defined by FDA to include brochures, bulletins, calendars, price lists, catalogs, letters, motion picture films, sound recordings, literature, reprints, and other similar pieces of material intended "for use by medical practitioners, pharmacists, or nurses containing drug information and which are disseminated by or on behalf of its manufacturer, packer, or distributor."[23] Promotional labeling also includes material provided directly to consumers. FDA includes refrigerator magnets, cups, and other giveaway items that show the drug's name in this category.[24] FDA only has definitive regulations for promotional labeling for prescription drugs, but also has the statutory authority to regulate promotional labeling of medical devices.

Promotional labeling must be accompanied by the drug's full prescribing information if

it mentions the drug's benefits and must comply with the "fair balance" requirement for presenting risks and benefits.[25]

Q 4.10 What is a "reminder advertisement"?

A reminder advertisement sets out the name of the drug, but not the drug's uses. Reminder advertisements are intended only to call attention to the name of the drug product or to convey price information. They do not include prescription information such as dosage. Reminder advertisements cannot be used for drugs with boxed warnings concerning serious hazards.[26]

Q 4.11 What is a "help-seeking advertisement"?

Help-seeking advertisements describe a particular disease or condition, but cannot recommend or suggest a particular prescription drug. These are advertisements that typically encourage a consumer with the disease or condition to consult a physician. These advertisements can include the name of a drug company and telephone number to call for more information. FDA does not typically regulate help-seeking advertisements if they are consistent with the guidelines; help-seeking advertisements are regulated by the FTC.[27]

Q 4.12 What is a "product claim advertisement"?

Product claim advertisements are materials, regardless of the medium used to disseminate them, that name a prescription drug and discuss the drug's benefits and risks.[28] These advertisements are subject to differing content requirements depending upon whether these are print advertisements or broadcast advertisements.[29] In general, product claim advertisements are subject to detailed content and style requirements set out in section 502(n) of the FDCA[30] and the Prescription Drug Advertising regulations found at 21 C.F.R. § 202.1. All product claim advertisements must include certain information, including the proprietary (brand) and established (generic) names for drugs, and a fair balance of the benefits and risks of the drug.[31] The advertisements must not be misleading and must not include unapproved uses or unsupported claims.[32]

Q 4.12.1 What is a "broadcast advertisement"?

"Broadcast advertisements" are those disseminated, most commonly directly to consumers, through "media such as radio, television, or telephone communications."[33] These advertisements are permitted to include less information than print product claim advertisements. Broadcast advertisements must include the drug's most important risk-related information, termed the "major statement." Such advertisements also must contain either a "brief summary" of the drug's risk information, or, alternately, are allowed to include only the major side effects and contraindications of the drug so long as the advertisement makes "adequate provision" to tell viewers where to obtain the full FDA-approved prescribing information.[34]

Q 4.12.2 What must be included in a broadcast advertisement's "major statement"?

The "major statement" in a broadcast advertisement must include the drug's most important risks and must be presented in a neutral manner that neither emphasizes nor downplays risks and benefits.[35] This is similar to the "fair balance" requirement in print ads, but typically is in a shortened format. In addition, for product claim advertisements for prescription drugs "presented directly to consumers in television or radio format and stating the name of the drug and its conditions of use, the major statement relating to side effects and contraindications shall be presented in a clear, conspicuous, and neutral manner."[36]

In March 2010, FDA proposed an amendment to 21 C.F.R. § 202.1(e)(1) that would set out four specific criteria for the "clear, conspicuous, and neutral" requirement for direct to consumer broadcast advertisements' major statements.[37] These proposed standards are:

(1) Information is presented in language that is readily understood by consumers."

(2) "Audio information is understandable in terms of volume, articulation, and pacing used."

(3) "Textual information is placed appropriately and is presented against a contrasting background for sufficient duration and in a size and style of font that allows that information to be read easily."

(4) "The advertisement does not include distracting representations."

While the proposed amendment to this regulation is still pending, these criteria provide insight into how FDA evaluates broadcast advertisements.

Q 4.12.3 What must be included in the "brief summary"?

The "brief summary" must include all the risk information about the drug, but it may omit non-risk information such as chemical description of the drug, directions for use, and how the drug works.[38] Instead of including the "brief summary," a broadcast advertisement may include an "adequate provision" for the audience to find the drug's more detailed prescribing information.[39] For example, the advertisement can direct the audience to a toll-free number, website, or current print advertisement.

Q 4.12.4 What is a "consumer brief summary"?

In an effort to make consumer-directed print advertising and the risk and use information more effective, the FDA issued a draft guidance offering an alternative called a "consumer brief summary."[40] "To provide better and more actionable information for consumers, FDA believes that the brief summary should focus on the most important risk information rather than an exhaustive list of risks and that the information should be presented in a way most likely to be understood by consumers."[41] In large measure, FDA

issued this guidance in light of studies assessing consumer appreciation of risk information in print media. The guidance encourages the use of a conversational tone for accessibility by a broad range of literacy levels. The information should be presented in a readable format and should avoid the use of "technical language, scientific terms, and medical jargon."[42] According to FDA, "the consumer brief summary should provide clinically significant information on the most serious and the most common risks associated with the product and omit less pertinent information."[43] Among other things, the consumer brief summary should include "the indication for which the drug is being promoted, any clinically significant drug interactions and information regarding topics or issues consumers should discuss with their health care providers."[44] As with any guidance, a company should review it for the many examples of acceptable consumer brief summary language provided.

Q 4.12.5 How do the requirements for print advertisements differ from broadcast advertisements?

Print product claim advertisements for prescription drugs must include a brief summary of all the risks included in the prescribing information. This must include a "fair balance" of information. A fair balance of information does not require that equal space be given to benefits and risks, but is dependent upon the drug's actual risks and how the risks and benefits are set out.[45]

Direct-to-consumer print advertisements must also clearly include the statement: "You are encouraged to report negative side effects of prescription drugs to FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088."[46]

Enforcement Actions

Q 4.13 What are some of the most common grounds for enforcement action by FDA related to promotional materials?

Some of the most common grounds of enforcement action by FDA relate to promotional materials that omit or minimize risk information, make misleading efficacy claims, make misleading superiority claims, or promote unapproved uses of drugs.[47]

Q 4.14 What actions can the government take regarding improper promotion of pharmaceuticals?

FDA has many enforcement tools at its disposal, including warning letters, seizure and injunction actions, imposition of civil money penalties, and criminal prosecutions.[48] These administrative and judicial actions are discussed more fully in chapters 11 and 12. Whenever possible, however, FDA's policy is to afford responsible individuals and organizations an opportunity to correct violations before the agency initiates a formal enforcement action.[49] FDA uses two types of communications to provide notice of regulatory violations and achieve voluntary compliance: the "Warning Letter" and the "Untitled Letter."

Q 4.15 What is a "Warning Letter"?

A Warning Letter is FDA's principal means of achieving prompt, voluntary compliance with the FDCA and its implementing regulations. A Warning Letter notifies the recipient that FDA considers certain products, practices, or other activities to be in violation of the law, and affords the recipient an opportunity to correct the violation before FDA initiates an enforcement action, such as a seizure or injunction proceeding. FDA is not required to issue a Warning Letter before taking enforcement action, nor does issuance of a Warning Letter preclude the agency from taking concurrent enforcement activity.[50]

Q 4.15.1 Under what circumstances does FDA issue a Warning Letter?

FDA issues Warning Letters for significant regulatory violations. A "significant violation" is one that "may lead to enforcement action if not promptly and adequately corrected."[51] Although FDA generally seeks to afford individuals and organizations an opportunity to correct violations voluntarily, FDA may forgo a Warning Letter and proceed directly to an enforcement action if the violation is deemed intentional or flagrant, presents a reasonable possibility of injury or death, or reflects a history of repeated or continued conduct that has gone uncorrected despite prior notice.[52]

Q 4.15.2 What information is included in a Warning Letter?

Although Warning Letters may vary in form, style, and content, those involving advertising or promotional violations typically include the following elements:

- Title: "WARNING LETTER."
- Addressed to the highest known official in the corporation.
- A sufficiently detailed description of the violation to enable corrective action.
- Citations to the statutory or regulatory provisions violated.
- An acknowledgement of any corrective action the recipient may have promised to undertake (for example, in reply to an inspection that led to the Warning Letter).
- A statement that the recipient should take prompt corrective action and provide a written response within a specific period of time, usually within fifteen working days of receipt of the letter.
- A warning that failure to achieve prompt correction may result in enforcement action without further notice.
- A statement that other federal agencies may take the Warning Letter into account when considering the award of contracts.[53]

Q 4.16 What is an "Untitled Letter"?

FDA issues Untitled Letters, also known as "Notices of Violation," for violations that are not as significant as those that trigger Warning Letters.[54] Unlike a Warning Letter, an Untitled Letter requests (rather than requires) a written response within a reasonable period. In addition, given the absence of a "significant violation," the Untitled Letter does not include a warning that failure to take prompt corrective action could result in enforcement action.[55]

Q 4.17 Which FDA offices have authority to issue Warning Letters or Untitled Letters?

Warning Letters and Untitled Letters may be issued through an FDA District Office, except in specific program areas that require prior Center concurrence. Warning Letters and Untitled Letters may also be generated directly through center headquarters.[56]

Q 4.18 Are Warning Letters and Untitled Letters available to the public?

Yes. FDA posts all Warning Letters on its publicly available website.[57] Untitled Letters issued to pharmaceutical companies by the CDER headquarters and by the OPDP have been posted to the FDA website since January 1997 (although many are now archived and not easily accessible).[58] The Center for Biologics Evaluation and Research has posted Untitled Letters regarding the advertising and promotion of approved biologics on the Internet since November 2002.[59] Finally, as part of FDA's Transparency Initiative, the

Center for Devices and Radiologic Health agreed to begin posting its Untitled Letters regarding the advertising and promotion of medical devices beginning on October 1, 2011.[60] Letters posted on the FDA website are redacted or edited to remove certain confidential information.

Q 4.19 How should the recipient of a Warning Letter or Untitled Letter respond?

The failure to respond to a Warning Letter or to adequately address the violations identified in the notice may have serious consequences. For example, FDA may elect to proceed with enforcement action, such as imposing civil money penalties or initiating seizure or injunction proceedings, if the recipient fails to promptly and adequately address the violations specified in the letter. Although an Untitled Letter requests, but does not demand, a response from the recipient, it is also important to treat these letters seriously. Responding appropriately to FDA demonstrates good faith and a commitment to complying with the law.

In responding to a Warning Letter or Untitled Letter, the recipient should:

- Carefully review the letter to identify deadlines and all relevant issues and violations.
- Identify the individuals within the company most knowledgeable about the specific issues raised in the letter and secure their assistance, including the assistance of counsel, in formulating an appropriate response.
- Conduct a prompt but thorough investigation of the violations identified in the letter and memorialize all steps taken in the investigation.
- Identify any areas of disagreement regarding the alleged violations and gather evidence to support the company's differing position.
- Respond to FDA within the stated time frame or request additional time if needed.
- Request a meeting with FDA if the company is unclear about the agency's concerns or would like to clarify or provide additional information.
- Prepare a thorough response to FDA that:
    - Assures the agency that the company takes the issues identified in the letter seriously and is committed to correcting any violations in a prompt and effective manner.
    - Acknowledges and addresses each of the issues identified in the FDA's letter.
    - Identifies and explains any areas of disagreement regarding the perceived violations and provides evidence, including additional documentation, to support the company's position.

- Includes statements that are factually accurate and not misleading.
- Describes the corrective actions the company has taken or intends to take to address and rectify the violations.
- Does not over-commit the company to corrective actions that are beyond its ability to achieve.

- Monitor and document the company's progress in implementing and completing each of the corrections promised to FDA.

Q 4.20 How are Warning Letter matters concluded?

For Warning Letters issued on or after September 1, 2009, FDA may issue a "close-out letter" once the agency has confirmed that the company has taken corrective action to address the violations. A close-out letter will not be issued based solely on the company's representations that corrective action has or will be taken. Instead, the corrective actions must actually have been made and verified by FDA. For a close-out letter to issue, the company must have replied to the Warning Letter with enough information to demonstrate that the violations were adequately addressed. If the Warning Letter contains violations that by their nature are not correctable, then no close-out letter will issue.[61]

FTC

Q 4.21 What is the role of the FTC with respect to advertising of products regulated by FDA?

Under the FDCA, FDA has enforcement authority over labeling, which is broadly defined. Regulations define "label" as "any display of written, printed or graphic material on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity."[62] The statutory definition of "labeling" includes "all labels and other written, printed, or graphic materials (1) upon any article or any of its containers or wrappers or (2) accompanying such article."[63] Thus, in regulating labeling, FDA regulates advertising of prescription drugs. FDA also has oversight over the advertising of restricted medical devices, largely Class III medical devices. The FTC regulates the advertising of over-the-counter drugs, foods, dietary supplements, and non-restricted medical devices.[64]

A 2010 DDMAC Untitled Letter noted violations in relation to a consumer DVD containing testimonials (a common subject of enforcement action) about the effectiveness of a drug while minimizing or omitting required risk information. Note that, in 2009, the FTC approved final revisions to its guides on endorsements and testimonials.[65]

Bad Ad Program

Q 4.22 What is the "Bad Ad Program"?

Truthful Prescription Drug Advertising and Promotion (the "Bad Ad Program") is an FDA educational program instituted to "educate healthcare providers about the role they can play in helping the agency ensure prescription drug advertising and promotion is truthful and not misleading."[66] FDA's educational outreach program, launched on May 11, 2010 and administered by OPDP, includes reporting on complaints received and responses by OPDP to the complaints, informational videos, brochures and webinars, staffing by the OPDP at medical conferences and presentations at hospitals. Available online are five examples of enforcement actions taken recently as a result of "Bad Ad" complaints, including three Warning Letters and two Notices of Violation based upon promotional mailings, oral statements to a physician, and a video of a physician detail.[67] OPDP has indicated that it intends to continue and expand the program in coming years.

Internet and Social Media in the Promotion of FDA-Regulated Products

Q 4.23 What have been some of the recent specific enforcement actions taken in relation to promotion via the Internet?

Numerous Untitled Letters have been issued for promotions appearing on the Internet. One of the ways websites come into play is when an FDA review of a website reveals that claims are made for a product that bring it within the definition of a "drug" under section 201(g)(1) of the FDCA,[68] that is, claims indicating the products are intended for use in the cure, mitigation, treatment, or prevention of disease. Where such claims are made and the product is unapproved, a Warning Letter will be issued. Additionally, Warning Letters have been issued where a claim was made that a product is safe and effective for a use that is still investigational and not yet approved for marketing. Promotion of an investigational new drug is prohibited by regulation.[69] Several Warning Letters and/or Untitled Letters were issued in 2011 and since asserting these types of violations based on FDA review of company websites.[70] The more common types of violations with respect to promotion generally are also the subject of many recent Warning Letters and/or Untitled Letters over Internet advertising; for example, omitting material facts, minimizing risk information, overstating efficacy, making unsubstantiated superiority claims, otherwise making unsubstantiated and/or misleading claims, and making claims for unapproved new uses.[71]

But, probably the most impactful enforcement action FDA has taken with respect to promotion using the Internet occurred in April 2009, when FDA simultaneously sent fourteen Untitled Letters to pharmaceutical companies for their use of sponsored links on Internet search engines.[72] FDA stated that the companies had made representations and/or suggestions about efficacy without any requisite risk information, had overstated the efficacy of the products, and had failed to use the required established names for the products. In some cases, the letters stated inadequate information with respect to the drugs' indications had been communicated. The letters stated that although the sponsored links contained a link to the products' websites, this was insufficient to communicate risk. These letters caused companies to virtually stop using the so-called (and unrecognized by FDA) "one-click" rule, that is, placing the "risk" information only one click away from the "benefit" part of the advertisement. The regulatory risk associated with the "one-click" rule was generally regarded as a significant limitation on the promotional use of the Internet and social media—a source of a tremendous amount of marketing interest in the past few years.

Q 4.24 How has FDA reacted to the growing interest in the use of the Internet and social media in the promotion of FDA-regulated products?

In 2009, on November 12 and 13, FDA held a two-day public hearing on the promotion of FDA-regulated medical products using the Internet and social media tools at which more than seventy-five presentations were given by patient and consumer groups, Internet vendors, trade representatives, and advertising and pharmaceutical companies. Public comments were also filed. Questions posed in the *Federal Register* prior to the meeting centered around the topics of (1) accountability for online communications; (2) fulfillment of regulatory requirements relating to fair balance and disclosure of indication and risk information given the real-time communication capability and space limitations of certain tools; (3) corrective information; (4) the use of links; and (5) adverse event reporting.[73]

On June 17, 2014, FDA issued two draft guidances for industry related to social media. The first Guidance, *Internet/Social Media Platforms: Correcting Independent* Third-Party *Misinformation About Prescription Drugs and Medical Devices*, [74] allows, but generally does not require, pharmaceutical companies to correct misinformation about a product "when a firm is not responsible for a product-related communication that appears on the firm's own forum, an independent third-party website, or through social media, and the firm chooses to correct misinformation about its own product contained in that communication." The corrective information may be posted on the independent medium or supplied to the author to include on the independent medium. The corrective information should, among other things, be accurate and responsive to the misinformation, non-promotional in nature, consistent with FDA-required labeling, and disclose that the information is provided by or on behalf of the pharmaceutical company. A company will not be responsible if a third party does not correct any misinformation. This Guidance provides many examples of different approaches to responding to third-party misinformation on social media, and should be consulted before acting.

This Guidance does not apply to any product communication that is "owned, controlled, created, or influenced, or affirmatively adopted or endorsed, by, or on behalf of," a pharmaceutical company," and the company is "responsible for communications on the Internet and Internet-based platforms, such as social media, made by its employees or any agents acting on behalf of the firm." This position is consistent with other FDA-related advertising regulation.

In the second Guidance, *Internet/Social Media Platforms with Character Space Limitations —Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices*, [75] FDA addressed media such as Twitter, which are character limited. FDA expresses reservations about a pharmaceutical company's ability to present a "fair balance" of risks and benefits in these circumstances. At a minimum, each character limited promotional communication should include "the most serious risks associated with the product together with benefit information." FDA also suggested that supplemental hyperlinks to a product's home page, Package Insert, or brief summary be included in the character limited communication. This Guidance also included many examples of what would constitute permissible and impermissible communications and should be reviewed when developing character limited communication. The Guidance makes clear that FDA expects a fair

balance and is not entirely confident that this can be achieved in the context of character limited social media.

Although these Guidances provide outlines of what could constitute acceptable product-related communication on social media in two areas, uncertainty remains. These Guidances are clearly labeled as "draft," and are not binding on FDA (or industry).

The second Guidance has been criticized as merely fitting the old rules for traditional communication platforms (e.g., print media, radio, and television) to newer technologies (e.g., the Internet and social media). To respond to this criticism, FDA announced on November 7, 2016 in the *Federal Register* that it intends to research methods for including risk information about pharmaceutical and medical device products in promotional Internet communications that have character space limitations.[76] FDA proposed to use four studies to gather information regarding participants' retention of risk information communicated through sponsored links and microblog posts.[77] Each study will present a participant with different promotional communications about two fictional drugs:

- A sponsored link about a fictional weight loss drug, embedded in a Google search page about weight loss;
- A sponsored link about a fictional drug to treat migraine, embedded in a Google search page about migraine;
- A promotional tweet about a fictional weight loss drug, embedded in a Twitter search page about weight loss; or
- A promotional tweet about a fictional drug to treat migraine, embedded in a Twitter search page about migraine[78]

After viewing the material provided, the participant will be asked to complete a questionnaire that assesses the participants' retention of the risk information and their perceptions of the drugs' benefits.[79]

FDA hypothesized that participants will have a greater sense of the relevant risks when the risks are presented in the primary promotional communication compared to those where the risks must be accessed through a link.[80] Comments on the proposed studies closed on January 6, 2017.[81]

We can expect that if the studies support FDA's theory, FDA will not allow exceptions to the benefit/risk information requirement even as social media technology evolves. However, if the FDA's hypothesis is not supported by the data, it may reconsider whether alternative methods of communicating risk on social media platforms are acceptable.

Q 4.25 What are the top issues facing those interested in the promotion of FDA-regulated products via social media?

The top concerns facing those interested in the promotion of FDA-regulated products via social media include the following:

- How to comply with regulatory requirements governing labeling and advertising

and adverse event reporting.

- When, if ever, is FDA going to issue guidance tailored to the use of social media in the promotion of regulated products and what will the guidance cover?
- How to ensure social media is useful in providing information to physicians and patients and that it is used appropriately.
- How to counteract fraudulent or inaccurate information.
- How to assess utility and impact.

Q 4.26 What have been some of the messages of Warning Letters and Untitled Letters issued in relation to promotion via the Internet and social media since the April 2009 Untitled Letters?

Since the April 2009 Untitled Letters, FDA has issued other enforcement letters reiterating the insufficiency of links to risk information, and other Internet and social media-related violations. In July 2010, DDMAC issued an Untitled Letter to a pharmaceutical company over the use of a Facebook share social media widget. The Untitled Letter noted that the shared content included a hyperlink to various product websites that contained product risk information, but noted that such a hyperlink was insufficient to mitigate the omission of the required risk information. Earlier in 2010, a January 2010 Untitled Letter challenged the information presented on a webpage and in patient videos. DDMAC asserted the webpage omitted certain risk information, the "Contraindications" or "Warning and Precautions," and the videos overstated the efficacy of the product. A March 2010 Untitled Letter was issued by DDMAC asserting that a promotional webcast minimized important risks and omitted the drug's approved indication. An Untitled Letter was issued in April 2010 in relation to a direct-to-consumer email challenging the use of providing risk information at the bottom of the email in a smaller font size than efficacy claims made more prominently earlier in the email.

These are a few examples of regulatory action in relation to the use of the Internet and social media in the promotion of FDA-regulated products. For more examples, see the FDA website listing Warning Letters and Untitled Letters issued to Pharmaceutical Companies.[82] In the absence of further guidance from FDA, those companies utilizing the Internet and social media for product promotion do so with only the guidance of regulations and enforcement actions taken to date.

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1. Joseph J. Leghorn, a now retired partner at Nixon Peabody LLP, authored earlier ons of this chapter.

2. For information on OPDP within CDER, see U.S. FOOD AND DRUG INISTRATION, THE OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP) inafter FDA, THE OPDP], .fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm; for the APLB at CBER, see FOOD AND DRUG ADMINISTRATION, VACCINES, BLOOD & BIOLOGICS,

UT THE ADVERTISING AND PROMOTIONAL LABELING BRANCH (APLB), .fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/AdvertisingLabelingPromolMaterials/ucm164120.htm; and, for the OC of CDRH, see U.S. FOOD AND DRUG IINISTRATION, ABOUT THE CENTER FOR DEVICES AND RADIOLOGICAL LTH, ://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/HOffices/ucm115809.htm.

3. 21 U.S.C. § 352; 21 C.F.R. §§ 201.1 *et seq*., §§ 202.1 *et seq*.
4. 15 U.S.C. §§ 41–58.
5. 21 C.F.R. §§ 314.81(b)(3)(i), 314.550, 314.640.
6. 21 C.F.R. §§ 201.10(g)(2), 202.1(a)–(d); 21 U.S.C. § 321(n).
7. *Id*.
8. 21 U.S.C. § 331(a)–(d), (n), (kk); 21 U.S.C. § 352(a)–(n), (p); 21 C.F.R. § 202.1.
9. 21 C.F.R. § 314.81(b)(3)(i).
10. 21 U.S.C. § 353b.
11. 21 C.F.R. § 314.81(b)(3)(i); FDA, THE OPDP, *supra* note 1.
12. *Id*.
13. FDA, THE OPDP, *supra* note 1.
14. 21 C.F.R. §§ 314.550, 314.640.
15. *See* "Guidance for Industry. Fulfilling Regulatory Requirements for Postmarketing iissions of Interactive Promotional Media for Prescription Human and Animal Drugs and gics. FDA Draft Guidance, Jan. 2014. ://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances M381352.pdf
16. 21 C.F.R. § 202.1(e)(6), (7).
17. 21 U.S.C. § 352; 21 C.F.R. § 202.1.
18. 21 U.S.C. § 352(n).
19. As discussed later, a "help seeking" promotion is not subject to FDA jurisdiction at all if erly framed.
20. 21 C.F.R. §§ 200.1 *et seq*.
21. 21 U.S.C. § 352(a)–(m).
22. 21 C.F.R. §§ 201.1 *et seq*.
23. 21 C.F.R. § 202.1(l)(2).
24. U.S. FOOD AND DRUG ADMINISTRATION, DRUG ADVERTISING: A SSARY OF TERMS [hereinafter FDA, DRUG ADVERTISING], .fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htr
25. *Id*.
26. 21 C.F.R. §§ 200.200; 202.1(e)(2)(i). *See also* 21 C.F.R. § 201.100(f) (exempting ıder labels from containing directions for use).
27. U.S. FOOD AND DRUG ADMINISTRATION, BASICS OF DRUG ADS

inafter FDA, BASICS OF DRUG ADS], .fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072077.htr

28. *Id.*
29. *Id.*
30. 21 U.S.C. § 352(a), (n).
31. 21 C.F.R. §§ 201.10(g)(2), 202.1(a)–(d); 21 U.S.C. § 321(n).
32. *Id.*
33. 21 C.F.R. § 202.1(e)(1).
34. 21 C.F.R. § 202.1(e). Note that, when "adequate provision" is made, the labeling made ıble to the reader must be the full labeling and not the brief summary that normally suffices print advertisement.
35. 21 C.F.R. § 202.1(e)(1).
36. 21 U.S.C. § 352(n).
37. FDA-2009-N-0582, 75 Fed. Reg. 15,376–87 (Mar. 29, 2010).
38. 21 C.F.R. § 201.1(e).
39. 21 U.S.C. § 352(n).
40. Brief Summary and Adequate Directions for Use: Disclosing Risk Information in umer-Directed Print Advertisements and Promotional Labeling for Prescription Drugs, ed Draft Guidance, August 2015, .fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm06 .pdf.
41. *Id.* at 4.
42. *Id.* at 6.
43. *Id.* at 6–7.
44. *Id.* at 8.
45. For a definition of "fair balance," see U.S. FOOD AND DRUG ADMINISTRATION, IG ADVERTISING: A GLOSSARY OF TERMS, .fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htr A, THE OPDP, *supra* note 1.
46. 21 U.S.C. § 352(n).
47. Thomas Abrams, Director, OPDP, *OPDP Update on Oversight of Prescription Drug otion*, Food and Drug Law Institute (FDLI), Washington, D.C., October 1, 2012.
48. *See* U.S. FOOD AND DRUG ADMINISTRATION, REGULATORY CEDURES MANUAL (Mar. 2010) [hereinafter PROCEDURES MANUAL], at chs. 5–7.
49. *Id.* at ch. 4, § 4-1-1.
50. *Id.*
51. *Id.*
52. *Id.*
53. *Id.* § 4-1-10.

54. *Id.* § 4-2-1; TRANSPARENCY TASK FORCE, U.S. DEPARTMENT OF HEALTH
) HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, FOOD AND
'G ADMINISTRATION TRANSPARENCY INITIATIVE: DRAFT PROPOSALS FOR
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ESS TO THE AGENCY'S COMPLIANCE AND ENFORCEMENT DATA, at 4 n.19
3, 2011).

55. *Id.*

56. PROCEDURES MANUAL, *supra* note 47, at 4-1-3, 4-1-4, 4-2-1, 4-2-2.

57. *See* U.S. FOOD AND DRUG ADMINISTRATION, INSPECTIONS,
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58. *See* U.S. FOOD AND DRUG ADMINISTRATION, DRUGS, WARNING
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59. *See* U.S. FOOD AND DRUG ADMINISTRATION, VACCINES, BLOOD &
LOGICS, UNTITLED LETTERS REGARDING ADVERTISING & PROMOTIONAL
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60. *See* U.S. FOOD AND DRUG ADMINISTRATION, MEDICAL DEVICES,
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013).

61. PROCEDURES MANUAL, *supra* note 47, at 4-1-8.

62. 21 C.F.R. § 1.3(b).

63. 21 U.S.C. § 321(m).

64. The Federal Trade Commission regulates advertising of most medical devices, those that
ot restricted, under sections 12–15 of the Federal Trade Commission Act, 15 U.S.C.
2–55.

65. *See* Press Release, FTC, FTC Publishes Final Guides Governing Endorsements,
monials, Changes Affect Testimonial Advertisements, Bloggers, Celebrity Endorsements
5, 2009), www.ftc.gov/opa/2009/10/endortest.shtm; *see also*
//business.ftc.gov/documents/bus28-advertising-and-marketing-internet-rules-road.

66. *See* FDA, THE OPDP, *supra* note 1.

67. *See* U.S. FOOD AND DRUG ADMINISTRATION, DRUGS, TRUTHFUL
SCRIPTION DRUG ADVERTISING AND PROMOTION,
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68. 21 U.S.C. § 321(g)(1).

69. *See* 21 C.F.R. § 312.7(a).

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71. *Id.*

72. *Id.*

73. *See* Food and Drug Administration, Promotion of Food and Drug Administration-lated Medical Products Using the Internet and Social Media Tools; Notice of Public ing, 74 Fed. Reg. 48,083–88 (Sept. 21, 2009), http://edocket.access.gpo.gov/2009/E9-8.htm.

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76. AGENCY INFORMATION COLLECTION ACTIVITIES; PROPOSED ŁLECTION; COMMENT REQUEST; CHARACTER-SPACE-LIMITED ONLINE ŚCRIPTION DRUG COMMUNICATIONS, 81 Fed. Reg. 78,163 (Nov. 7, 2016).

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78. *Id.*

79. *Id.*

80. *Id.*

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Federal and State Regulation and Enforcement of Pharmaceutical Manufacturers' Advertising and Promotional Activity

Robert P. Reznick & Kathy O'Connor[1]

The U.S. Food and Drug Administration (FDA) is the agency in the U.S. Department of Health and Human Services (DHHS) responsible for assuring the safety and efficacy of human and veterinary drugs, medical devices, biological products, most food products, cosmetics, and products that emit radiation. In order to fulfill its role, FDA monitors the sale and manufacture of these products. FDA became known by its current name in 1930. The agency's origin goes back to 1848, when a single individual in the U.S. Department of Agriculture conducted chemical analyses of agricultural products.[2] Today, FDA is a global organization[3] with an annual budget of approximately $1 billion.[4]

FDA derives its oversight authority from the Food, Drug, and Cosmetic Act (FDCA),[5] legislation that originally was passed by Congress in 1938 after an untested pharmaceutical killed over 100 individuals. The FDCA provides FDA with the substantive framework to monitor the safety and efficacy of products. It also provides FDA with some enforcement tools. Specifically, the FDCA includes information regarding the approval process for drugs and medical devices, standards for factory inspections, and civil and criminal penalties for noncompliant manufacturers. Since the passage of the law, the FDCA has been amended numerous times. For example, the FDCA was amended in 1997 by the FDA Modernization Act,[6] which created a fast track approval process for drugs intended for serious diseases and expanded FDA's authority for over-the-counter drugs, among other changes.

This chapter primarily will focus on two specific activities undertaken by pharmaceutical manufacturers that are regulated by FDA—promotion and advertising. This chapter also will discuss how various federal and state authorities regulate the promotion and advertising of pharmaceutical products, independently and collaboratively.

As the reader will see, both the number and size of settlements by pharmaceutical manufacturers demonstrate the power of the enforcement tools available to government regulators. These agencies have promised to use these tools aggressively. Increased coordination between and among the federal and state agencies further enhance their investigatory and enforcement powers. Pharmaceutical manufacturers must fight back in the form of an effective corporate compliance program designed to ensure that advertising and promotional activities conducted by the pharmaceutical manufacturer are consistent with federal and state laws.

Basics of Pharmaceutical Advertising and Promotion Regulation

Definition of "Promotion" and "Advertising" by a Pharmaceutical Manufacturer

Q 5.1 What is "promotion" and "advertising" by a pharmaceutical manufacturer?

Lawful promotion and advertising of a drug by a pharmaceutical manufacturer are dependent on the content of the drug's "label," a term defined in the FDCA as "a display of written, printed, or graphic matter upon the immediate container of any article."[7] FDA does not approve drugs for universal use; rather, it approves them for one or more specific uses for which safety and efficacy have been demonstrated through clinical research.

Labeling is an important concept for several reasons. For example, "misbranding" occurs when a manufacturer makes a claim that is inconsistent with a product's labeling. The FDCA describes many activities that constitute misbranding, including: (i) a false or misleading drug label; (ii) a drug's package does not contain a label with certain required information about the drug and the manufacturer; (iii) required information does not contain sufficiently prominent placement in the label; (iv) a drug's label does not contain its name and the quantity of each active ingredient; or (v) the label contains inadequate directions for use or an inadequate warning regarding pathological conditions, use in children, or unsafe dosage, methods or duration of administration or applications.[8]

Additionally, labeling is an important concept as it relates to promotional activity by a pharmaceutical manufacturer. A pharmaceutical manufacturer may promote a product only for the use(s) contained within the drug's label that have been approved by FDA. Promotion of a pharmaceutical product for a purpose other than that which is specifically included in its label is "off-label promotion," a practice prohibited by the FDCA. This restriction exists to prevent the promotion of drugs for uses that have either been deemed unsafe or ineffective, or that have not been sufficiently examined by FDA. However, it is important to note that this restriction applies only to the promotion of a pharmaceutical product. Because FDA does not have the legal authority to regulate the practice of medicine, healthcare providers may prescribe a drug for an off-label use without violating the FDCA.

FDA also regulates the advertisement of prescription drugs.[9] Although FDCA does not define "advertisement," FDA differentiates advertisements from labels by stating that advertisements are "in published journals, magazines, other periodicals, and newspapers, and . . . broadcast through media."[10] Generally, every advertisement for an approved drug must state at least one approved use for the drug, the drug's generic name, and risks associated with the product's use.[11] Advertisements must be fair, balanced, and not contain

claims that are unsupported by adequate evidence.[12]

Regulating Federal Agencies

Generally

Q 5.2 Which federal agencies regulate pharmaceutical advertising and promotion?

FDA, Federal Trade Commission (FTC), Department of Justice (DOJ), and DHHS Office of Inspector General (OIG) each have responsibility for regulating advertising and promotional activities conducted by pharmaceutical manufacturers.

Food and Drug Administration

Q 5.3 Which offices and centers within FDA regulate pharmaceutical advertising and promotion?

FDA consists of the Office of the Commissioner and four directorates that oversee different core functions of the agency: Medical Products and Tobacco; Foods; Global Regulatory Operations and Policy; and Operations.[13] Each of these directorates presides over various offices and centers.

One prominent center organizationally located within the Medical Products and Tobacco directorate is the Center for Drug Evaluation and Research (CDER), which regulates over-the-counter and prescription drugs.[14] Specifically, CDER evaluates all new drugs before they are available to consumers and ensures that drugs already on the market continue to meet safety and efficacy standards. CDER describes itself as a "consumer watchdog" that tests and restricts drugs in order to protect individuals, and that also provides both doctors and patients with important information about drugs.[15]

Another relevant office is the Office of Prescription Drug Promotion (OPDP).[16] OPDP's mission is to protect the public health by assuring that prescription drug information provided by pharmaceutical manufacturers to healthcare professionals and consumers is truthful, balanced, and accurate. OPDP seeks to accomplish this mission through "a comprehensive surveillance, enforcement, and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers."[17]

One key activity undertaken by OPDP is the review and analysis of prescription drug advertising and promotional labeling to ensure that the information contained therein is neither false nor misleading in any respect. OPDP reviews materials independently, receives submissions for review and comment from pharmaceutical companies directly, and reviews complaints from the public about potentially problematic materials.

Q 5.4 Does FDA provide guidance to pharmaceutical manufacturers

regarding appropriate advertising and promotion?

Yes, FDA issues Guidance Documents to pharmaceutical manufacturers regarding appropriate activities. Although Guidance Documents neither bind FDA nor the public, they communicate FDA's current thinking on specific subjects. A comprehensive list of Guidance Documents issued by FDA are available on FDA's website, at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

One such Guidance Document issued by FDA in 2014 was a revised draft guidance document titled, "Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices."[18] This revised draft Guidance Document summarizes the FDA's recommended practices for distributing scientific or medical journal articles, reference texts, or clinical practice guidelines that discuss unapproved new uses for approved drugs marketed in the United States to healthcare professionals or entities. In 2017, FDA issued a Guidance titled, "Product Name Placement, Size, and Prominence in Promotional Labeling and Advertisement" to address formatting issues made more complicated by the proliferation of Internet promotion.[19]

Q 5.5 What type of enforcement activity does FDA take against pharmaceutical manufacturers for inappropriate advertising and promotion?

FDA has issued numerous Warning Letters to pharmaceutical manufacturers in recent years related to all types of problematic promotional materials and advertising, including direct-to-consumer advertising and social media.[20] In addition to a docket driven by routine instances of law enforcement, FDA increasingly is using warning letters to promote identifiable policy objectives, such as the fight against opioid abuse[21] and the illegal promotion of health benefits associated with marijuana use.[22]

Warning Letters issued by FDA and other violations of the FDCA have formed the basis for government investigations and settlements with pharmaceutical manufacturers. For example, in 2015, Inspire Pharmaceuticals, Inc. (Inspire) agreed to pay federal and state governments $5.9 million to settle civil allegations that it violated the FCA.[23] As part of the settlement, Inspire also admitted in court that it commenced an advertising campaign in 2008 designed to broaden the customer base for AzaSite by focusing on, among other things, AzaSite's claimed anti-inflammatory effects, a use not approved by FDA.[24] Referencing an April 2011 FDA letter that stated that certain advertisements for AzaSite were "false or misleading because it broadens the indication, makes unsubstantiated claims, and omits and minimizes important risks associated with the use of AzaSite,"[25] the complaint-in-intervention against Inspire alleges that "Inspire knowingly and actively promoted AzaSite as a safe and effective treatment for non-FDA approved uses in order to induce doctors to write prescriptions for non-FDA approved uses, causing Medicare, Medicaid and other federal healthcare programs to pay millions of dollars for uncovered claims."[26]

Federal Trade Commission

Q 5.6 What is the role of the Federal Trade Commission in regulating pharmaceutical advertising and promotion?

The FTC is a federal agency that seeks to protect and advance the interests of consumers.[27] The FTC was created in 1914 by the Federal Trade Commission Act (FTCA)[28] for the purpose of preventing unfair methods of competition. Its authority to police anticompetitive practices has expanded significantly since the enactment of the FTCA. As amended by the Wheeler-Lea Act of 1938,[29] the FTCA empowers the FTC to perform the following functions: "to (a) prevent unfair methods of competition, and unfair or deceptive acts or practices in or affecting commerce; (b) seek monetary redress and other relief for conduct injurious to consumers; (c) prescribe trade regulation rules defining with specificity acts or practices that are unfair or deceptive, and establishing requirements designed to prevent such acts or practices; (d) conduct investigations relating to the organization, business, practices, and management of entities engaged in commerce; and (e) make reports and legislative recommendations to Congress."[30]

Q 5.7 What powers are provided to the FTC to enforce the FTCA?

Three sections of the FTCA grant the FTC specific investigative powers.[31] The FTC relies on these powers when investigating the competitive practices of pharmaceutical companies and other businesses. Section 6 of the FTCA empowers the FTC to ask questions of businesses and organizations, and require them to file reports or answers in order for the FTC to discover information about them.[32] Section 6 also enables the FTC to publicize certain information obtained in a section 6 query where disclosure would serve the public interest,[33] a tool the FTC utilized when issuing its July 2002 report, "Generic Drug Entry Prior to Patent Expiration."[34]

Section 9 of the FTCA authorizes the FTC to "require by subpoena the attendance and testimony of witnesses and the production of all such documentary evidence relating to any matter under investigation."[35] Section 9 is often utilized by the Bureau of Competition to investigate alleged antitrust violations.

Additionally, section 20 of the FTCA authorizes the Bureau of Consumer Protection to use a civil investigative demand (CID) to investigate potential unfair practices.[36] Although section 9 subpoenas and section 20 CIDs may both be used to obtain existing documents or oral testimony, a CID also may require its recipient to file additional reports or answers.[37]

Q 5.8 Is there coordination between FDA and the FTC relevant to pharmaceutical advertising and promotion?

Because the FTC and FDA may both investigate pharmaceutical companies, the two agencies entered into a memorandum of understanding (MOU) in 1971 to describe the

authority of each agency, and to maximize efficiency and coordination between them.[38] For example, the MOU established that, except for prescription drugs, the FTC has primary responsibility for "the regulation of the truth or falsity of all advertising (other than labeling) of foods, drugs, devices, and cosmetics."[39] Similarly, the MOU provided primary responsibility to FDA for "preventing misbranding of foods, drugs, devices, and cosmetics shipped in interstate commerce," as well as "the regulation of the truth or falsity of prescription drug advertising" and "all matters regulating the labeling of food, drugs, devices, and cosmetics" in the absence of an arrangement between the two agencies to the contrary.[40]

The MOU also limited the situations in which both agencies could initiate proceedings involving the same parties to those in which "it is clear that the public interest requires two separate proceedings."[41] The document describes three such situations: (i) "[t]he same, or similar claims are found in both labeling and advertising"; (ii) "[w]ritten, printed or graphic material may be construed as either advertising or as accompanying labeling or both, depending upon the circumstances of distribution"; or (iii) "[t]he article is a drug or device and appears to be misbranded solely because of inadequacy of directions for use appearing in the labeling for conditions for which the article is offered in advertising generally disseminated to the public."[42]

Q 5.9 What enforcement activity has the FTC taken in recent years against pharmaceutical manufacturers relevant to advertising and promotion?

Like FDA, the FTC has exercised its authority over pharmaceutical companies in an effort to advance policy objectives and agency priorities, often following the consumer demand that drives illegal marketing. In 2017, for example, the FTC settled charges against parties making unsupported claims for opiate withdrawal treatments[43] and manufacturers and distributors of dietary supplements. Targets of these enforcement efforts included bogus weight loss products[44] and products sold via "fake" magazine and news websites,[45] thirty-minute radio ads formatted to sound like educational talk shows,[46] and ads styled as scientific journals.[47]

Department of Justice

Q 5.10 What is the role of the DOJ in regulating pharmaceutical advertising and promotion?

The DOJ is the federal agency that enforces the FDCA through its statutory authority granted by the False Claims Act (FCA).[48] The DOJ has two investigative branches: the U.S. Attorney General's Office and the Federal Bureau of Investigation (herein collectively referred to as "DOJ"). The DOJ has both civil and criminal prosecutorial authority over unlawful promotion.

Q 5.11 What is the Federal False Claims Act?

The DOJ enforces its civil authority through the FCA. The FCA provides that, those who knowingly submit, or cause another person or entity to submit, false claims for which payment may be made by a federal healthcare program[49] are liable for three times the government's damages plus inflation adjusted civil penalties that in 2017 were between $10,957 and $21,916.[50] The terms "knowing" and "knowingly" are defined as: (a) actual knowledge; (b) acts in deliberate ignorance of the truth or falsity of the information; or (c) acts in reckless disregard of the truth or falsity of the information.[51]

The DOJ also enforces its criminal authority using a variety of statutes,[52] including 18 U.S.C. § 287—*False, Fictitious and Fraudulent Claims*. Additionally, the federal Anti-Kickback Statute (AKS)[53] also may be enforced by the DOJ. The conviction of a criminal offense related to the delivery of an item under the Medicare or Medicaid program will result in a mandatory exclusion from federal healthcare programs for a minimum period of five years.

Q 5.12 What are the whistleblower provisions of the Federal False Claims Act?

The FCA has "qui tam" provisions that enable private citizens, known as "relators" or "whistleblowers," to file a case under seal on behalf of themselves and the government.[54] Because of the requirement that the whistleblower have independent knowledge regarding the conduct at issue, a whistleblower may be a current or former employee or customer of the pharmaceutical manufacturer defendant.

The whistleblower provisions of the FCA provide incentives for whistleblowers to file a case. Specifically, if the government decides to take over prosecution of a whistleblower's case, known as an intervention, the whistleblower receives 15% to 25% of the award or settlement. If the government declines to intervene in a whistleblower case, the whistleblower may proceed with that matter on his/her own and will receive 25% to 30% of any award or settlement.[55] To further encourage whistleblowers, the FCA protects whistleblowers from retaliation.[56]

Before the DOJ decides whether to intervene in a case filed by a whistleblower, the DOJ is given the opportunity to investigate the claims contained in the sealed complaint. The DOJ has investigatory powers under both criminal and civil statutes. For example, the DOJ may issue a CID to require a party to: (i) produce documents for inspection or copying, (ii) provide written answers to interrogatories relating to the documentary material; and/or (iii) give oral testimony regarding the documentary materials.[57] The DOJ also may issue a subpoena in a criminal matter, requesting witness testimony and/or production of documents.

The DOJ may request extensions of time from the court, resulting in investigations that last months or years before formal action is taken. During this investigatory period, the complaint remains under seal and is not served on the defendant pharmaceutical company

until ordered by the court.[58] A case filed under the FCA generally must be brought no later than six years after the violation was committed or no more than three years after the material facts were known or should have been known to the DOJ, whichever is later.[59]

Q 5.13 Is there coordination between FDA and the DOJ relevant to pharmaceutical advertising and promotion?

Because pharmaceutical manufacturers do not submit claims for payment of their products directly to Medicare, Medicaid or other federal healthcare programs, the DOJ prosecutes pharmaceutical manufacturers under the FCA based on an "indirect" liability theory. Specifically, a pharmaceutical manufacturer may only market or promote a drug for the approved uses specified in the product's FDA approved labeling. The DOJ argues that a pharmaceutical manufacturer that promotes its product for an off-label use in violation of the FDCA "causes" the filing of a false claim that may be reimbursed by a federal healthcare program.

FDA also may refer cases directly to the DOJ, particularly when FDA would like to use more than administrative enforcement.[60] Increased cooperation between these government agencies is expected as the federal government continues to make the prosecution of healthcare fraud a top priority.

In 2009, the DOJ and DHHS created the Health Care Fraud Prevention and Enforcement Action Team (HEAT), composed of officials from DOJ, DHHS, state Medicaid Fraud Control Units (MFCU) and local police agencies.[61] The mission of HEAT is to prevent, deter and prosecute healthcare fraud, waste, and abuse. Collectively, the HEAT team coordinates federal and state efforts in combating fraud in healthcare programs, and in 2017 announced that its efforts have resulted in the filing of almost 1,000 cases, and the sentencing of more than 1,200 defendants to prison terms of about forty-eight months.[62]

Q 5.14 What enforcement activity has the DOJ taken in recent years against pharmaceutical manufacturers relevant to advertising and promotion?

Recent examples of DOJ enforcement for off-label and related promotion practices have resulted in multi-billion dollar recoveries. The largest to date involved GlaxoSmithKline LLC (GSK), which in 2012 pled guilty to misbranding Paxil® and Wellbutrin®, and failing to report data to FDA regarding Avandia®.[63] GSK agreed to pay $3 billion in fines and penalties to resolve these allegations, the largest combined federal and state healthcare fraud recovery in a single global resolution in the United States to date. Among other things, the DOJ alleged that GSK promoted Paxil® and Wellbutrin® for uses not approved by FDA, paid kickbacks to healthcare professionals to induce them to prescribe these drugs, made false and misleading representations to healthcare professionals about Avandia's safety profile, and falsely reported drug prices.

In 2017, Celgene Corporation paid $280 million for alleged conduct including off-label

promotion of Revlimid® and Thalomid®;[64] and Aegerion Pharmaceuticals paid $28.2 million for criminal violations of federal marketing rules in connection with Juxtapid®.[65]

DHHS Office of Inspector General

Q 5.15 What is the role of the OIG in regulating pharmaceutical advertising and promotion?

The OIG enforces many of the federal laws and regulations enacted to combat fraud and abuse in the healthcare industry. The OIG derives significant authority from the Inspector General Act,[66] which created the OIG and granted it the authority to prevent and detect fraud and abuse in Medicare and Medicaid programs. This agency has considerable power, including the ability to investigate fraud; issue subpoenas;[67] impose civil monetary penalties under the Civil Monetary Penalties Law,[68] the federal AKS[69] and the federal FCA;[70] exclude individuals and entities from participation in federal healthcare programs; and negotiate CIAs.[71] Because the OIG is an administrative agency, it does not have the power to bring criminal prosecutions. The OIG may refer cases to the DOJ for criminal action, although the decision to prosecute is in the sole discretion of the DOJ.

Q 5.16 Does the OIG provide guidance to pharmaceutical manufacturers regarding appropriate advertising and promotion?

Yes, the OIG issues Advisory Opinions[72] to pharmaceutical manufacturers that submit requests for advice, and publishes various guidance documents to highlight risk areas identified by the OIG. Advisory Opinions are legal opinions by the OIG regarding whether a proposed business arrangement violates federal healthcare law. Pharmaceutical manufacturers may request an Advisory Opinion and the OIG's response is legally binding only between the requesting party and DHHS.[73] However, these Advisory Opinions often act as guidance for the industry by providing insight into the OIG's interpretation of various activities, including promotional activity.

The OIG also provides various guidance documents to assist pharmaceutical manufacturers in implementing internal controls and procedures that promote voluntary compliance with applicable federal statutes and regulations. For example, the OIG's "Compliance Program Guidance for Pharmaceutical Manufacturers"[74] establishes the seven elements of an effective corporate compliance program and highlights risk areas that may be violative of applicable federal statutes and regulations. The OIG also publishes an annual Work Plan that identifies areas of interest to, and activities to be undertaken by, the OIG.[75]

The OIG also issues Special Fraud Alerts, Special Advisory Bulletins and other guidance documents.[76] Special Fraud Alerts provide guidance on specific instances of risk that the OIG has identified or otherwise highlights significant regulatory changes or practices. OIG Special Advisory Bulletins provide guidance on broad statutes, and other guidance

documents issued by the OIG provide guidance on a variety of issues or statutes that may be of importance to the healthcare industry.

Q 5.17 May a pharmaceutical manufacturer report potential noncompliance to the OIG?

Yes. The OIG developed the Provider Self-Disclosure Protocol for pharmaceutical manufacturers and other providers "who wish to voluntarily disclose self-discovered evidence of potential fraud to [the] OIG . . . Self-disclosure gives providers the opportunity to avoid the costs and disruptions associated with a government-directed investigation and civil or administrative litigation."[77] In order to be accepted into the Self-Disclosure Protocol, a pharmaceutical manufacturer must submit an initial disclosure to the OIG.[78] The initial disclosure should include information related to the potential fraud identified by the manufacturer during its review. The initial disclosure generally includes the following information:

1. Name, address, type of healthcare provider, provider identification number(s), and tax identification number(s) of the disclosing party and the government payors to which the disclosing party submits claims or a statement that the disclosing party does not submit claims.
2. If the disclosing party is an entity owned or controlled by or otherwise part of a system or network, then an organizational chart, a description or diagram describing the pertinent relationships; the names and addresses of any related entities; and any affected corporate divisions, departments, or branches.
3. Name, street address, phone number, and email address of the disclosing party's designated representative for purposes of the voluntary disclosure.
4. A concise statement of all details relevant to the conduct disclosed, including, at minimum, the types of claims, transactions, or other conduct giving rise to the matter; the period during which the conduct occurred; and the names of entities and individuals believed to be implicated, including an explanation of their roles in the matter.
5. A statement of the federal criminal, civil, or administrative laws that are potentially violated by the disclosed conduct.
6. The federal healthcare programs affected by the disclosed conduct.
7. An estimate of the damages to each federal healthcare program relevant to the disclosed conduct, or a certification that the estimate will be completed and submitted to OIG within ninety days of the date of submission.
8. Description of the disclosing party's corrective action upon discovery of the conduct.

9. A statement of whether the disclosing party has knowledge that the matter is under current inquiry by a government agency or contractor.

10. Name of an individual authorized to enter into a settlement agreement on behalf of the disclosing party.

11. Certification by the disclosing party stating that to the best of the individual's knowledge, the submission contains truthful information and is based on a good faith effort to bring the matter to the government's attention for the purpose of resolving potential liability to the government and to assist OIG in its resolution of the disclosed matter.[79]

The OIG will then determine whether to accept the pharmaceutical manufacturer into the Self-Disclosure Protocol and verify the information provided by the manufacturer.

Pharmaceutical manufacturers that make a voluntary disclosure to the OIG may avoid criminal prosecution and/or a CIA. The voluntary disclosure also is a mitigating factor considered when fines and penalties are being assessed. However, voluntary disclosure will not insulate the manufacturer from civil or criminal action by the government.

Q 5.18 Is there coordination between FDA, DOJ, and OIG relevant to pharmaceutical advertising and promotion?

Yes. There are several MOUs between FDA and OIG.[80] FDA and OIG also are administrative agencies with some investigatory powers that may be used to gather information regarding a pharmaceutical manufacturer. These agencies may then refer a matter to the DOJ for civil and/or criminal enforcement. Further, the OIG coordinates with the DOJ through various collaborative taskforces.

Q 5.19 What types of enforcement activity are available to the OIG?

The OIG has the two administrative powers that it uses to enforce compliance with federal laws and regulations: (i) the authority to exclude individuals and entities from participating in any federal healthcare program; and (ii) CIAs.

Q 5.19.1 What is the OIG administrative power to exclude individuals or entities?

The OIG's most powerful administrative penalty is the authority to exclude individuals or entities from participation in any federal healthcare programs.[81] The effect of OIG exclusion from participation in any federal healthcare programs is that no federal healthcare program payment may be made for any item or service: (i) furnished by an excluded individual or entity; or (ii) directed or prescribed by an excluded physician.[82]

The OIG may exclude an individual or entity for several reasons including, but not limited to, an individual's or entity's: (i) criminal conviction related to a federal healthcare program; (ii) felony and misdemeanor convictions related to healthcare fraud generally; (iii)

conviction of fraud related to a non–healthcare program; and (iv) participation in any conduct that is prohibited by federal healthcare laws and regulations, such as off-label promotion.[83] OIG exclusion may be mandatory or permissive based on the circumstances. There are five instances that trigger mandatory exclusion: (i) criminal conviction related to Medicare and Medicaid programs or other state healthcare programs;[84] (ii) conviction relating to patient abuse or neglect;[85] (iii) felony conviction related to healthcare fraud, theft, or other financial misconduct;[86] (iv) felony conviction related to unlawful manufacture, distribution, prescription, or dispensing of a controlled substance;[87] and (v) failure to enter into an agreement to repay or default on a health education assistance loan.[88] The length of the mandatory exclusion is five years, but it may be lengthened if aggregating factors exist.

Permissive exclusion is triggered by other forms of misconduct, such as misdemeanor criminal convictions, licensing violations and false claims submissions. The length of permissive exclusion depends on the offense, and the OIG has discretion to lengthen, shorten or waive the exclusion period. If the OIG intends to exclude an entity or individual, it first issues a "Notice of Intent to Exclude." All OIG exclusions may be appealed to a DHHS administrative law judge, and then appealed to the DHHS Departmental Appeals Board (DAB).[89] Judicial review in federal court also is available after a final decision from the DAB. The OIG maintains a list of entities or individuals that have been excluded that is available publicly on the OIG's website at http://oig.hhs.gov/exclusions/index.asp.

Q 5.19.2 What is a CIA and what does it require?

The CIA is a contract between the OIG and a pharmaceutical manufacturer, usually entered into at the time of a settlement. The CIA provides that the OIG will not exercise its exclusion authority if the pharmaceutical manufacturer complies with the terms of the CIA. The CIA imposes significant compliance obligations on the pharmaceutical manufacturer, typically for a period of five years. The CIA generally instructs the pharmaceutical manufacturer to take, among other things, the following actions:

- Hire a compliance officer and appoint a compliance committee;
- Develop written standards and policies related to the sale and marketing of the pharmaceutical manufacturer's products;
- Implement a comprehensive employee training program related to the company's compliance program and the sale and marketing of the pharmaceutical manufacturer's products;
- Establish a confidential disclosure program, which provides a method for vendors and employees to confidentially report to the pharmaceutical manufacturer any potential non-compliance with laws or company policies;
- Restrict employment of ineligible persons;[90]

- Engage an independent review organization to conduct audits on specific risk areas set forth in the CIA; and
- Submit a variety of reports to the OIG, including annual reports about compliance activities and certain investigations or legal proceedings.[91]

More recent CIAs between the OIG and pharmaceutical manufacturers have included additional compliance requirements, such as certifications of compliance by employees, chief compliance officers and/or board of directors; board of director oversight of the corporate compliance program; public disclosure of certain payments and other transfers of value provided to healthcare providers; audits of specific high-risk areas and/or implementation of an executive financial recoupment program.[92]

Regulating State Agencies

Generally

Q 5.20 Which state agencies regulate pharmaceutical advertising and promotion?

State attorneys general ("state AGs") and state MFCUs each have responsibility for regulating advertising and promotional activities conducted by pharmaceutical manufacturers.

State Attorneys General

Q 5.21 What is the role of state attorneys general in regulating pharmaceutical advertising and promotion?

The state AGs are charged with safeguarding the public by enforcing state laws and bringing civil suits on behalf of their citizens. Historically, state AGs have predominantly enforced regulations in the area of consumer protection. Expanding on this mandate, today state AGs have become another tool in combating healthcare fraud and abuse, including improper advertising and promotion by pharmaceutical manufacturers. In this regard, key focus areas for state AGs have included promotion of off-label uses for pharmaceutical drugs; deceptive drug clinical trial, efficacy and/or risk information provided to consumers; and marketing, payments and other gifts provided by pharmaceutical manufacturers to healthcare providers.

Many of the recent pharmaceutical settlements have resulted from collaborations between state AGs working in "multistate executive committees" or "multistate working groups." Each state involved in the collaboration then shares in a portion of the recovery. However, enforcement activity by state AGs has not been limited to monetary penalties. For example, state AGs may require pharmaceutical companies to change problematic practices; disclose deceptive advertising campaigns; and/or comply with state required punitive and injunctive activities.

Additionally, every state has some form of consumer protection statute that aims to protect the public's health, safety and welfare. While these statutes vary widely in scope, some state consumer protection statutes, referred to as "Little FTC Acts," closely mirror the language of section 5 of the FTCA.[93] Most state consumer protection units are divisions within the state AG Office, thus giving state AGs the power to enforce these consumer protection laws. Other government agencies and private citizens, suing in the name of the state AG, also may bring suit under these statutes in some states.

Combating misleading, deceptive and fraudulent pharmaceutical advertising and promotion through state consumer protection statutes is attractive for states because of the

civil damage provisions available in some states, including treble and punitive damages and attorneys' fees. States also may join forces in these consumer protection cases, leading to significant settlements.

Q 5.22 How do state attorneys general coordinate with federal enforcement authorities related to pharmaceutical advertising and promotion?

State AGs may work closely with federal enforcement agencies, occasionally taking the lead. States often join federally led investigations and work closely with federal agencies to pursue pharmaceutical companies for violations of federal and state laws, in exchange for a share in any recovery.[94]

Q 5.23 What enforcement activity have state attorneys general taken in recent years against pharmaceutical manufacturers relevant to advertising and promotion?

In 2014, Organon USA Inc. agreed to pay $31 million to settle allegations from New York, Kentucky, and several other states, as well as the federal government, that the manufacturer underpaid Medicaid rebates, offered improper financial incentives to pharmacy companies, promoted products for unapproved uses, and misrepresented drug prices.[95] The settlement resulted from two whistleblower lawsuits.

Similarly, in 2015, the Oregon Attorney General reached a $1.1 million settlement and entered into an Assurance of Voluntary Compliance with Insys Therapeutics, Inc. ("Insys").[96] The state alleged that Insys, the manufacturer of the schedule II opioid drug Subsys®, marketed the drug in the state for off-label uses not approved by the FDA, such as pain associated with non-cancer back and neck pain; deceptively promoted Subsys for the treatment of mild pain; provided improper financial incentives to physicians in order to increase prescriptions; and targeted physicians for aggressive promotion who were not qualified to prescribe the drug.[97]

Medicaid Fraud Control Units

Q 5.24 What is the role of the Medicaid Fraud Control Units in regulating pharmaceutical advertising and promotion?

The MFCUs are state agencies created to investigate and prosecute Medicaid fraud.[98] MFCUs are staffed by attorneys, investigators, and auditors who focus exclusively on Medicaid fraud cases.[99] Each state, except North Dakota,[100] and the District of Columbia are required to have an MFCU.[101] Each state is entitled to a 75% Federal Financial Participation grant to operate the office, with the state matching the remaining 25%.[102] An MFCU must be established as a "single identifiable entity of the State government"[103] and "separate and distinct" from the state Medicaid agency to avoid conflicts of interest concerns.[104] Typically, the MFCUs are a part of the state AG Office, but an MFCU may

be housed in other state departments.[105] Each MFCU operates under the federal OIG,[106] and must be certified annually by the Secretary of DHHS.[107] The MFCUs may be represented in cases by the National Association of Medicaid Fraud Control Units (NAMFCU).[108]

Cases may be referred to the MFCU by the state Medicaid agency, other states and law enforcement agencies.[109] If a case is referred by the Medicaid agency, the MFCU must accept or decline the case in writing.[110] In FY 2016, the MFCUs recovered $1.9 billion as a result of civil and criminal cases, with 998 civil judgments and settlements and 1,564 criminal convictions.[111] Matters against pharmaceutical manufacturers that include the MFCUs generally relate to off-label promotion, physician kickbacks and "best price" issues.

Q 5.25 How do the Medicaid Fraud Control Units coordinate with federal enforcement authorities related to pharmaceutical advertising and promotion?

MFCUs regularly coordinate with federal agencies, including the DOJ, in global settlements. When the DOJ negotiates a potential settlement with a pharmaceutical manufacturer, it will consult with the NAMFCU, which will then appoint a settlement team to assist the DOJ in completing the settlement.[112] By statute, each MFCU is required to share information and coordinate with federal agencies in "investigations and prosecutions involving the same suspects or allegations" in fraud cases.[113] Coordination between the state MFCUs and federal agencies is important because the federal government cannot settle a case's Medicaid component without the state MFCU.[114] Additionally, defense counsel will require state consent to any potential settlement to avoid a subsequent action by the state.[115]

Q 5.26 What enforcement activity have the Medicaid Fraud Control Units taken in recent years against pharmaceutical manufacturers relevant to advertising and promotion?

MFCUs frequently participate in settlements involving pharmaceutical manufacturers. For example, Astellas Pharma US Inc. ("Astellas") agreed to pay $7.3 million to resolve FCA allegations related to its marketing of Mycamine® in 2014. The federal government and the NAMFCU, acting on behalf of the states, alleged that Astellas knowingly marketed and promoted the sale of Mycamine for pediatric use, which was not a medically accepted indication and, therefore, not covered by federal healthcare programs.[116]

Expansion of Federal Law

Q 5.27 How did the Fraud Enforcement and Recovery Act of 2009 (FERA)[117] impact the regulation of pharmaceutical advertising and promotion?

The enactment of FERA increased funding to enforcement agencies and expanded the reach of the civil FCA, enhancing one of the key enforcement tools used against pharmaceutical manufacturers. Most notably, FERA amended the intent standard of the FCA, requiring only that a false record be "material to" a fraudulent claim in order to trigger liability. FERA defined material as "having a natural tendency to influence, or be capable of influencing, the payment or receipt of money or property"[118] and a "claim" was revised to include any request or demand made to a contractor, grantee or other recipient if the money or property is to be spent or used on the government's behalf.[119]

FERA also increased the coordination between federal and local governments by permitting the government to share information obtained during an investigation with qui tam relators and other local government agencies. If the government intervenes in a whistleblower complaint, FERA allows the government's amended complaint to relate back to the date when the qui tam complaint was filed.[120]

Q 5.28 How did the Patient Protection and Affordable Care Act (PPACA)[121] impact the regulation of pharmaceutical advertising and promotion?

When PPACA was enacted in March 2010, it further broadened FERA and the federal FCA. PPACA amended the FCA to provide that a violation of the federal AKS constitutes a fraudulent act under the FCA.[122] PPACA also amended the intent requirement of the AKS, providing that "with respect to violations of [the AKS] a person need not have actual knowledge of the [AKS] or specific intent to commit a violation of this section."[123]

Additionally, PPACA made significant changes to the "public disclosure" bar of the FCA. PPACA now authorizes a person to qualify as an "original source" in a whistleblower action if the person "has knowledge that is independent of and materially adds to the publicly disclosed allegations or transitions . . . ."[124] PPACA also provides that a public disclosure resulting from a government report, hearing, audit or investigation must be from a federal government source in order to bar the relator's claim. Public disclosures in state or local government reports or proceedings will not trigger the jurisdictional bar.

Further, section 6002 of PPACA required manufacturers to report annually to the Centers for Medicare & Medicaid Services (CMS) certain payments and other transfers of value provided to physicians and teaching hospitals and physician ownership and

investment interests. CMS adopted a final rule in 2013 implementing section 6002 of PPACA.[125] The information reported each year is made publicly available by CMS.[126]

Compliance Considerations and Better Practices for Pharmaceutical Manufacturers

Q 5.29 What are some compliance considerations and better practices for pharmaceutical manufacturers relevant to promotional and advertising activities?

Pharmaceutical manufacturers are facing significant challenges related to the advertising and promotion of their products. Federal and state governments are both increasingly active in the fight against fraud, waste and abuse in the healthcare industry. One way to reduce exposure to enforcement activity is for pharmaceutical manufacturers to establish an effective corporate compliance program designed to prevent, detect, and correct potential issues. Three aspects of an effective corporate compliance program directly related to promotional and advertising activities are (i) a code of conduct and other written policies and procedures; (ii) an advertising/promotional review committee; and (iii) monitoring and auditing activities.

Q 5.30 What are some compliance considerations and better practices related to the code of conduct and written policies and procedures?

Pharmaceutical manufacturers should develop and implement a Corporate Code of Conduct as one tool to foster compliance with federal and state laws and regulations. The Code of Conduct typically outlines general principles regarding compliance and ethics to govern the day-to-day activities of the company and its employees, contractors and agents.

Pharmaceutical manufacturers also should develop and implement a comprehensive suite of written policies and procedures related to all aspects of their business activities, including sales, marketing, promotional and advertising activities. These written standards should be designed to guide an employee in the performance of his/her duties related to compliance risk areas. Sources to identify such compliance risk areas include the OIG Compliance Program Guidance for Pharmaceutical Manufacturers; other OIG guidance documents; industry codes, such as the "Pharmaceutical Research and Manufacturers of America Code on Interactions with Healthcare Professionals"; industry guidelines, such as those provided by the American Medical Association and the Accreditation Council for Continuing Medical Education; and institutional policies and practices.

Training on the Code of Conduct and the company's policies and procedures should be provided to all new employees, as well as annual retraining for all employees. The company also should consider providing training to vendors and other agents responsible for key compliance risk areas.

Q 5.31 What are some compliance considerations and better practices related to advertising/promotional review?

Pharmaceutical companies should have an advertising/promotional review committee that is responsible for reviewing and approving advertisements, promotional materials, and other promotional activities, whether in print or electronic format. This includes, but is not limited to, promotional materials used by sales representatives during meetings with healthcare professionals, direct-to-consumer advertisements, and materials posted via social media. This review committee should be a cross-functional team that includes representatives from Legal, Regulatory, Medical and Marketing, among other possible business units. The advertising/promotional review committee should have a charter or similar document that outlines the roles and responsibilities of each committee member.

The role of the advertising/promotional review committee is to ensure that all advertising and promotional materials used by the company are appropriate and otherwise in compliance with federal and state laws and regulations. Key risk areas include claims related to unapproved or off-label uses of the product; minimizing risks and/or overstating benefits of a drug; and superiority, comparative or competitive claims. The advertising/promotional review committee should utilize FDA Warning Letters and similar guidance documents as tools to identify new and developing risks areas.

Q 5.32 What are some compliance considerations and better practices related to compliance monitoring and auditing activities?

Pharmaceutical manufacturers also should develop robust monitoring and auditing programs in an effort to detect and correct potential noncompliance. Such monitoring and auditing activities should include the review of policies, procedures, processes and/or practices related to key compliance risk areas, including promotional and advertising activities.

Pharmaceutical manufacturers should start by identifying compliance risk areas ripe for monitoring and/or auditing. Sources to identify such risk areas include settlement agreements, CIAs, securities filings, OIG work plans, OIG fraud alerts, public announcements by enforcement officials, and trade group publications and conferences.

Once risk areas are identified, the pharmaceutical company should develop a monitoring work plan for contemporaneous reviews and an auditing work plan for a "look back" at past activities. The company's compliance committee and/or the Board of Directors should review these work plans, as well as receive regular updates regarding the progress and findings of monitoring and auditing activities.

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1. This chapter was originally prepared by Wendy C. Goldstein and Sarah K. diFrancesca e law firm Cooley LLP. The chapter was revised and updated for this edition by Mr. ick and Ms. O'Connor.

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107. 42 C.F.R. § 1007.15.

108. NAMFCU, MFCUS, *supra* note 98.

109. NATIONAL ASSOCIATION OF MEDICAID FRAUD CONTROL UNITS, QUENTLY ASKED QUESTIONS [hereinafter NAMFCU, FAQs], .namfcu.net/about-us/about-mfcu.

110. 42 C.F.R. § 1007.9(g).

111. OFFICE OF THE INSPECTOR GENERAL, MEDICAID FRAUD CONTROL TS FISCAL YEAR 2014 ANNUAL REPORT, http://oig.hhs.gov/oei/reports/oei-09-17-0.pdf.

112. NAMFCU, FAQS, *supra* note 108 (NAMFCU settlement teams will consist of sentatives of three or four member states who will negotiate the settlement on behalf of all e states that are a part of the NAMFCU).

113. 42 C.F.R. § 1007.11(e) ("the unit will make available to Federal investigators or cutors all information in its possession concerning fraud in the provision or administration edical assistance under the State plan and will cooperate with such officials in coordinating ederal and State investigations or prosecutions involving the same suspects or allegations").

114. NAMFCU, FAQS, *supra* note 108.

115. *Id.*

116. Press Release, Dep't of Justice, Astellas Pharma US Inc. Pays $7.3 Million to Resolve Claims Act Allegations Relating to Marketing of Drug Mycamine (July 11, 2014), .justice.gov/opa/pr/astellas-pharma-us-inc-pay-73-million-resolve-false-claims-act-tions-relating-marketing.

117. Fraud Enforcement and Recovery Act (FERA), Pub. L. No. 111-21 (2009) (codified as ded in scattered sections of 31 U.S.C.).

118. *See* FERA § 4123.

119. *Id.*

120. *Id.*

121. Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148, 124 Stat. 2010) (codified as amended in scattered sections of 42 U.S.C.).

122. PPACA § 6402(f)(1); 42 U.S.C. § 1320a-7b.

123. *Id.*

124. PPACA § 10104(j)(2); 31 U.S.C. § 3730.

125. Centers for Medicare & Medicaid Services, Medicare, Medicaid, Children's Health
ance Programs; Transparency Reports and Reporting of Physician Ownership or
tment Interests, 78 Fed. Reg. 9458 (Feb. 8, 2013),
.cms.gov/OpenPayments/Downloads/Affordable-Care-Act-Section-6002-Final-Rule.pdf.

126. *See* OPENPAYMENTDATA.CMS.GOV, https://openpaymentsdata.cms.gov/.

Regulatory and Compliance Implications of Disseminating Medical Information and the Distinction with Off-Label Promotion

Howard L. Dorfman

No issue relating to the U.S. Food and Drug Administration (FDA) regulatory practice has presented greater challenges for the pharmaceutical industry and invited more intensive government oversight than the implications arising from allegations that a pharmaceutical company's dissemination of accurate and non-misleading scientific and medical information constitutes promotion of its prescription drugs for indications outside of FDA-approved product labeling—a practice commonly referred to as "off-label" promotion. Regulatory and compliance concerns over such activities off-label promotions have prompted an increasing number of investigations by FDA as well as state and federal government bodies and agencies such as the Office of Inspector General of the Department of Health and Human Services (OIG), the Department of Justice (DOJ), and various state attorneys general.

In preparing to address compliance obligations arising from allegations of off-label promotion, the pharmaceutical manufacturer must be cognizant of and familiar with the key regulatory statutes, regulations, and guidance documents; OIG pronouncements; industry codes; and the elements that gave rise to investigations that resulted in the imposition of regulatory requirements mandated as part of the Corporate Integrity Agreements (CIAs) entered into between manufacturers and the government in settlement of litigation arising from alleged violations of law.

The following chapter will review the above statutory bases upon which oversight of promotional activities is founded, and the regulatory framework relied upon by the various government bodies that seek to investigate and act upon allegations of off-label promotion by pharmaceutical manufacturers. The chapter will also look at the development and impact of FDA Guidance for Industry relating to the promotional use of social media, as well as provide an analysis of industry activities associated with the dissemination of scientific and medical information mischaracterized as off-label promotion, and the processes and procedures required to reduce potential regulatory and

compliance exposure when engaged in legitimate scientific exchange with healthcare professionals.

Statutory Basis for FDA and Government Oversight

Q 6.1 What is the statutory basis for government action against pharmaceutical manufacturers involving allegations of off-label promotion?

The foundation for FDA and related government oversight with regard to the issue of promotion of approved pharmaceuticals beyond those indications approved by the agency is based upon the various Food, Drug, and Cosmetic Act (FDCA) regulatory requirements pertaining to the drug review and approval process. Through the development of various regulations governing the approval and commercialization of drugs, FDA established a barrier to market entry for compounds lacking "substantial evidence" of both safety and efficacy.

To obtain FDA approval for a drug to be marketed in interstate commerce, a manufacturer must demonstrate that its product is safe and effective for each of its intended uses.[1] That requirement is addressed by having the sponsor provide, at minimum, data and results from "two adequate and well-controlled" clinical trials in support of those indications for which approval is requested. In addition, the manufacturer is required to submit proposed labeling that reflects the relevant safety and efficacy information applicable to those indications. It is important to note that the approved "intended" use thereafter becomes a key element of the product's labeling and establishes the parameters of both final approval and the scope of promotional activity.

Further clarification of FDA's authority is found in the statutory framework relative to the concept of misbranding. A drug is misbranded if its labeling is "false or misleading in any particular."[2] In light of the expansive characterization of labeling to include all labels and other written, printed, or graphic matter that appears on any drug product or on any of its containers or wrappers as well as any material accompanying the drug, the inclusion of information regarding an unapproved use would subject the manufacturer to government action that can include seizure and civil and criminal prosecution as a violation of the FDCA. The Office of Prescription Drug Promotion (OPDP), formerly the Division of Drug Marketing, Advertising and Communications (DDMAC), relies on this statutory authority in their review of all advertising and promotional materials in taking administrative action against drug manufacturers in the form of Notice of Violation (NOV) and Warning Letters issued for the use of materials that are ". . . misleading if they suggest that a drug is useful in a broader range of conditions or patients that has been demonstrated by substantial evidence or substantial clinical experience." DDMAC refers to such conduct as "broadening the indication" of the drug, which translates to utilizing off-label information in the promotional process.

Recent changes to the law suggest a continuing reliance on the statute as a basis for government prosecutions arising from alleged off-label promotion, and will likely have a

significant impact on government investigators, pharmaceutical manufacturers, and private litigants ("whistleblowers"/qui tam parties) that will directly supplement the FDA regulatory process. By way of example, the amendment to the FCA regarding Civil Investigative Demands (CIDs) in 2009 allows the government to request and obtain a wide range of documents for inspection and copying, obtain answers to written interrogatories and oral testimony, and any combination that may be relevant to potential FDCA violations.[3] In addition, the U.S. Attorney General no longer is required to authorize requests for CIDs in advance and local Department of Justice (DOJ) prosecutors are permitted to share the information obtained with qui tam relators, thereby increasing expedited access to materials perceived to be relevant to allegations of off-label promotional activities.

Q 6.2 Are there other statutes that implicate illegal off-label promotion?

In addition to the FDCA, there are additional major statutes that have been relied upon extensively by federal (and under particular circumstances, state) prosecutors in support of actions brought against pharmaceutical companies arising from allegations of off-label promotion. Those most frequently cited are the federal Anti-Kickback Statute (AKS) and the federal False Claims Act.[4]

The federal AKS states that it is a felony to ". . . offer, pay, solicit or receive any remuneration in return for referring an individual to a person for the furnishing of an item or service, or purchasing, leasing, ordering . . . any good, facility, service or item, for which a federal health care program may pay." Penalties for violation of the statute may include fines, imprisonment, civil monetary penalties and, of greatest concern for the pharmaceutical manufacturer, "exclusion from the Medicare, Medicaid and/or other Federal or state health care programs." A review of charging documents and the resulting Corporate Integrity Agreements (CIAs) provide guidance as to conduct that may trigger an investigation and serve as a basis of prosecution under the statute. They include:

- Likelihood of increased costs incurred by government reimbursement processes;
- Likelihood of "overutilization" or other inappropriate use of a manufacturer's product; and
- Likelihood of increased concerns involving patient safety and/or inappropriate interference with a healthcare provider's clinical judgment.

The second and most frequently utilized statute relied upon by prosecutors, particularly in the context of possible off-label promotion, remains the federal civil False Claims Act (FCA).[5] The FCA generally prohibits "any person from knowingly presenting (or causing to be presented) a claim for payment or approval to the Federal government that is false or fraudulent."[6] Penalties include imposition of civil monetary fines for each act constituting a "false claim" and the availability of treble damages.

There are state statutes in place patterned on the federal FCA that serve as an additional basis for state action against pharmaceutical manufacturers, and that are often used in

conjunction with other state regulations, such as consumer protection laws. A major impetus for the passage and implementation of state FCA legislation are the added financial incentives and increased recovery amounts available in those jurisdictions that have such laws. The OIG, in consultation with the state Attorney General, determine whether those state FCAs qualify for the incentive payments pursuant to section 1909 of the Social Security Act. If found to qualify, those regulations would entitle the state to a minimum ten percentage point increase in their share of any amounts recovered by the federal government.[7]

Off-Label Activities

Q 6.3 What is the impact of standards of medical practice on the manufacturer's dissemination of medical and scientific information relating to indications not reflected in a product's approved product labeling?

Any evaluation of the concept of off-label promotion must begin with an analysis of the underlying issues raised by standards of medical practice, government regulations that relate to off-label prescribing by healthcare professionals, as well as the recognized role of pharmaceutical companies in providing accurate, timely, and balanced medical information to the medical community.

It is important to understand the limitations imposed by the provisions of the FDCA, which does not expressly define either "promotion" or the concept of "scientific exchange." Regulations prohibit representing a drug under investigation pursuant to an IND or NDA "in a promotional context" but that prohibition is not intended "to restrict the full exchange of scientific information" concerning a drug, "including dissemination of scientific findings in scientific or lay media."[8]

The first part of the analysis is drawing the distinction between related, but independent concepts: off-label prescribing versus the dissemination of off-label, albeit scientifically recognized and accepted, information may be perceived as constituting active off-label promotion.

Q 6.4 What constitutes "Off-Label Prescribing"?

Off-label prescribing arises when a licensed healthcare provider prescribes a drug for an indication that does not appear in the FDA-approved product labeling. Off-label prescribing may also refer to the prescribing of a drug in dosages or in combination with other therapeutic options other than expressly stated in the product label.

Apart from standards of accepted medical practice, healthcare providers may lawfully prescribe FDA-approved drugs in any manner that is consistent with available scientific data—a concept recognized by the government.[9] FDA has no jurisdiction over the practice of medicine and "recognizes that once it approves a product for marketing, health care practitioners are the most important managers (of patient care) . . . and does not have the authority to control decisions made by qualified health care practitioners to prescribe products for conditions other than those described in the FDA-approved professional labeling . . . ."[10] In fact, in several therapeutic areas, such as oncology and psychiatry, utilization of FDA-approved drugs outside of the parameters of the label in terms of dosage, patient populations, indications, and in combination with other drugs, is considered the standard of accepted medical practice documented in treatment guidelines.

Q 6.5 What activities constitute dissemination of medically relevant and accurate scientific and medical information outside of approved labeling?

The process relative to dissemination of off-label information relates to the role played by pharmaceutical companies in providing truthful, balanced, and non-misleading medical and scientific information to healthcare providers in response to an unsolicited request. Both the medical community as well as FDA recognize that the company that developed the compound, undertook clinical trials, filed a marketing application in the form of a New Drug Application (NDA), committed to undertake post-approval (Phase IV) studies, as well as monitored the state of the medical literature and adverse event information, would be best suited to provide current medical information that, in the absence of FDA approval, may constitute the recognized standard of care in the diagnosis and treatment of disease. In this regard, authoritative clinical practice guidelines issued by recognized medical authorities (such as the American Society of Clinical Oncology (ASCO)) recommend treatment options that require utilization of drugs alone or in combination that are specifically contained in FDA-approved labeling. (Relevant to ASCO guidelines, Medicare is required to reimburse for prescribing prescription drugs for off-label indications if that use is listed in and recognized by approved Compendia such as the USP DI Oncology (Micromedex) or the AHFS DI.)

Q 6.6 What activities constitute "Off-Label Promotion"?

When examining industry activities that may be viewed by FDA, the DOJ, and/or state attorneys general as constituting off-label promotion and violating federal and state statutes and regulations, it is critical to examine all aspects of a company's activities, both from chronological (from initial product research development through the post-approval period) as well as functional (including research and development, marketing, sales, medical communication, public affairs, and Continuing Medical Education (CME)) activities. As reflected in FDA regulatory actions as well as DOJ charging documents, the full spectrum of industry practices have been scrutinized and relied upon as a basis for investigation, prosecution, and settlements that impose regulatory requirements.

By way of example, the following functional areas and subject matter present opportunities for allegations of off-label promotion and have frequently served as a basis for government action.

- *Pre-Approval Promotion of Investigational Products*. Broadly stated, there are few opportunities and methods by which pharmaceutical manufacturers may provide product-specific information that would not be scrutinized as potentially constituting pre-approval (and therefore off-label) promotion. While companies may elect to develop Institutional ads (reflecting a company's activities in a particular therapeutic area without any reference to product name or direct or inferred product indication or claims) or "Coming Soon" ads (which merely name the drug and company name without any claims, representations, or indications),

other activities have given rise to government action. While disclosure requirements imposed on companies listed on various stock exchanges may lead to the development of a press release, these vehicles are likewise viewed as sharing a promotional component. Therefore, while a release may provide data in the form of study results, drawing conclusions as to efficacy and safety for an unapproved product would most likely be viewed as a violation of FDCA and other related statutes.[11]

Regarding the issue of pre-approval promotion, recent OPDP enforcement activity has begun to focus on promotion of unapproved drugs rather than the traditional area of advertising. In 2016, at the end of an extremely quiet year for enforcement letters, OPDP issued two relating to pre-approval promotion.[12] One was issued regarding Remoxy ER, a long-acting abuse-deterrent formulation of oxycodone. The company, DURECT, posted a product webpage with specific efficacy claims. While the site mentioned that Remoxy ER was "in development," the FDA expressed the opinion that such language was insufficient to avoid FDA enforcement. The Remoxy ER letter came shortly after one issued to Celator Pharmaceuticals, a subsidiary of Jazz Pharmaceuticals, for active promotion of an investigational cancer drug at a booth at the annual meeting of the American Society for Clinical Oncology (ASCO). The booth presentation had made both safety and efficacy claims ("optimal anti-cancer activity") and claimed improved survival rates compared to other treatment options.

These letters suggest a new focus for FDA enforcement relating to activities deemed off-label promotion.

- *Advisory Boards, Consultants, and Speaker Bureaus*. Commercialization of an FDA-approved drug frequently includes identifying and retaining healthcare providers to serve in various capacities to provide research and expert input for use in developing relevant messaging to the medical community (Advisory Boards and Consultants) or as presenters of on-label product information to other practitioners as part of an institutional process. The relationship between the pharmaceutical industry and healthcare providers has been under intense scrutiny, which has intensified over the past decade, where the Office of Inspector General (OIG) of the Department of Health and Human Services (HHS) (in addition to members of Congress, medical institutions, and other interested parties) have identified these relationships as inherently susceptible to creating an inappropriate environment whereby clinical decision-making is impaired by industry remuneration to physicians and negatively impacting patient health as well as increasing healthcare costs and government reimbursement. The argument that these relationships serve as a conduit for the delivery of off-label product information by the company and thereafter result in inappropriate prescribing activity on the part of healthcare providers, has led to significantly greater attention

paid to these relationships, an increase in reporting and transparency requirements regarding retention of and payments made, as well as rigorous obligations contained in CIAs.

- *Continuing Medical Education*. The support of CME programming by pharmaceutical companies has been the subject of intense debate based upon the same arguments raised in the context of the overall relationship between industry and the healthcare community whereby payments made introduce a significant potential for bias. With regard to CME, which by its nature is designed to provide current and clinically relevant medical information irrespective of FDA approval for a product under discussion, concern with regard to its potential as a delivery system for off-label information has led to intense scrutiny and resulted in development of processes and procedures pursuant to internal industry guidance,[13] as well as medical institutions engaged in developing and presenting CME programs. Relying upon the "General Final Compliance Program Guidance for Pharmaceutical Manufacturers" issued by OIG in 2003, companies have been implementing the guidance that ". . . Manufacturers should separate their grant making functions from their sales and marketing functions . . . [as] effective separation of these functions will help insure that [CME] grant funding is not inappropriately influenced by sales or marketing motivations . . . ."
- *Posting Clinical Trial Results*. A relatively overlooked area for potential issues arising from allegations of off-label promotion involves the company's disclosure and dissemination of the results of clinical trials undertaken by a pharmaceutical manufacturer. This concern is heightened by the fact that many (if not a majority) of such clinical trials involve evaluation of a new compound or a new indication for a marketed drug, neither of which have gone through the rigors of the FDA review and approval process. The first initiative taken in this regard was a number of prosecutions in New York, by then-New York State Attorney General Eliot Spitzer, against several drug companies. The most prominent action involved allegations that GlaxoSmithKline PLC (GSK) committed fraud by disseminating the results of several clinical trials on the use of Paxil® in children and adolescents while withholding other internal clinical data that suggested that such therapy in that patient population was neither effective nor safe. That action led to a settlement whereby GSK agreed to create a website to list clinical trial information on all its marketed drugs. As we discuss below, these activities were resurrected in the context of a subsequent DOJ prosecution that resulted in a $3 billion settlement and a CIA in 2012.

There can be additional circumstances that can be deemed off-label promotion by FDA that are frequently overlooked by companies in their review of marketing activity. In September 2013, FDA issued a Warning Letter[14] against Aegerion arising from the CEO (Marc Beer) having stated on CNBC's *Fast Money*, that Juxtapid®, a marketed company drug, was effective on cardiovascular morbidity and mortality. He further indicated that the

drug was effective as monotherapy. However, none of these claims were approved by FDA, and therefore do not appear in the approved product labeling. Aegerion was required to run corrective advertising on CNBC and conduct an internal review of Juxtapid® promotional materials for additional violative promotional messaging.

While the FDA regulatory action was resolved in 2014, DOJ issued a subpoena in late 2013 requesting documents and other materials relating to the company's promotion, marketing, and sales of the drug.

Q 6.6.1 What are the regulatory implications for companies in the disclosure of clinical trial results?

The requirement that companies disclose clinical trial results, albeit in a non-promotional form, has been addressed by the federal government, various states, as well as by PhRMA (the prescription pharmaceutical industry trade organization). On July 15, 2009, FDA released a "Draft Guidance for Industry—Postmarketing Studies and Clinical Trials—Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act,"[15] which provides additional context and implementation guidance pertaining to the clinical trial posting requirements found in the provisions of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The posting and disclosure provisions of FDAAA will be supplemented by a requirement on the part of pharmaceutical manufacturer websites to prepare and post summaries of the results of the clinical trials completed. While implementation of this latter provision has yet to be undertaken and specific guidance as to the appropriate format and content has yet to be issued, the opportunity to post such information on publicly accessible websites relating to non-FDA reviewed and approved information presents significant challenges, as well as the need to develop internal company policies and procedures with regard to drafting, review, and use to address the risks of claims of engaging in off-label promotion.

Social Media and Off-Label Promotion

FDA Case-by-Case Evaluation and Industry-Created Practices

Q 6.7 What is the impact of social media on off-label promotion?

Just as the approval process involved in FDA-regulated labeling is hard-pressed to keep pace with the release of scientific information and clinical trial data reflecting the ongoing evolution of standards of medical practice, so too has the means of dissemination of medical information to healthcare professionals and to the lay public changed with dramatic speed. Regarding physicians, Sermo®, the largest online network for healthcare providers (HCPs), provides a venue for over 125,000 physicians to exchange opinions regarding drug therapy, utilization of medical devices, and clinical issues. However, due to the extensive regulatory scheme in place regarding dissemination of product information, no comparable forum exists for pharmaceuticals.

FDA's initial foray into the issue came in 1996 when the agency convened a series of public meetings on the issue of advertising and promotion on the Internet, ostensibly to help develop clear guidance to manufacturers on the appropriate method of promoting their products, while avoiding regulatory action. Notwithstanding several hints at a future release of such guidance, FDA informed the industry in 1999 that it would evaluate such issues on a "case-by-case" basis, while a decision whether separate Internet-related regulations would be reviewed at a later date.[16] Left to their own independent analysis of regulatory as well as compliance-related risks, pharmaceutical companies developed internal policies that took into account the practices utilized in the development, review, and approval of advertising and promotional materials designed for the more standard print and broadcast media.

In the absence of clear agency guidance, and given the differences between traditional media and the Internet platform, issues arose that required the development of non-traditional methods in the presentation of product information. An example can be seen in the method by which many in the industry addressed the requirement of providing FDA-mandated fair balance information in the form of access to Important Safety Information (ISI) in the context of their Internet advertising. In an effort to accommodate the space limitations of the Internet, companies felt compliant with FDA regulations as long as the visitor to the promotional site could retrieve the ISI and Full Prescribing Information directly (commonly referred to as the "One-Click Rule"). It was not until 2009 when the viability of that self-made rule was called into question by FDA; the agency issued a series of Untitled Letters to fourteen companies that used banner advertisements that appeared on Google and that failed to include the requisite safety information in immediate proximity to the ads in question. To FDA, the inclusion of the name and indication automatically triggered the requirement to include fair balance. The "One-Click Rule,"

FDA later stated, was an industry-created practice that had never been sanctioned or approved by FDA.[17]

FDA Draft Guidance (2011–2014)

Q 6.8 What guidance has FDA provided relating to the use of social media in a promotional context?

In November 1999, FDA convened a public hearing with the announced purpose of obtaining input from a wide range of sources, including representatives of the pharmaceutical industry, social media authorities, and patient advocacy groups, to assist the agency in developing guidance on the appropriate and compliant use of social media in the advertising and promotion of medical products.[18] Although the topic of "Promotion of Prescription Drug Products Using Social Media Tools" was ultimately dropped from FDA's 2010 Guidance Agenda, action was still anticipated during 2011.

Ultimately, FDA issued a draft guidance in December 2011 entitled, "Guidance for Industry—Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices" (the "Draft Guidance").[19] As the title suggests, the Draft Guidance has a somewhat narrower scope than providing a definitive clarification of FDA's regulatory scheme relating to the use of social media in a promotional context. Discussion of the Internet and other forms of social media are, instead, referenced as examples in providing clarification on the appropriate methods for medical product manufacturers, and distributors can respond to unsolicited requests for information regarding unapproved indications or conditions of use ("off-label") for pharmaceuticals and medical devices. The fact that the Draft Guidance is referred to as the first of the expected series of advisories relating to the use of social media stems from the utilization of various popular forms of social media communication to illustrate the primary objective of providing a narrow definition and construction of what constitutes a truly unsolicited request for off-label information. The Draft Guidance indicates that if the company would follow the approach outlined, FDA would not use such responses ". . . as evidence of the firm's intent that its product be used for an unapproved or uncleared use . . ." and would not be expected to comply with the disclosure requirements applicable to promotional labeling and advertising.

PRACTICE NOTE: At the outset, it is important to understand what the Draft Guidance does not set out to accomplish. The Draft Guidance does not change or otherwise modify existing FDA regulations. Instead, the agency has provided additional information and context in order to illustrate the manner in which the agency would view and interpret its existing regulations dealing with off-label promotion. The references to examples of social media as the platform for requesting and responding to requests for off-label information again serve to

reiterate the need to rely on existing regulations and the manner in which FDA has previously implemented them in regulatory action in response to companies' promotional activities.

Notwithstanding, the Draft Guidance sheds some much needed light on one recurring question raised by manufacturers relating to the Internet and social media: a company may elect on its own to respond to an unsolicited request for off-label information, but is not obligated to do so. This clarification addresses one of the issues raised during FDA's 2009 public hearings; whether industry was required to "police the Internet" and respond to misstatements regarding its products when the response would require the inclusion of off-label information. (Assuming this provision is eventually integrated into a final guidance, it may provide some protection to a company in the product liability context.)

A further discussion of the issue of FDA guidance in the area of social media as well as the release of several additional draft guidance documents on the issue in 2014 will be discussed in Q 6.11.2 below.

Q 6.9 How does the Draft Guidance address "unsolicited" requests for off-label information?

With respect to off-label promotion and the steps companies should take to fulfill their obligation to provide critical and medically valid scientific information without facing regulatory or compliance-related exposure, the Draft Guidance discusses several key issues, particularly

- distinguishing between "solicited" and "unsolicited" requests, and between "public" and "non-public" requests (and their responses);
- articulating the appropriate manner to respond to unsolicited requests made in a non-public setting;
- and stating the procedures to be utilized to be certain that unsolicited *public* requests, whether in a public gathering or in the "open forum" of social media, be answered in a private manner to the individual who made the request.

The Draft Guidance provides a departure from what has been considered standard industry practice.

As to the distinction between "solicited" and "unsolicited" requests, FDA requires that an unsolicited request must be initiated by an entity totally independent of the company. The issue of total independence goes beyond any possible financial relationship, but also includes a circumstance where a company representative serves to directly or indirectly prompt the request for off-label information, even where the prompt itself did not specifically reference off-label information. Circumstances where such inappropriate conduct may take place include interaction with members of a company's speakers' bureau

or Medical Science Liaison at a promotional event, promotional messaging (including exhibits at medical congresses) where information as to unapproved products or indications in the form of clinical trial data, or a "Coming Soon" advertisement that references a "new indication" (even if unspecified), as well as electronic media.

FDA Draft Guidance Impact on Industry Practice

Q 6.10 What kinds of electronic media usage have the potential for off-label promotion?

FDA has described numerous examples where use of electronic media may be construed as soliciting requests for off-label information. These include:

- Providing URLs or a username that contains a word or alpha phrase/representation that suggests or implies the availability of off-label information upon request (such as linking a drug name and an unapproved indication in the URL address);
- Directing individuals to publically post their individual experiences with the company's drug, even on a third-party site, if the information posted is off-label (such as posting a video on YouTube and soliciting comments);
- Soliciting "bloggers" who are provided off-label information to disseminate;
- Tweeting, which is encouraging discussion of off-label uses or safety experiences; and
- Creating an online website that provides visitors with prepared responses describing the company's products, which is accessible through drop-down menus that relate to off-label uses; a procedure that would likewise be considered a solicited request would allow the visitor to utilize search terms to generate standard responses that go beyond the scope of the original request to access off-label information.

Q 6.11 What are some of FDA's articulated concerns relative to electronic media?

In its discussion of other circumstances that may give rise to inappropriate conduct, FDA guidance goes beyond addressing the distinction between solicited and unsolicited requests. FDA views the Internet and social media as methods of establishing permanent and durable sources of off-label information, where processes for responding to unsolicited public requests for information outside the scope of approved labeling can be facilitated. The concept of permanence is of concern to the agency for various reasons, including:

- The potential for outdated information remaining available; and
- Allowing individuals to access information in a public area online that was drafted in response to another person's request, thereby expanding the function of providing scientific information to full off-label promotion of a drug.

Q 6.11.1 What procedures does FDA recommend a company take in responding to requests made online?

In an effort to address these issues, FDA provides recommended procedures to be followed by manufacturers, including:

- Responding only when a question requiring reference to off-label information made in public refers to a specific product and an indication not in the approved labeling (for example, "Is it appropriate to use Drug X during pregnancy in patients with diabetes?" where Drug X is not indicated for that use). The guidance reiterates the long-standing requirement, contained in FDA guidance pertaining to disseminating off-label medical reprints and authoritative texts, that a company's response would need to include any known risk information applicable to the off-label use of the drug.
- As a general proposition, a company should not provide off-label information in a public forum, and only provide direction to an information source responsible for responding to such inquiries where a tailored response could be delivered privately. Such a source would include a Medical Communications function that would not include input from non-medical personnel such as sales or marketing.
- When an off-label inquiry is made in public, the company must disclose the fact that the question relates to an off-label use.
- The information provided should be truthful, balanced in tone and content, non-promotional, and carefully limited to responding to the inquiry. Full prescribing information should be included with the information provided; reference to a company's promotional sites is not permitted.
- The responding entity should identify themselves as representatives of the company.

In addition to these procedures, FDA also requires enclosing specific material in addition to the information provided in response to the inquiry. Those familiar with FDA guidance on dissemination of off-label reprints will find these elements familiar.

- As indicated previously, the Full Prescribing Information must be provided.
- The response must be accompanied by a statement that "FDA has not approved or cleared the product as safe and effective for the use addressed in the materials provided."
- Notwithstanding the inclusion of the full labeling, a statement describing the approved indication(s) for the product must be displayed.
- Inclusion of a statement containing all important safety information that accompanies the approved product, including any boxed warning, is mandatory.
- The company must provide a complete list of all references (published in peer-

reviewed journals and authoritative texts, as well as relating to Data on File and abstracts) for all information provided. Although not specifically articulated, this requirement would appear to include the inclusion of such references for those studies and materials that have raised safety issues regarding the off-label use that is the subject of the response.

Q 6.11.2 What additional guidance has FDA provided in the context of social media and its impact on regulatory and compliance concerns?

In response to repeated requests from pharmaceutical manufacturers for specific direction regarding the utilization of various social media platforms in communicating with third parties (particularly HCPs, patients, and caregivers), FDA indicated that the 2011 Draft Guidance on Unsolicited Requests was only the first in a series on this issue.

In 2014, FDA issued three additional draft guidance documents addressing specific social media issues, which are *Fulfilling Regulatory Requirements for Post-marketing Submissions of Interactive Promotional Material* (January 2014), *Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information* (June 2014), and *Internet/Social Media Platforms—Correcting Independent* Third-Party *Misinformation* (June 2014). FDA had provided direction to the pharmaceutical industry on the general use of the Internet only through issuance of regulatory letters to companies having failed to follow traditional regulatory requirements in advertising and promotion long required in print media. However, the explosive growth of social media generally and the concern of pharmaceutical companies in embarking on widespread use of social media while facing possible regulatory action led Congress to require FDA to complete social media guidelines by July 2014.

The guidance on post-marketing submissions reflects the agency's current views on fulfilling regulatory requirements for submission of interactive promotional materials where technology allows promotional messaging in "real time communication and interactions . . . ." In determining if a manufacturer is responsible for submitting interactive promotional materials, the FDA indicated it would consider whether the manufacturer or parties acting on their behalf is influencing or controlling the messaging in whole or in part. As for the traditional requirement to submit all advertising and promotional material in whatever form at the time of "initial dissemination," the FDA indicated that the challenges imposed by the instantaneous nature of social media would dictate some enforcement discretion due to the high volume of information posted within a brief period of time and would consider "bundling" of materials as a possible method of meeting the Form FDA 2253 filing requirement.[20]

The guidance on Internet and social media platforms with strict character space limitations suggests methods to meet the rigorous requirements of "fair balance" when considering such social media platforms as Twitter (where "tweets" are limited to 140 characters) and online paid searches (for example, "sponsored links" on search engines such

as Google and Yahoo). Most important, the guidance offers critical direction where failure to include relevant risk information when presenting a drug's benefits renders the product misbranded pursuant to the FDCA.

Factors to consider in communicating benefit and risk information under such circumstances would include the following:

- Benefit information must be accurate, non-misleading, and include material facts within each individual character-space-limited communication (for example, each individual "tweet");
- Benefit information should be accompanied by appropriate risk information within each character-space-limited communication;
- Manufacturers should carefully consider whether the space limitations allow the sponsor to adequately convey other required information; and
- If the social media platform will not permit adequate communication of required information, that platform may not be suitable for delivery of that product message.

The guidance on correcting independent third-party misinformation as to a company's product addresses issues raised by manufacturers following the FDA's Part 15 Public Hearing in 2009, particularly for which online communications are manufacturers accountable and what parameters should apply to posting corrective information on sites controlled by third parties?

In seeking to answer these questions, the guidance outlines what FDA considers to be permissible actions.

- Companies may, but are not obligated to, correct misinformation;
- The correction must be balanced, and the source of the revision or update must be disclosed;
- The corrective information should not be promotional in tone or content, and must be factually correct and non-misleading;
- Material being added to or revised on the site must be consistent with FDA-approved labeling, and should be posted adjacent to the information being addressed; and
- Companies should contact the authors (for example, bloggers) to voluntarily make changes.

Q 6.11.3 Has FDA issued any additional guidance regarding social media since 2014? Are any anticipated?

FDA has not issued any additional guidance regarding social media since the initial group first appeared, notwithstanding the fact that an additional guidance entitled *Internet/Social Media Advertising and Promotional Labeling of Prescription Drugs—Uses of*

Links to Third-Party *Sites* had appeared on the FDA/CDER Guidance Agenda in 2014, 2015 and 2016. However, it does not appear on the New and Revised Draft Guidances list issued by CDER on February 15, 2017.[21] It would appear that there are no current plans to issue additional social media guidance at this time.

Practice Note

The FDA has long utilized the Draft Guidance process to advise pharmaceutical companies of its thinking on an aspect of industry practice subject to regulation. The agency made it abundantly clear when issuing a Draft Guidance by including language that stated that the document "does not establish any rights for any person and is non-binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations." An alternative explanatory note would state FDA's guidance documents ". . .do not establish legally enforceable responsibilities…." and the information provided "is suggested or recommended, but not required." (Emphasis added.)

That approach has now been discredited by recent activity of the DOJ which issued a series of directives stating that it would no longer permit its attorneys to utilize guidance documents issued by its client agencies as a basis for civil enforcement and directed use of the formal rulemaking procedures set out in the Administrative Procedure Act.

It remains to be seen how the DOJ's decision, issued in January 2018 through a memorandum issued by DOJ Associate Attorney General Rachel Brand and later in a coordinated series of public addresses by other highly placed senior DOJ attorneys, will be enforced, particularly if prosecutions will be continue to be based in part on previously issued draft guidance documents.

Q 6.11.4 Has FDA taken any regulatory action against a pharmaceutical manufacturer based on promotion on social media since the draft guidances were issued?

Although the comment period for the Draft Guidance on Internet and social media platforms with character-space limitations had been extended to October 29, 2014, the FDA continued to exercise its regulatory authority prior to the close of the comment period. On September 24, 2014, FDA issued letters to three companies relating to their promotion and marketing of products allegedly effective in the treatment of the Ebola virus, claims that require FDA approval as a New Drug under the FDCA. The promotional messaging appeared on Pinterest, Facebook, and blog posts.[22]

Clearly, any drug promoted prior to final FDA approval would be deemed in violation of FDCA requirements, and would further be deemed "off-label" in the absence of any

approved labeling. The regulatory action taken demonstrates FDA's continued vigilance in reviewing all forms of social media to address conduct considered violative.

Q 6.11.5 What is the most recent pronouncement by FDA regarding medical products communication?

On January 18, 2017, FDA issued two draft guidances relating to the agency's current thinking on communicating medical information. The first, *Drug and Device Manufacturer Communications with Payors, Formulary Committees and Similar Entities—Questions and Answers*,[23] provides direction long requested by the suppliers of medical products for clarity regarding the appropriate use of healthcare economic information (HCEI) in presentations to payors and formulary committees regarding both approved drugs as well as dissemination of information regarding investigational drugs and devices prior to FDA approval. HCEI information must relate to the economic consequences of clinical outcomes of disease treatment or of preventing or diagnosing a disease, and be based on "competent and reliable scientific evidence" or CARSE.[24]

Specifically, FDA endorsed the presentation of such data in a number of ways (including a product dossier, a peer-reviewed publication, or through computer modeling). The information would not be considered false or misleading if, among other criteria, it is related to an approved indication. The determination whether the HCEI information is related to an approved indication is made by analyzing whether there is a relation to a disease or condition or a manifestation of that disease or condition for which the drug has been approved. The guidance also addresses the type of audience capable of receiving such information and limits the recipients to those with sufficient expertise in healthcare economic analyses.

The second draft guidance is entitled *Medical Product Communications That Are Consistent with the* FDA-Required *Labeling—Questions and Answers*.[25] It provides recommendations for a company to follow in its promotional review process to deliver medical information consistent with the FDA-required labeling that would be deemed truthful and non-misleading. Although the guidance breaks no new ground, its utility is based on providing somewhat greater latitude to companies in interpreting FDA's manner of reviewing promotional materials. For example, the agency will permit reliance on one "adequate and well-controlled study" to substantiate promotional claims consistent with approved labeling. By way of example, the FDA guidance states that a comparative claim may be based on a single head-to-head study which indicates that a drug approved for the treatment of hypertension has superior efficacy when compared to a second drug in the same therapeutic category approved for the same indication.

The draft guidance lists the three factors the agency will utilize to determine if a communication is consistent with labeling: (1) Does the communication differ from the labeled indication, patient population, limitations as to use or specific directions for handling, preparation or use; (2) Is there a potential for increased risk as to patient health, thereby altering the benefit/risk profile of the drug; and (3) Is the approved label's

directions for use compromised by the information being communicated? Affirmative responses to the first two factors or a negative response to the third will render the communication inconsistent with the product's approved labeling.

In addition to the two draft guidance documents, the FDA also released a memorandum as follow-up to the November 2016 meeting convened to discuss the issue of oversight relating to off-label promotion in the context of the evolving First Amendment case law.[26] Unfortunately, the memorandum does not articulate a position different from that presented by the agency in its defense of the several Second Circuit opinions that relied upon the First Amendment to uphold challenges to FDA's authority to limit dissemination of accurate and non-misleading medical information.

PRACTICE NOTE: The Draft Guidance reiterates many of the major concepts put forward by FDA over the past decades when discussing the balancing of a pharmaceutical company's responsibility to provide sound and accurate medical information to HCPs regardless of its off-label nature, with the need to adhere to regulations prohibiting off-label promotion in violation of the FDCA. The agency itself noted the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products."[27] However, the inclusion of language that apparently seeks to limit a company representative's ability to provide any response to an unsolicited public inquiry requiring reference to off-label information other than to direct the questioner to a non-public source, has introduced an element of uncertainty beyond the utilization of the Internet and social media in the promotion of medical products. In particular, the procedures utilized with reference to the use of medical authorities as members of promotional speaker bureaus must be examined together with the mandatory FDA regulatory training for these speakers.

It is important to note that the various Draft Guidances have no binding effect on medical products companies; the comment period required by law has not run and the final guidances, if issued, may contain significant revisions. Yet, the Draft Guidances provide the most expansive articulation of the attitude of the agency not only on issues relating to the use of the Internet and social media but on the proper role of companies in serving as an authoritative source of medical information for the healthcare community in establishing appropriate medical standards. The Draft Guidances also serve to help in the development of processes and procedures to avoid both regulatory and government compliance exposure. In particular, the guidances on character-space limitations and correcting misinformation on third-party sites are important for manufacturers to consider in developing and disseminating product information, not only in relation to FDA regulatory requirements, but to oversight by OIG and DOJ for a manufacturer's having introduced a misbranded product into interstate commerce, as well as increasing

product liability risk in a failure to warn context.

Oversight by the Executive Branch, Judicial Branch, and State Governments

Generally

Q 6.12 Does FDA have sole responsibility for supervising and restricting dissemination of scientific information relating to the authority to take action for alleged off-label promotion?

It is undisputed that FDA has responsibility for safeguarding the public health when introducing non-misbranded medical products, such as pharmaceuticals, into interstate commerce.[28] The availability of truthful, scientifically accurate, and non-misleading product information is the foundation for HCPs and the lay public to become familiar with new products and new indications for existing products. Yet, to determine industry practices that constitute proper and lawful exercises of information delivery critical to patient care versus practices that are violations of law as evidence of off-label promotions, the function of FDA has been supplemented, and in some cases overshadowed, by the executive and judicial branches of the federal government. To avoid both civil and potential criminal liability, pharmaceutical companies and related members of the healthcare field must consider the role of the DOJ and the OIG in examining not only marketing practices, but a wide range of other functions.

The OIG's ever-increasing concern with and attention to the interaction between the healthcare industries and HCPs has focused largely on allegations of promoting pharmaceuticals for off-label indications, with a corresponding rise in healthcare costs and government reimbursements, as well as potential safety concerns for patients receiving therapies that have not gone through the rigorous FDA approval process.

The importance of taking into account the various FDA regulations and healthcare laws in identifying the basis for agency and DOJ actions against pharmaceutical companies is critical. Separate and distinct from FDA action in the form of NOVs and Warning Letters, both federal and state prosecutors are increasing their oversight of pharmaceutical company activities as reflected in litigation and the imposition of rigorous CIAs that are quasi-regulatory in nature.

Office of Inspector General and Department of Justice

Q 6.13 What have been the results of recent government actions relating to off-label promotions on the pharmaceutical industry?

The increasing number of both federal and state government investigations and prosecutions has led to a series of settlements with significant monetary recoveries by the government, as well as the imposition of CIAs, which require the creation of rigorous

compliance programs, independent oversight over company functions, and complex reporting obligations.

Q 6.14 What kinds of settlements with pharmaceutical companies has the government been able to secure?

The following Table 6-1 (based on "Pharmaceutical Public Settlements Related to Marketing and Associated Activities") describes select settlements during the 2011–2017 time period. While the number of the settlements and the magnitude of the amounts paid by the companies for a two-year period are noteworthy, of greater importance to the pharmaceutical and related industries is an analysis of the allegations by government investigators. These investigations almost invariably arise, in whole or in part, from marketing activities that were reviewed and considered off-label promotions and violations of federal law. It is therefore instructive to review a select number of these settlements for guidance as to what the OIG and the DOJ consider inappropriate conduct in the marketing function. It is also important to study the resulting CIAs, as they illustrate the type of internal controls that the government believes are critical to prevent illegal conduct.

TABLE 6-1

Pharmaceutical Company Public Settlements Related to Marketing and Associated Activities[29]

2011–2017 Select Settlements

Pharmaceutical Company	Settlement Amount	Settlement Date	Product	Summary of Significant Allegations
Shire PLC	$350 million	January 2017	Dermagraft®	Violations of the FCA and the AKS for kickbacks, lavish gifts and entertainment, unwarranted payments for purported speaking engagements, and bogus case studies.
Celgene Corp.	$280 million	July 2017	Thalomid®, Revlimid®	Off-label promotion and other violations of the FCA and payments of kickbacks under the AKS.
Salix	$54 million	June 2016	Various Salix Products	Excessive number of speaker programs (10,000 between 2009–2013), sham speaker programs, no speaker monitoring program.

Genentech and OSI Pharmaceuticals, LLC	$67 million	June 2016	Tarceva®	False and misleading promotion regarding efficacy (survival data) in off-label promotion.
Warner Chilcott	$125 million	October 2015	Actonel®, Asacol®, Atelvia®, Doryx®, Enablex®, Estrace®, Loestrin®	Allegations in the civil and criminal complaint alleged illegal payments to HCPs to prescribe Warner Chilcott drugs, including providing payments, meals and other remuneration associated with sham Medical Education Events; additional charges included preparing and submitting false prior authorizations forms and making false unsubstantiated superiority claims for Actonel without supporting clinical evidence. Of particular note was the criminal indictment of the company president for allegedly paying kickbacks to HCPs in the form of speaker fees.
Novartis	$390 million	October 2015	Myfortic®, Exjade®, and others	Novartis was charged with making illegal payments to specialty pharmacies to induce dispensing costlier company products in place of lower cost drugs.
Genzyme Corp.	$32.59 million	September 2015	Hyalgan®	Settlement resolved allegations Genzyme violated the FCA and the AKS by providing free product to HCPs to induce additional purchases and prescribing; additional allegations included submitting false Average Sales Price data to

				the government.
Amgen	$71 million	August 2015	Aranesp®, Enbrel®	Company agreed to settle allegations brought by forty-eight states to settle charges of violating state consumer protection laws by promoting its anemia and plaque psoriasis drugs off-label. Amgen had previously settled similar charges brought by the DOJ which were resolved in 2012 by payment of $762 million. Of particular interest is the reliance by the states on an FDA Warning Letter to the company in 2005 which addressed several of the activities that later served as the basis for the state and federal actions.
GSK	$105 million	June 2014	Advair®, Paxil®, Wellbutrin®	GSK negotiated a $105 million settlement with forty-four states and the District of Columbia resolving allegations that the company had promoted its drug off-label in violation of the states' respective consumer protection laws. Of note is the fact that the allegations are nearly identical to those brought by the federal government and settled in 2012 for $3 billion; in addition, the states imposed additional requirements on GSK conduct over and above those contained in the CIA negotiated with the DOJ.

Johnson & Johnson	$2.2 billion	November 2013	Risperdal®, Invega®, Natrecor®	Johnson & Johnson and subsidiaries (Janssen Pharmaceuticals, Scios, Inc.) resolved civil and criminal investigations into unapproved (off-label) promotion of several of its drugs. In particular, the government alleged illegal promotion of several antipsychotic medications to HCPs and patients in nursing homes, including payments of kickbacks for such prescribing activities.
GlaxoSmith Kline, LLC	$3 billion ($2 billion civil $1 billion criminal)	July 2012	Paxil® Wellbutrin® Avandia®	*Settlement:* GlaxoSmithKline, LLC agreed to pay $3 billion to resolve its criminal and civil liability arising from the company's unlawful promotion of certain prescription drugs, its failure to report certain safety data, and its civil liability for alleged false price-reporting practices. The criminal agreement addresses two counts of introducing misbranded drugs, Paxil and Wellbutrin, into interstate commerce and one count of failing to report safety data about the drug Avandia to FDA. Under the terms of the plea agreement, GSK will pay a total of $1 billion, including a criminal fine of $956,814,400 and forfeiture in the amount of $43,185,600. GSK will also pay $2 billion to resolve its

				civil liabilities with federal and state governments under the False Claims Act. *CIA:* GSK also has entered into a five-year corporate integrity agreement with the OIG.
GlaxoSmithKline PLC (Related Settlement)		July 2012	Avandia® Paxil® Wellbutrin®	Settlement: GlaxoSmithKline PLC agreed to pay $3 billion to settle criminal and civil investigations by the government, including probes into its marketing of Avandia, Paxil, and Wellbutrin (and other drugs) and possible abuses of Medicaid's rebate program. The settlement ended probes by the U.S. Attorney's Office for the District of Massachusetts and the DOJ.
Orthofix Inc.	$41.8 million ($34 million civil $7.8 million criminal)	June 2012	Bone growth stimulators	*Settlement:* Orthofix Inc. agreed to pay the United States $34 million to settle allegations under the civil FCA relating to the company's sale of bone growth stimulator devices. The company also agreed to plead guilty to a felony of obstruction of a federal audit, and to pay a $7.8 million criminal fine. The civil settlement resolves a whistle-blower lawsuit that alleged that Orthofix improperly waived patient co-payments, thus misstating their true cost and resulting in overpayments by federal programs, paid kickbacks to

				physicians in the form of "fitter fees," referral fees, and other fees to induce the use of Orthofix products; caused the submission of falsified certificates of medical necessity; and failed to advise patients of their right to rent rather than purchase Orthofix products. The company's guilty plea involved its failure to disclose information concerning its practices regarding certificates of medical necessity to a Medicare contractor during a June 2008 audit. Five individual Orthofix employees previously pleaded guilty to criminal charges in connection with this matter. *CIA:* As part of the settlement, Orthofix also agreed to enter into a corporate integrity agreement with the OIG.
Abbott Laboratories, Inc.	$1.5 billion ($700 million criminal $800 million civil)	May 2012	Depakote®	*Settlement:* Abbott Laboratories, Inc. has agreed to pay $1.5 billion to resolve its criminal and civil liability arising from the company's unlawful promotion of the prescription drug Depakote for uses not approved by FDA. The resolution is the second largest payment by a drug company, and Abbott will be subject to court-supervised probation and reporting obligations for

				Abbott's CEO and Board of Directors. Abbott pleaded guilty to misbranding Depakote by promoting the drug to control agitation and aggression in elderly dementia patients and to treat schizophrenia from 1998 through 2006. In addition, from 2001 through 2006, the company marketed Depakote in combination with atypical antipsychotic drugs to treat schizophrenia, even after clinical trials failed to demonstrate that adding Depakote was any more effective than an atypical antipsychotic alone for that use. Abbott has pleaded guilty to a criminal misdemeanor for misbranding Depakote in violation of the FDCA.
Merck Sharp & Dohme Corp.	$950 million ($321.6 million criminal $628.3 million civil)	April 2012	Vioxx®	*Settlement:* Merck Sharp & Dohme Corp. agreed to pay $950 million to settle criminal and civil allegations related to illegally marketing the painkiller Vioxx for off-label uses and misleading customers about the safety of the drug. In the plea agreement, Merck admitted to marketing Vioxx for the treatment of rheumatoid arthritis for three years before FDA approved it for that use in 2002. The plea agreement was approved by a judge in the district of

				Massachusetts. *CIA:* The settlement deal also includes a five-year corporate integrity agreement between Merck and the OIG.
Johnson & Johnson and subsidiary Ortho-McNeil-Janssen Pharmaceuticals, Inc.	$1.2 billion	April 2012	Risperdal®	*Settlement:* An Arkansas judge sentenced Johnson & Johnson ("J&J") and a subsidiary to more than $1.2 billion in penalties for deceptive marketing of the antipsychotic drug Risperdal. In a 2007 complaint, the Arkansas attorney general's office accused J&J and a subsidiary, Janssen Pharmaceuticals, of falsely claiming that Risperdal was safer and more effective than similar, cheaper drugs. The companies were also accused of failing to adequately warn about the drug's possible side effects, including diabetes and neurological problems. As a result, the state said, public funds were improperly used to pay for Risperdal through programs like Medicaid.
Dava Pharmaceuticals Inc.	$11 million ($5.7 million federal $5.1 million state)	February 2012	Cefdinir, Clarithromycin, and Methotrexate	*Settlement:* Dava Pharmaceuticals Inc. has agreed to pay $11 million to settle allegations that it violated the False Claims Act by misreporting drug prices in order to reduce its Medicaid Drug rebate obligations. The settlement resolves allegations that Dava

				Pharmaceuticals falsely claimed the lower rebate amount by incorrectly classifying its version of the drugs Cefdinir, Clarithromycin, and Methotrexate as "non-innovator" drugs, rather than "innovator" (single source or innovator multiple source) drugs. According to court documents, Dava used those incorrect methodologies in calculating average manufacturer prices for these drugs, thus permitting Dava to underpay its rebate obligations to the Medicaid Drug Rebate Program, and to overcharge certain entities that participated in the Public Health Services Drug Pricing Program.
Johnson & Johnson subsidiary Ortho-McNeil-Janssen	$158 million	January 2012	Risperdal®	*Settlement:* Johnson & Johnson ("J&J") agreed to pay $158 million to settle Texas officials' claims that the drug maker fraudulently marketing its Risperdal antipsychotic drug for unapproved uses, including for children with psychiatric disorders. The state also claimed the drugmaker downplayed the health risk of Risperdal in regard to risk of diabetes. The state's lawsuit sought at least $579 million in damages over the companies' Risperdal marketing practices.

				Whistleblower Allen Jones claimed that J&J had defrauded the state Medicaid program.
Johnson & Johnson subsidiary Ortho-McNeil-Janssen	$1 billion	Reported January 2012	Risperdal®	*Settlement:* Johnson & Johnson ("J&J") will reportedly pay more than $1 billion to settle civil claims made by the federal government and several states that it illegally marketed the antipsychotic drug Risperdal. The federal government and the attorneys general of twelve states have accused J&J subsidiary Ortho-McNeil-Janssen Pharmaceuticals, Inc. of illegally marketing Risperdal for uses not approved by FDA. The company allegedly pushed Risperdal aggressively to physicians for off-label uses, such as treatment for dementia and certain disorders in children.
KV Pharma (On behalf of former subsidiary Ethex Corp.)	$17 million	December 2011	Hyoscyamine sulfate ER Nitoglycerin ER	*Settlement:* KV Pharmaceutical Co. agreed to pay $17 million to resolve the role played by Ethex Corp., a former subsidiary, in a False Claims Act qui tam action alleging it wrongly reported to Medicaid and Medicare programs that two drugs were qualified for coverage under federal healthcare programs.
Genentech	$20 million	November	Rituxan®	*Settlement:* Genentech Inc.

		2011		will pay $20 million to resolve a whistleblower suit by a former Genentech sales manager over alleged illegal promotion of a Genentech drug for off-label uses. The government alleged that Genentech billed Medicare and Medicaid between 2000 and 2005 by bribing healthcare providers to prescribe its lymphoma and leukemia treatment drug Rituxan for off-label uses, such as maintenance therapy for asymptomatic
				lymphoma patients who had completed an initial course of Rituxan® therapy, and first-line and maintenance therapy for patients with autoimmune diseases.
Amgen Inc.	$780 million	Announced October 2011	Aranesp®	*Settlement:* Amgen Inc. announced that it will pay $780 million to settle allegations over its sales and marketing practices stemming from civil and criminal investigations related to Aranesp. The federal investigations, according to Amgen, involve marketing, pricing, and dosing of Aranesp and Epogen, and its dissemination of information about clinical trials on the safety and efficacy of those drugs.
Pfizer, Inc.	$14.5 million	October 2011	Detrol®	*Settlement:* Pfizer, Inc. agreed to pay $14.5 million to

				resolve claims brought by two ex-employee whistleblowers and the DOJ that it used kickbacks and deceptive marketing to convince Medicaid providers to prescribe a bladder control drug for off-label purposes.
Novo Nordisk, Inc.	$26.7 million (DOJ, Maryland, and New York) $1.73 million (U.S. Government)	June 2011	NovoSeven® Novolin® N Novolin® 70/30 Novolog® Novolog® 70/30	*Settlement:* Novo Nordisk, Inc. announced that it would pay $26.7 million to resolve federal investigations by the DOJ and False Claims Act lawsuits in New York and Maryland brought by former employees and a physician over the marketing of its drugs for bleeding disorders and diabetes. The government alleged that it improperly promoted NovoSeven for unapproved uses, and offered kickbacks to physicians for promoting the off-label use of the drug. Separately, the company also agreed to pay $1.73 million in a settlement with the government to resolve allegations that its sales representatives accessed confidential patient information and submitted false Medicaid claims related to the marketing of diabetic drugs, including Novolin and Novolog Novo Nordisk also agreed to enter into
				corporate integrity agreements with the OIG as part of both settlements.

Serono	$44.3 million ($34.6 million federal $9.7 million state)	May 2011	Rebif®	*Settlement:* Serono agreed to pay $44.3 million to settle claims that it provided kickbacks to doctors and knowingly submitted false claims to federal healthcare programs. *CIA:* As part of the settlement, Serono also signed an addendum to its 2005 CIA, extending the CIA for three additional years.
AstraZeneca	$68.5 million	March 2011	Seroquel®	*Settlement:* AstraZeneca will pay $68.5 million as part of a multistate settlement over allegations that it promoted its psychiatric drug Seroquel for unapproved uses, such as treating insomnia and Alzheimer's disease. The Settlement will be shared by thirty-seven states and the District of Columbia. AstraZeneca agreed to not market the drug in
				a misleading manner or for unapproved uses, and to provide accurate responses to requests about off-label usage. The company must also enact policies to ensure that no financial incentives are given to sales representatives for unapproved marketing, and it must post on a website any payments made to physicians.
Pfizer, Inc.	$142.1 million	January 2011	Nuerotin®	*Settlement:* Pfizer, Inc. will pay a total of $142.1 million

				in damages for violating U.S. racketeering laws in the marketing of its epilepsy drug Neurotin for unapproved uses. The court upheld a jury finding and tripled the jury's award of $47.3 million under a provision of the Racketeer Influenced and Corrupt Organizations Act of 1970.
Eisai Inc.	$11 million	December 2010	Zonegran®	*Settlement:* Eisai Inc. will pay $11 million to resolve civil allegations under the False Claims Act and related state statutes that the company illegally promoted Zonegran and caused false claims to be submitted to government healthcare programs for uses that were not medically accepted indications and, therefore, not covered by those programs.
Elan Corporation, PLC and Elan Pharmaceuticals, Inc.	$214.5 million ($97,050, 266 criminal $3.6 million forfeiture $102,890, 517 civil) ($11 million already paid to resolve civil liability for off-label marketing)	December 2010	Zonegran®	*Settlement:* Elan Corp., PLC and its U.S. subsidiary Elan Pharmaceuticals, Inc. agreed to pay more than $203 million to resolve criminal and civil liability arising from the illegal promotion of the epilepsy drug Zonegran®. Elan also agreed to plead guilty to an information charging it with misdemeanor misbranding of Zonegran®, in violation of the FDCA. *CIA:* Elan has agreed to enter into a five-year CIA with the OIG.

Q 6.15 How will the most recent corporate integrity agreements impact the various functions of pharmaceutical manufacturers?

Although settlements that result in the imposition of various compliance obligations contained in the respective CIAs are crafted to address specific examples and patterns of conduct on the part of the individual company, the increasing nature of the obligations imposed by successive CIAs illustrate a pattern of government concern with industry practice. By focusing on company functions and alleged misconduct, the settlements establish guidance, if not a specific directive, to all pharmaceutical manufacturers to undertake an examination of all methods of interacting with healthcare professionals, particularly relating to dissemination of medical and scientific information so as not to run afoul of the FCA and AKS in relation to off-label promotion.

The most comprehensive CIA to date arose in the settlement of the DOJ action brought against GlaxoSmithKline LLC (GSK) on July 2, 2012.[30] Concluding an investigation that had begun approximately ten years prior to the settlement, GSK agreed to plead guilty to three misdemeanors under the FDCA and pay $3 billion dollars to resolve both criminal and civil liability relating to various allegations concerning the marketing and promotion of nine drugs, off-label promotion involving five products, as well as other charges arising from, among other areas, violations of Good Manufacturing Practices, "Best Price" reporting, and failure to adequately report safety data to the FDA.

Aside from the size of the payment, the GSK case presents a CIA that is both a reflection of the cumulative nature of government-imposed CIAs developed over years of settlement activity between the government and industry, and an unprecedented expansion of federal oversight into an ever-widening scope of company activities and functions.

The GSK CIA did not represent the only settlement exceeding $1 billion dollars in 2012 (in light of Abbott's $1.5 billion payment to resolve allegations of off-label promotion relating to the marketing of an anti-seizure drug[31]). Nevertheless, the expansion of compliance requirements particularly designed to control off-label promotion, together with the increased involvement of the DOJ in supervision of company conduct, is unprecedented. For the first time, a settlement introduced the DOJ into the enforcement of compliance requirements, while required GSK to provide reports on a regular basis to the Health Care Fraud Unit of the U.S. Attorney's Office to the DOJ Consumer Protection Branch. A compelling case can be shown that the FDA may have been consigned to a somewhat reduced role in the enforcement of the FDCA relative to other government entities.

With regard to the specific areas of off-label promotion, the GSK CIA is another example of how CIAs develop over time based on prior settlements when addressing conduct considered a violation of law as well as the corrective measures required. Allegations had been made that GSK promoted one of its drugs as safe and effective for the treatment of several serious conditions (including ADHD, depression, and bipolar disorder) in a pediatric population, while possessing internal clinical data that use in children suffering from depression actually increased the risk of suicide. (These allegations[32] mirror

those made by then-New York Attorney General Eliot Spitzer, which accelerated reporting requirements for clinical trial data.) The 2012 settlement, therefore, imposes research transparency and reporting requirements, in addition to those already in place (which require postings on www.clinicaltrials.gov).

The GSK case also presents a novel theory relating to off-label promotion. Unlike other examples where a company is alleged to promote a drug for a non-approved use not contained in the approved labeling, GSK was accused of engaging in illegal conduct arising from the promotion of an asthma drug (Advair®) for the approved indication, but beyond the limitations of the disease. These allegations suggest that one branch of the government (DOJ) can interpret the meaning of a drug label originally implemented by another branch of government (FDA). Although the allegations are artifacts of the settlement, the conundrum facing pharmaceutical manufacturers remains.

The GSK CIA also introduces two unprecedented requirements designed to disincentivize company personnel from engaging in marketing activities that can be construed as off-label promotion.

- First, the company is required to modify its executive compensation program to permit recovery of up to three years of annual bonus payments and long-term incentives from certain current and former senior executives if the executives engaged in significant misconduct, or if those executives knew or should have known of serious misconduct by their subordinates and failed to take appropriate action.
- Second, GSK can no longer base compensation or discipline field-based sales personnel on sales goals or volume of sales in their territories. Such measurements of performance would be replaced by metrics, including scientific knowledge of the products detailed, customer engagement, and general business acumen.[33]

The most recent settlement arising in large part from allegations of active off-label promotional activities was announced on November 4, 2013 when the DOJ reached an agreement with J& J arising from the investigations into off-label promotion of three drugs and other violations of both criminal and civil statutes and regulations. The global settlement was in excess of $2.2 billion, making it the third largest settlement of healthcare fraud violations, exceeded only by Pfizer and GSK settlements discussed elsewhere in this chapter.[34]

The J&J settlement resolved criminal and civil actions filed in several federal district and state courts under the False Claims Act as well as for improper Medicare and Medicaid payments. In particular, a primary charge against the company arose from the introduction by Jansssen Pharmaceuticals, a J&J subsidiary, of the antipsychotic drug, Risperdal, into interstate commerce for off-label indications that targeted inappropriate patient populations, particularly minors and the elderly. Specifically, Janssen acknowledged in its plea agreement to a misdemeanor violation of the FDCA for promoting the drug in nursing homes and similar healthcare facilities for the treatment of dementia and similar conditions when the drug was only approved for schizophrenia.[35]

In addition to the fines and forfeiture of profits, the settlement included imposition of a five-year CIA that incorporated the increased oversight of all aspects of company activities observed in recent settlements (most notably GSK), including independent review, written standards of compliant conduct, recoupment of bonuses and other incentive payments to executives if they or their reports engaged in inappropriate conduct, as well as increased disclosure and reporting of payments to HCPs and transparency as to J&J funding of third-party educational programs.

J&J is still actively engaged in a series of product liability actions arising from injuries allegedly sustained following exposure to Risperdal, as well as state actions alleging fraud on state Medicaid systems. (See Q 6.17 below.)

Judicial System

Q 6.16 What role does the judicial system play in determining limits on the dissemination of truthful, non-misleading (albeit off-label) medical and scientific information?

In investigating industry conduct, government agencies will begin with a determination of whether conduct constituted a violation of any of the provisions of the FDCA.[36]

In addition to the FDCA, investigators rely on non-FDA specific legal authority, the most commonly cited being the federal AKS and the federal FCA. The AKS states that it is a felony to "offer, pay, solicit or receive any remuneration in return for referring an individual to a person for the furnishing of an item or service, or purchasing, leasing, ordering . . . any good, facility, service or item, for which a federal health care program may pay." Company activities would be reviewed to determine the likelihood that "overutilization" or other inappropriate use of a drug would result, as well as any potential for adverse consequences to patients and/or inappropriate interference with a HCP's clinical judgment.

The FCA is arguably the most often utilized basis for prosecutions arising from allegations of off-label promotion. The FCA generally prohibits ". . . any person from knowingly presenting (or causing to be presented) a claim for payment or approval to the Federal government that is false or fraudulent." The Civil War-era statute[37] has been adopted by the government in the healthcare context, claiming unlawful promotional activities served as the predicate for filing medical reimbursement claims for drugs prescribed for unapproved uses.

As discussed in Q 6.14 above, the government's theories of liability against pharmaceutical companies for off-label promotion are reflected in the various charging documents and referenced in the CIAs. The CIAs are the method by which a settling party implements changes in its internal processes and procedures, which allegedly allowed the offending conduct to occur, as well as an articulation of OIG's current theories of compliant conduct for the industry. However, both federal and state prosecutions, as well as private litigants filing product liability lawsuits, provide additional controls over industry

practice. In fact, there are circumstances where FDA regulatory practice and OIG compliance requirements present conflicting standards of appropriate conduct.

State Actions

Q 6.17 What actions have states taken to address the off-label issue?

In light of the continuing financial pressure on states relating to reimbursement of healthcare costs, states have added their authority to the issue of appropriate marketing by pharmaceutical manufacturers. An increasing number of jurisdictions have passed state FCA statutes (spurred on by federal support for such legislative initiatives) and filed suit for reimbursement of Medicaid expenditures for the off-label use of drugs. Many of these actions are filed in conjunction with OIG and DOJ initiatives, and result in additional settlement funds provided to the various states at the resolution of federal actions.

The state litigation brought against J&J arising from allegations that its antipsychotic drug, Risperdal, was marketed for off-label indications (thereby defrauding state Medicaid programs) is an example of a particularly aggressive state action. In addition to the ongoing federal litigation, states have instituted independent actions. In Louisiana, J&J was held liable for misleading state regulators, HCPs, and patients on the safety and efficacy of the drug as prescribed, with a jury award of $258 million. (An intermediate state appellate court upheld the verdict in August 2012.)

In addition to monetary damages, state actions are imposing their own prohibitions relating to pharmaceutical marketing practices. A settlement of state claims brought by the Attorney General of Oregon and multiple states against J&J and its Janssen division alleging the off-label promotion of Risperdal and another antipsychotic drug resulted not only in a settlement of $181 million, but also restricted the company's ability, through its sales force, to distribute reprints of peer-reviewed medical articles that discuss off-label uses, unless the company has previously filed a supplemental New Drug Application with FDA. Thus, the states have imposed a restriction above that which FDA has clearly permitted in its Guidance on Distribution of Off-Label Reprints, as discussed in chapter 7.

However, not all states have taken action to curb the dissemination of information regarding off-label treatment. On March 21, 2017, Governor Doug Ducey of Arizona signed HB 2382 (The Free Speech in Medicine Act), which lifted the prohibition on off-label promotional activity and specifically authorized pharmaceutical companies to communicate information regarding the safe and effective albeit alternative (i.e., off-label) uses of previously approved drugs. As seen in the decisions from the Second Circuit, the argument is that the safeguards in place by virtue of the First Amendment support a pharmaceutical company's activities in disseminating truthful and non-misleading information that may appear in authoritative journals or that has been observed in clinical research.

It is interesting to note that such legislative initiatives have often been supported by patient advocacy groups previously active in expanding the scope of "Right to Try" laws and increase patient access to therapies unavailable prior to formal FDA approval.

TABLE 6-2

Pharmaceutical Drugs Mentioned in This Chapter

Full Trade Name	Generic Name	Trademark Information
Paxil®	paroxetine hydrochloride	is a registered trademark of GSK
Wellbutrin®	bupropion hydrochloride	is a registered trademark of GSK
Avandia®	rosiglitazone maleate	is a registered trademark of GSK
Depakote®	divalproex sodium	is a registered trademark of AbbVie Inc.
Vioxx®	rofecoxib tablets and oral suspension	is a registered trademark of Merck
Risperdal®	risperidone	is a registered trademark of Janssen
Omnicef®	Cefdinir	is a registered trademark of Abbott
Biaxin®	Clarithromycin	is a registered trademark of the various manufacturers
Levsin®/SLtablets	Hyoscyamine Sulfate ER	is a registered trademark of Alaven
Rituxan®	rituximab	is a registered trademark of Genentech
Aranesp®	darbepoetin alfa	is a registered trademark of Amgen
Detrol®	tolterodine tartrate	is a registered trademark of Pfizer
NovoSeven®	coagulation factor VIIa recombinant	is a registered trademark of Novo Nordisk
Novolin® N	NPH, human insulin isophane suspension [recombinant DNA origin]	is a registered trademark of Novo Nordisk
Novolin® R	regular, human insulin injection [recombinant DNA origin]	is a registered trademark of Novo Nordisk
Novolin® 70/30	70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection	is a registered trademark of Novo Nordisk
Novolog®	insulin aspart [rDNA origin] injection	is a registered trademark of Novo Nordisk
Novolog® 70/30	70% insulin aspart	is a registered trademark of Novo Nordisk

	protamine suspension and 30% insulin aspart injection, [rDNA origin]	
Rebif®	interferon beta-1a	is a registered trademark of Pfizer-EMD Serono, Inc.
Seroquel®	quetiapine fumarate	is a registered trademark of AstraZeneca
Neurontin®	gabapentin	is a registered trademark of Pfizer
Zonegran®	zonisamide	is a registered trademark of Elan Pharma International Ltd.
Advair®	fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder	is a registered trademark of GlaxoSmithKline
Botox®	onabotulinumtoxinA	is a registered trademark of Allergan Pharmaceuticals Ireland
Megace®	megestrol acetate, USP	is a registered trademark of Bristol-Myers Squibb
Tarceva®	erlotinib tablets	is a registered trademark of OSI Pharmaceuticals, LLC
Dermagraft®	Human fibroblast-derived dermal substitute	is a registered trademark of Organogenesis, Inc.
Thalomid®	thalidomide	is a registered trademark of Celgene Corporation
Revlimid®	Lenalidomide capsules for oral use	is a registered trademark of Celgene Corporation
Tarceva®	Erlotinib hydrochloride	is a trademark of OSI Pharmaceuticals, LLC, USA, an affiliate of Astellas Pharma US, Inc. OSI Pharmaceuticals, LLC, is an affiliate of Astellas Pharma US, Inc., and Genentech, Inc.
Actonel®	(risedronate sodium (tablets)	is a trademark of Warner Chilcott (USA), LLC
Asacol®	mesalamine	N/A
Atelvia®	risedronate sodium	N/A
Enablex®	(darifenacin)extended release tablets	is a trademark of Warner Chilcott (USA), LLC
Doryx®	doxycycline	N/A

Estrace® Cream	estradiol vaginal cream	is a registered trademark of Allergan Pharmaceuticals International Limited
Loestrin® Lo Loestrin Fe®	(norethindrone acetate & ethinyl estradiol tablets, ethinyl estradiol tablets & ferrous fumarate tablets)	are registered trademarks of Allergan Pharmaceuticals International Limited

1. 21 U.S.C. § 355(a), (d).
2. 21 U.S.C. § 352(a), (n). *See* 21 C.F.R. § 202.1(e)(5), (e)(6)(i) and (ii), (e)(7)(viii).
3. 31 U.S.C. § 3733(a).
4. The Deficit Reduction Act of 2005 rewards states for local investigations and cutions if state law "is as effective in rewarding and facilitating *qui tam* actions as the al statute."
5. 31 U.S.C. § 3729–33.
6. 31 U.S.C. § 3729(a).
7. There are currently twenty-nine states plus the District of Columbia with laws that seek centivize prosecution for violations of the local FCA statutes. Of those, twenty-one have licaid-only" statutes, sixteen are deemed at least as strictly constructed as the federal statute, by making those jurisdictions eligible for a 20%–35% increase in their share of any caid recoveries under the federal FCA. *See* TAXPAYERS AGAINST FRAUD CATIONAL FUND, STATES WITH FALSE CLAIMS ACTS, www.taf.org/states-false-s-acts.
8. 21 C.F.R. § 312.7(a).
9. 37 Fed. Reg. 16,503 (Aug. 15, 1972).
10. U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY DEVELOPMENT OF RISK MINIMIZATION ACTION PLANS (Mar. 2005).
11. A DDMAC enforcement letter issued on January 28, 1999 concluded that a press e issued weeks earlier promoted an unapproved drug product by making implied claims of and effectiveness that had not been demonstrated by "substantial evidence" as well as ding a misleading headline regarding an FDA Advisory Panel's recommendations ining to the product.
12. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementitiesbyFDAWarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm42.htm
13. PHARMACEUTICAL RESEARCH MANUFACTURERS OF AMERICA RMA), ACCREDITATION COUNCIL FOR CONTINUING MEDICAL CATION (ACCME®).
14. Warning Letter from U.S. Food and Drug Administration to Marc Beer, Chief ıtive Officer, Aegerion Pharmaceuticals, Inc. (Nov. 8, 2013),

.fda.gov/WarningLettersandNoticeofViolation/2013.

15. U.S. FOOD AND DRUG ADMINISTRATION, DRUGS, GUIDANCE, ‘IPLIANCE, & REGULATORY INFORMATION, .fda.gov/drugs/guidancecomplianceregulatoryinformation/default.htm.

16. While FDA issued guidance documents on communications in specific contexts (*see* U.S.)D AND DRUG ADMINISTRATION, GUIDANCE FOR Industry—Consumer-:ted BROADCAST ADVERTISEMENTS (Aug. 1999), .fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07 .pdf), a specific guidance on the Internet as a platform for disseminating product mation was never issued.

17. FDASM, QUESTIONS FOR THE FDA REGARDING “NEXT STEPS” FOR DANCE RELATED TO THE PROMOTION OF FDA-Regulated MEDICAL DUCTS USING THE INTERNET AND SOCIAL MEDIA TOOLS (Dec. 11, 2009), .fdasm.com/docs/FINAL%20DDMAC%20Responses%20to%20FDASM_Questions.pdf.

18. Department of Health and Human Services, Food and Drug Administration. Promotion)A-Regulated Medical Products Using the Internet and Social Media Tools, Public Hearing 15 (Nov. 12, 2009), www.fda.gov/AboutFDA/CentersOffices/CDER/ucm184250.htm.

19. FDA, Guidance for Industry Responding to Unsolicited Requests for Off-Label mation About Prescription Drugs and Medical Devices, 76 Fed. Reg. 82,303 (Dec. 30,), .fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm28 .pdf.

20. FDA, Guidance for Industry Fulfilling Regulatory Requirements for Postmarketing ıissions of Interactive Promotional Media for Prescription Human and Animal Drugs and ıgics (Jan. 2014), .fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm38135 .

21. See 21 C.F.R. § 10.115 for details relating to the Guidance Agenda.

22. Warning Letter from U.S. Food and Drug Administration & Federal Trade Comm’n, to l Spinelli, Ebola-C Inc. (Nov. 18, 2014), .fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm423685.htm. For a full iption of the promotional materials, see Abby Ohlheiser, *FDA Warns Three Companies ıst Marketing Their Products as Ebola Treatments or Cures*, WASH. POST (Sept. 24, 2014), //washingtonpost.com/news/to-your-health/wp/2014/09/24/fda-warns-three-companies-st-marketing-their-products-as-ebola-treatments-or-cures.

23. FDA, *Drug and Device Manufacturer Communications with Payors, Formulary Committees ;imilar Entities—Questions and Answers*, .fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

24. 21 U.S.C. § 352(a), as amended by section 114 of the Food and Drug Administration ernization Act of 1997 (FDAMA) and section 3037 of the 21st Century Cures Act.

25. FDA, *Medical Product Communications That Are Consistent with the* FDA-Required

ling—Questions and Answers,
.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

26. 82 Fed. Reg. 6367 (Jan. 19, 2017).

27. Dissemination of Information on Unapproved/New Uses for Marketed Drugs,
gics, and Devices, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998).

28. 21 U.S.C. §§ 331(a), 393(b).

29. HOWARD L. DORFMAN, WENDY C. GOLDSTEIN & SARAH DIFRANCESCA,
RMACEUTICAL PUBLIC SETTLEMENTS RELATED TO MARKETING AND
)CIATED ACTIVITIES (2011–2012) (used with permission). An updated version,
RMACEUTICAL, BIOTECHNOLOGY, AND MEDICAL DEVICE
NUFACTURERS SELECT PUBLIC GOVERNMENT SETTLEMENTS (current as of
ber 2014), provides updated information for the period 2013–2014.

30. Press Release, Department of Justice, Office of Public Affairs, GlaxoSmithKline to Plead
y and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data,
st Health Care Fraud Settlement in U.S. History (July 2, 2012) [hereinafter DOJ, Office
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31. Arundhati Parmar, *$1.5B Abbott Fine Proves Feds Serious About Penalizing* Off-Label
otion, MedCity News (May 7, 2012 3:33 PM), http://medcitynews.com/2012/05/1-5-
n-abbott-fine-shows-government-more-serious-about-penalizing-off-label-promotion/.

32. DOJ, Office of Public Affairs Press Release, *supra*note 30.

33. For a copy of the GSK settlement, see DOJ, Complaint, No. 11-10398-RWZ (Oct.
011), www.justice.gov/opa/documents/gsk/us-complaint.pdf.

34. www.justice.gov/opa/pr/2013/November/13-ag-1170.html.

35. Court documents related to the J&J settlement can be viewed at www.justice.gov/opa/jj-
)cs.html.

36. A source of information reflecting FDA's determination that a company's promotional
ices violate the FDCA can be found in regulatory action taken by the agency in the form of
ning and Notice of Violation (NOV) letters. Common violations include failure to include
red safety-related information in promotional materials ("risk minimization") and
nsion of the approved indication," which can be considered by the OIG as an FDA
mination that the promotion reviewed did not reflect the approved labeling and therefore
bel.

37. Originally drafted to prosecute suppliers of defective armaments to the Union Army.

Current Status of the Impact of the First Amendment on Off-Label Promotion

Howard L. Dorfman & Phillip V. DeFedele

The question of whether the First Amendment affects the ability of pharmaceutical manufacturers to communicate off-label information has been hotly contested over the past several years. As a result, the opinions issued by federal courts, most notably the U.S. Supreme Court and the Court of Appeals for the Second Circuit, play a critical role in the formulation of industry practices in both the promotional and scientific exchange functions.

The First Amendment to the United States Constitution prohibits the federal government from imposing unreasonable restrictions on freedom of speech. This restriction on government activity also applies to the individual states through the Fourteenth Amendment. The promotion of pharmaceutical products is considered "commercial speech" under the First Amendment, meaning that it relates "solely to the economic interest of the speaker and its audience."[1] The U.S. Supreme Court articulated a four-part test in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York* to determine whether the regulation of commercial speech is permissible under the First Amendment. First, the commercial speech worthy of protection under the First Amendment must be truthful and not false or misleading or related to unlawful activity. Second, the asserted governmental interest in regulating the commercial speech must be substantial. Third, the regulation concerning commercial speech must directly advance the asserted governmental interest. Lastly, the regulation must not be more extensive than necessary to achieve the governmental interest.[2] Clearly, the four-pronged *Central Hudson* test is applicable to the promotional activities of the pharmaceutical industry.

Early First Amendment Challenges and FDA Reaction

Q 7.1 How have courts addressed the question of whether the First Amendment affects a pharmaceutical manufacturer's promotional activities involving information not contained in approved FDA labeling?

The *Central Hudson* test was first applied in a pharmaceutical context in the case of *Washington Legal Foundation v. Henney*.[3] In this case, Washington Legal Foundation (WLF) sued FDA arguing that the provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA) were overly restrictive. Specifically, FDAMA imposed significant obligations on pharmaceutical companies when distributing peer-reviewed journal articles or reference texts on potential new uses for prescription drugs. These obligations included, among other things, requiring pharmaceutical companies to submit a supplemental New Drug Application (sNDA) for the new uses. The court examined these provisions under the *Central Hudson* test and determined that they unconstitutionally restricted protected commercial speech under the First Amendment.[4] It is important to note that the court agreed with FDA's position that encouraging manufacturers to seek FDA approval of indications relating to off-label uses through the filing of sNDAs is a substantial government interest, but the court declared that requiring the filing of an sNDA *before* a manufacturer can disseminate truthful, non-misleading off-label information was not a proper means to achieve that interest.[5]

Another case addressing government oversight of commercial free speech in the pharmaceutical context was *Sorrell v. IMS Health Inc.*, [6] a 2011 decision by the U.S. Supreme Court that overturned a Vermont state law prohibiting dissemination of healthcare provider (HCP) utilization data on First Amendment grounds. The Vermont statute under review, "The Confidentiality of Prescription Information Act," prohibited the sale, disclosure, and use of pharmacy data in marketing efforts by pharmaceutical manufacturers. A coalition of "data miners" (IMS) and the Pharmaceutical Research and Manufacturers of America (PhRMA) (the prescription pharmaceutical industry trade organization) brought suit, challenging the state regulation as a violation of the First Amendment. The Supreme Court, in applying the *Central Hudson* test, overturned the lower court's decision and found that the law violated the First Amendment. Although not strictly a case involving off-label promotion, the decision reinforces the constitutional principle that truthful, non-misleading commercial speech is protected under the First Amendment.

Q 7.2 Does FDA recognize a public health interest in the dissemination of truthful and non-misleading medical information even if off-label?

FDA has long recognized the need of healthcare providers to obtain current, clinically relevant medical and scientific information regarding therapeutic options independent of the regulatory approval process. The agency further acknowledges the unique expertise of drug manufacturers as to the current research involving their products and the therapeutic areas involved. Acknowledging the societal need, FDA has specifically indicated that it is not engaged in restricting the "full exchange of scientific information."[7] The inherent conflict between providing medically relevant (and often state-of-the-art) information to HCPs without violating FDA regulations and the Food, Drug, and Cosmetic Act (FDCA) requires pharmaceutical manufacturers to develop and implement appropriate policies and procedures to strike a balance between the industry's right to engage in First-Amendment protected scientific exchange and the need to avoid unlawful promotion of drug uses that FDA has not approved.

Q 7.3 Has FDA provided guidance to manufacturers on the dissemination of off-label information?

Yes. In an effort to provide regulatory direction, FDA issued an initial guidance in January 2009, *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*[8] (the "Guidance"). The Guidance incorporates elements previously promulgated by the agency in FDAMA. An updated and expanded guidance was subsequently released by FDA in March 2014, which is discussed in more detail at Q 7.4.2 below.

Q 7.4 Does FDA Guidance provide a "safe harbor" for a pharmaceutical company in disseminating off-label reprints?

FDA guidance, if strictly followed by the pharmaceutical manufacturer in the dissemination of the medical information described, provides a safe harbor from FDA enforcement activity for conduct that may violate the FDCA, and FDA will not consider the materials evidence of off-label promotion. FDA guidance provides a detailed process, beginning with the appropriate content of the material to be disseminated, which should consist of information pertaining to "adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety and effectiveness of the drug or device."[9]

Q 7.4.1 What steps should a pharmaceutical company take to take advantage of the "safe harbor"?

FDA Guidance provides extensive detail regarding all aspects of the dissemination process, which includes the following:

- Articles should be published by an organization that has an editorial board that uses experts with demonstrated expertise in the subject matter of the article who

objectively select, reject, or provide comments about proposed articles. The organization should also have a publicly stated policy of full disclosure of any conflict of interest or other biases.

- Articles considered for dissemination must be peer-reviewed and published in accordance with peer-reviewed procedures.
- The article may not be presented in an industry-funded special supplement or publication.
- The material must comprise truthful and non-misleading content.
- The article must be distributed as an unabridged reprint or copy and not marked, highlighted, summarized, or characterized in any way.
- The reprint must include a disclosure statement regarding the unapproved nature of the use described, relevant financial interest, and information as to any significant risks or safety concerns known to the manufacturer that are not discussed in the publication.
- The article must be accompanied by FDA-approved labeling pertaining to the product as well as a comprehensive bibliography of publications related to the off-label use.
- All reprints are to be disseminated with any representative publication reaching contrary or different conclusions than those expressed in the reprint regarding the off-label use (if any).
- The article must be provided separately from any information that may be considered promotional in nature.

The FDA guidance is certainly a useful tool for manufacturers in the development of the necessary internal procedures for identifying appropriate material for distribution. Typically, for a safe harbor to apply, a company must follow every single requirement. Many companies, however, find it difficult to do this, due to the number of requirements. In such cases, it may still be beneficial to comply with both the letter and spirit of the FDA guidance by incorporating as many of the requirements as possible to minimize legal risks to the company.

Q 7.4.2 Has FDA updated the Guidance since its release in 2009?

In March 2014, FDA released updated and expanded recommendations for dissemination of medical information to healthcare professionals titled *FDA Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses-Recommended Practices* ("2014 Draft Guidance"). The 2014 Draft Guidance[10] provides more explicit directions to manufacturers while adding two additional reprint categories to those contained in the 2009 Guidance: medical reference texts and Clinical Practice Guidelines (CPGs).

The 2014 Draft Guidance provides a checklist of additional requirements to be followed if a company intends to rely on FDA's guidance documents as a safe harbor. For example, only the most recent editions of any medical texts or CPGs are appropriate for dissemination; further, the CPGs must be deemed trustworthy and based on a systematic review of all existing medical evidence, including therapeutic options other than those of the distributing manufacturer.[11]

FDA likewise reinforces its often articulated position on the issue of dissemination of off-label information in the 2014 Draft Guidance. While acknowledging that dissemination of accurate scientific information is of considerable value to the medical profession in making therapeutic decisions, the agency reminds manufacturers that ". . . this information is in no way a substitute for the FDA premarket review process . . . ."[12]

The 2014 Draft Guidance is not without its critics. For example, in comments submitted in response to the *Federal Register* Notice, WLF asserted that the 2014 Draft Guidance violates a 1999 federal court injunction that prohibits the agency from taking action to prevent pharmaceutical manufacturers from disseminating peer-reviewed reprints that contain truthful, albeit off-label, information as well as raising serious First Amendment issues.[13]

PRACTICE NOTE: It is important to note that the 2009 and 2014 Guidance documents, by their very nature, do not address all circumstances under which medical and scientific information contained in a peer-reviewed article and published in a peer-reviewed journal as well as in an authoritative medical text, may be disseminated. The subject matter must relate to unapproved "new uses" of "approved drugs" and/or "medical devices." That definition removes numerous articles from consideration for distribution, notwithstanding the fact that the material comports with all other guidance requirements and may represent the very type of medical information that may be most relevant to current medical practice. Another issue for manufacturers to address before embarking on any dissemination program is to determine the mechanism by which articles will be provided to healthcare practitioners. Because of the importance of separating the delivery of the article from any promotional information, the question of utilization of members of the sales force or any company personnel reporting through a commercial (as compared with a medical) function must be seriously considered.

While the Guidance documents certainly can be said to be designed to provide clarity with regard to FDA's requirements regarding dissemination of off-label material and the protections provided by strict adherence by manufacturers, it is critical to recognize the limitations as to the defensive use of both the 2009 and 2014 Guidance documents. Neither the OIG nor the DOJ have expressly adopted either FDA Draft Guidance as controlling authority. In fact, our review of DOJ materials targeting off-label promotion suggests that having a reprint dissemination

program that complies with FDA's Draft Guidance is given little, if any, weight in the government's prosecution of companies alleged to have engaged in unlawful off-label promotion.

The Caronia Decision

Q 7.5 Have there been any successful First Amendment challenges to prosecutions of pharmaceutical representatives allegedly promoting a drug for off-label or unapproved uses?

Yes. A seminal successful challenge to an individual prosecution based on off-label promotion was *United States v. Caronia*.[14] Decided in December 2012, this case relied upon the *Central Hudson* test to reverse the conviction of a pharmaceutical sales representative who promoted truthful and non-misleading off-label uses of an FDA-approved pharmaceutical.

Q 7.6 What were the facts of Caronia?

In *Caronia*, Alfred Caronia, a sales representative for Orphan Medical, Inc., allegedly promoted Xyrem® for off-label indications and use in unapproved patient populations. Xyrem was approved for only two indications (that is, narcolepsy patients with cataplexy and those with excessive daytime sleepiness) and contained a "Black Box" warning stating that safety and effectiveness had not been established in patients under sixteen years old and that there was very limited clinical experience in elderly patients. A physician who cooperated with the government allegedly recorded Caronia promoting the drug for off-label uses, including insomnia, fibromyalgia, periodic leg movement, and muscle disorders, as well as for use in unapproved populations, on two separate occasions. Caronia was convicted at a jury trial of conspiring to introduce a misbranded drug into interstate commerce in violation of the FDCA.[15] His conviction was reversed on appeal.

Q 7.7 Why was Caronia's conviction reversed?

Caronia appealed his conviction on First Amendment grounds. Specifically, he argued that the First Amendment prohibits the government from criminalizing a pharmaceutical manufacturer's "truthful and non-misleading promotion of an FDA-approved drug to physicians for off-label use where such use is not itself illegal and others are permitted to engage in such speech."[16] The Second Circuit used the *Central Hudson* factors to determine that, although the government had substantial governmental interests in drug safety and public health, the complete prohibition of off-label promotion does not directly advance these interests and is not narrowly drawn to achieve them.[17] Therefore, the Second Circuit reversed Caronia's conviction, stating that "[w]e conclude simply that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[18] The court disagreed with the government's reading of the FDCA, holding that such an interpretation would violate the First Amendment.

Q 7.8 Does Caronia mean that off-label promotion is legal?

No. *Caronia* stands for the proposition that the prosecution of an individual for the truthful, non-misleading off-label promotion of an FDA-approved drug violates the First Amendment. This holding is limited to drugs that have already been approved for at least one indication by the FDA. Additionally, the Second Circuit in *Caronia* did not strike down any provision of the FDCA or its implementing regulations as unconstitutional. Moreover, *Caronia* is only binding in the U.S. Court of Appeals for the Second Circuit, which encompasses New York, Vermont, and Connecticut.

Additional First Amendment Challenges

Q 7.9 What is the current environment for government oversight of the dissemination of off-label medical and scientific information?

The clearest example of the conflict facing pharmaceutical manufacturers can be seen in relation to actions taken by Allergan, Inc. (Allergan) with regard to the marketing of Botox®. Although most widely recognized for its use in cosmetic procedures in reducing wrinkles, Botox's ability to reduce certain muscular activity and block nerve impulses has led to additional indications. So, in addition to the various FDA-approved indications, Botox had been prescribed by HCPs for conditions outside the scope of the approved label, including post-stroke spasticity, migraine, and juvenile cerebral palsy. In light of FDA regulatory policy, the proactive dissemination of information to HCPs regarding the use of Botox for these indications opened the company to FDA action for violation of the FDCA.

The issue came to a regulatory crossroads in April 2009 when FDA required revisions to Botox labeling in the form of a "Black Box" warning to ensure the continued safe use of the drug. The warning applied to labeled indications and to certain (but not all) off-label uses. In September 2009, the FDA implemented a risk management program, known as a Risk Evaluation and Mitigation Strategy (REMS), pursuant to its authority under the provisions of the Food and Drug Administration Amendments Act of 2007 to request upgraded warnings and communications to HCPs to ensure the continued appropriate balance between benefits and risk. Allergan faced the Hobson's choice of complying with the FDA's request, which would preclude dissemination of safety information to HCPs for all known off-label uses and increase risk of liability for adverse events, or issuing non-FDA-approved product information and facing prosecution under the FDCA for introducing a mislabeled drug into interstate commerce.

Allergan filed a lawsuit in October 2009 against FDA,[19] challenging FDA's authority under both the FDCA and the First Amendment to restrict the dissemination of truthful and non-misleading medical and scientific information pertaining to its drug. Allergan's justification rested on its determination that information regarding appropriate patient selection, injection site, and dosage would be necessary for HCPs for all Botox uses, as well as provide a modicum of protection in the defense of potential product liability litigation.

As discussed in chapter 5, pharmaceutical manufacturers must be prepared to address issues raised by additional government agencies. The DOJ filed suit against Allergan for off-label marketing of Botox, citing FDCA provisions relating to misbranding, as well as the FCA. Thereafter, Allergan entered into a settlement with the DOJ, agreeing to a payment of $375 million, additional payments of $225 million, resolution of several qui tam actions, and a five-year corporate integrity agreement. What made the settlement unique was the requirement that Allergan dismiss its declaratory judgment action against FDA. A similar lawsuit was instituted against FDA by Par Pharmaceuticals in December 2011, which is

discussed in Q 7.10 below.

Q 7.10 What is the current and potential future position of the U.S. Supreme Court on the FDA's authority to limit off-label promotion?

The federal courts continue to play a crucial role in the ongoing debate regarding the authority of the government to impose restrictions of any kind in the dissemination of authoritative medical information to HCPs notwithstanding the fact that the use described does not appear in the approved product labeling. While it is impossible to know under what circumstances the issue will be before the U.S. Supreme Court, recent judicial activity warrants closer analysis.

In November 2013, the U.S. Attorney's Office in the Southern District of New York filed a statement of interest in *United States ex rel. Matthew Cestra v. Cephalon, Inc.*[20] In *Cephalon*, a former employee brought an FCA suit against Cephalon under the act's qui tam provisions. The former employee alleged that Cephalon caused false claims to be submitted to the government for reimbursement by, among other things, engaging in off-label promotion. The defendant manufacturer had filed a motion to dismiss the case based in large part on the *Caronia* decision. Cephalon argued that, under *Caronia*, its off-label promotion was protected under the First Amendment as commercial speech and, therefore, could not be the basis for an FCA claim. In its statement of interest, the government stressed that reliance on *Caronia* was misplaced because *Caronia* did not involve the FCA. (Rather, the conviction in *Caronia*, which was later overturned, was for conspiracy to introduce a misbranded drug into interstate commerce in violation of the FDCA.) In *Cephalon*, the government argued, "the central question is whether defendant's marketing caused the submission of the claims . . . [,]" which sought reimbursement for off-label uses not covered by any government reimbursement program.[21]

The Southern District of New York never decided whether there was any merit to Cephalon's motion because the relator transferred the case to the Eastern District of Pennsylvania, which is located in the Third Circuit where *Caronia* does not control.[22] Although the *Cephalon* case is still in discovery, it provides guidance to the pharmaceutical industry regarding the current position of the DOJ and the OIG regarding the intersection of off-label promotion and the FCA.

It is difficult to anticipate when and under what circumstances a direct challenge to FDA's regulatory authority over the dissemination of off-label information will come before the Supreme Court. The *Allergan* case could have been a direct challenge if it had proceeded through the appellate system; however, the case was dismissed by the company, as demanded by the OIG, to resolve charges brought for violation of the FCA and related statutes.

A similar lawsuit was filed by Par Pharmaceuticals., Inc. (Par) against FDA in the U.S. District Court for the District of Columbia. The action sought a declaratory judgment barring the agency from enforcing certain regulations that seek to prohibit Par from disseminating "truthful and non-misleading" information to healthcare professionals

concerning the use of its FDA-approved prescription drug.[23] The case arose from Par's desire to provide HCPs with information pertaining to Megace®, a prescription drug approved for the treatment of AIDS-related wastage, although HCPs more often prescribe the drug for geriatric and cancer patients, both off-label uses although consistent with accepted standard of care. In fact, such uses would make it impossible for Par to undertake the placebo-controlled clinical trials necessary to gain approval from FDA. In its filing, Par relied on the reasoning articulated by the Supreme Court in *Sorrell* and drew a distinction with the *Allergan* complaint. Allergan had sought to avoid criminal prosecution for disseminating information relating to off-label uses of Botox to provide important information to HCPs as to dosage, appropriate patient selection, and other critical issues relating to patient safety (not to mention as a proactive means of defending potential product liability claims). In contrast, Par suggested its intention was to provide on-label information, albeit to physicians who may choose to utilize its product for off-label indications. As was the result in the *Allergan* case, the *Par* case resulted in settlement with the government, and the Supreme Court did not have the vehicle to review FDA's authority to restrict dissemination of truthful albeit off-label information.

Q 7.11 Have courts in the Second Circuit dealt with off-label promotion cases since Caronia was decided?

Yes. Two pharmaceutical manufacturers, Amarin Pharma, Inc. (Amarin) and Pacira Pharmaceuticals, Inc. (Pacira), each filed lawsuits against FDA challenging its restrictions on off-label promotion under the First Amendment in the Southern District of New York. Both manufacturers based their challenges on the precedent set forth in *Caronia*.

Q 7.12 What circumstances led to the Amarin litigation?

In 2012, Amarin received FDA approval of its drug Vascepa® for use as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500mg/dL) hypertriglyceridemia. Amarin also sought FDA approval for Vascepa to reduce triglycerides in adults with persistently high triglycerides (200–499mg/dL) by entering into a Special Protocol Assessment (SPA) Agreement with FDA. Under the SPA Agreement, FDA would approve this additional indication if Amarin's ANCHOR study met its endpoints (that is, the reduction of triglycerides). Amarin also entered into a separate SPA Agreement covering a second study to determine whether Vascepa helps prevent major cardiovascular events in patients with persistently high triglycerides. The basis for the additional indication, however, was to be based solely on the ANCHOR Study.

Since the ANCHOR study met all of its endpoints, Amarin filed an sNDA for the additional indication in early 2013. Later that year, FDA held an advisory committee meeting that focused on whether lower triglyceride levels observed in the ANCHOR study resulted in meaningful reductions in cardiovascular risk, which the ANCHOR study was not designed to determine. FDA rejected Amarin's sNDA and explained, in its Complete Response Letter, that the clinical rationale for using Vascepa to treat patients with

persistently high triglycerides was to reduce cardiovascular risk. Because data did not support the reduction of cardiovascular risk, FDA would not approve the sNDA, although the ANCHOR study had proven that Vascepa lowers triglycerides in patients with persistently high triglycerides, which was the indication Amarin sought.

In May 2015, Amarin filed suit and a preliminary injunction against FDA seeking to prevent the agency from prosecuting the company for truthful, non-misleading statements it wanted to disseminate about the use of Vascepa in patients with persistently high triglycerides that were supported by the ANCHOR study and other investigations. Amarin based its argument on the *Caronia* decision, arguing that such statements were protected under the First Amendment.

Q 7.13 What was the outcome of Amarin's First Amendment challenge?

In ruling on Amarin's motion for a preliminary injunction, the court agreed with Amarin's position and stated that, "[w]here the speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech, under *Caronia, cannot* be the act upon which an action for misbranding is based."[24] The court, therefore, granted Amarin's motion which permits Amarin to engage in the truthful and non-misleading promotion of Vascepa to treat patients with persistently high triglycerides. In addition, Amarin submitted various statements and disclosures to the court as modified with input from FDA. The court also found these statements and disclosures to be truthful and non-misleading with minimal alterations.

After that ruling, FDA and Amarin obtained a stay to allow for settlement discussions. The court's decision granting the preliminary injunction is significant because it involved a direct application of the holding in *Caronia*. The court looked at whether or not the speech at issue was false or misleading without the need to analyze the speech under *Central Hudson*. A settlement was reached between FDA and Amarin in February 2016. In that settlement, among other things, FDA agreed to permit Amarin to make some of the promotional claims it had previously viewed as objectionable and invited Amarin to submit future materials addressing off-label use for FDA evaluation and comment.

Q 7.14 What gave rise to Pacira's suit against FDA?

Pacira received FDA approval of its product Exparel® for post-surgical analgesia by infiltration into the surgical site in 2011. The approval of Exparel was based on two clinical studies in which the drug was administered to patients undergoing bunionectomy and hemorrhoidectomy. The broad indication of Exparel was in no way limited to these two procedures. Consistent with the FDA-approved label, Pacira representatives spoke with physicians about using Exparel on various surgical sites. In September 2014, however, FDA issued a Warning Letter demanding that Pacira stop promoting Exparel for uses outside of a bunionectomy or hemorrhoidectomy. The Warning Letter also took issue with statements asserting that Exparel demonstrated pain control beyond twenty-four hours even though an FDA reviewer acknowledged that the drug significantly reduced pain through seventy-two

hours when compared to placebo in one of the pivotal trials.

Pacira responded to the Warning Letter, in October 2014, contesting FDA's assertions. FDA did not discuss these issues with Pacira and instead continued to demand that Pacira correct its statements. Pacira eventually acquiesced but continued to dispute FDA's position. In July 2015, FDA "closed out" the Warning Letter without ever addressing Pacira's contentions. Pacira then filed suit and moved for a preliminary injunction against FDA to prevent it from taking enforcement action against the company for truthful and non-misleading speech about lawful uses of Exparel or from deeming speech misleading when not supported by two adequate and well-controlled studies. Pacira asserted that such enforcement actions would violate the First Amendment and based its argument on *Caronia* and *Amarin*.[25]

Q 7.15 How did the court rule on Pacira's First Amendment argument?

The court did not rule on Pacira's First Amendment argument because the case settled on December 14, 2015. Under the terms of the settlement agreement, FDA confirmed that Exparel has been approved for use in a variety of surgeries, not just those studied in the pivotal trials. FDA also formally acknowledged the rescission of its Warning Letter to Pacira, which it withdrew in October 2015, and approved a labeling supplement to the drug. Pacira can, therefore, promote Exparel for use in a variety of surgeries and state that it can relieve pain for up to seventy-two hours despite reliance on only one clinical trial supporting that promotional claim.

Q 7.16 What do Caronia, Amarin, and Pacira mean for the pharmaceutical industry?

The true impact of these three cases, both in a legal and practical sense, is still unclear. *Caronia* is limited to the Second Circuit, and the government declined to appeal the case to the U.S. Supreme Court. Neither *Amarin* nor *Pacira* were decided on the merits, but the willingness of FDA to reach a settlement in both cases is noteworthy. FDA was likely receptive to settling these cases because they were filed in district courts that are subject to the *Caronia* decision. FDA may have been more willing to further litigate these cases had they been filed in a jurisdiction not bound by *Caronia*.

It is well established that First Amendment protections do not apply to false or misleading speech and the test set forth in *Central Hudson* will continue to control in other jurisdictions until the U.S. Supreme Court says otherwise. Therefore, although FDA's prosecution of off-label promotion as a violation of the FDCA must be considered vulnerable to attack in the Second Circuit, pharmaceutical companies must always take care to communicate only truthful and non-misleading medical and scientific information in any process where pharmaceutical company personnel or those acting on their behalf (for example, speaker bureaus, MSLs) interact with HCPs. In addition, it is critical to recognize that at this time, only the Second Circuit has squarely acted on this issue, and that the DOJ and the OIG remain active in monitoring and investigating industry conduct for possible

violations of the FCA and the Anti-Kickback Statute. In addition, it is important to note that states are increasingly relying on local laws and regulations, such as consumer protection acts, to bring actions against pharmaceutical manufacturers for activities deemed to violate of those statutes.

Q 7.17 How has industry responded to these cases?

On July 27, 2016, PhRMA and the Biotechnology Innovation Organization (BIO) released their joint *Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers* (Joint Principles).[26] The Joint Principles "are intended to form the basis for defining new and clear regulatory standards governing responsible, truthful and non-misleading communications to inform health care professionals about the safe and effective use of medicines."[27] Key concepts embodied in the Joint Principles are the commitments of PhRMA's and BIO's member companies to science-based communication, to provide appropriate context about data, and to the accurate representation of data.

The Joint Principles address the dissemination of, among other things, on-label communications, off-label communications, and healthcare economic information, and emphasize that such communications benefit patient care when truthful and non-misleading. The Joint Principles provide various recommendations on how companies can make such communications in a truthful and non-misleading manner. For example, the Joint Principles state that when presenting scientific data that is not contained in the FDA-approved labeling to HCPs, companies should make various disclosures, including the design of the study, limits on study methodology, the statistical analysis plan, and other relevant evidence, such as peer-reviewed contrary evidence. In addition, companies should provide sufficient contextual information to HCPs to enable them to fully and fairly assess the data. The Joint Principles further explain that such data can be provided from randomized, controlled clinical trials, pharmacoeconomic information, post hoc analyses of clinical trial results, observational data and real world evidence, and treatment guidelines. Notably, most of these sources would not constitute substantial evidence under FDA regulations.

Of particular note is the Joint Principles' challenge to the 2014 Draft Guidance on distributing scientific and medical publications on off- label uses detailed above. The Joint Principles criticize certain practices in the 2014 Draft Guidance for restricting truthful and non-misleading communications that may delay providing accurate information to HCPs. For instance, the Joint Principles criticize the requirement that a reprint should be independent from a manufacturer, effectively eliminating reprints of their own sponsored studies. In addition, the Joint Principles advocate that oral and written summaries of reprints should be permissible. This is in direct conflict with the 2014 Draft Guidance's mandate that reprints should be unabridged.

The Joint Principles are illustrative of industry's thoughts on all types of communications, especially those concerning off-label uses, as well as setting forth a

proposal for the future regulation of off-label communications. They also reiterate industry's belief that the current FDA "safe harbors" for disseminating off-label information are insufficient. The Joint Principles ultimately stand for the proposition that so long as communications are truthful and non-misleading, companies should be able to provide information about off-label uses and data to HCPs to allow them to make well-informed treatment decisions. As discussed above, the heart of the *Caronia, Amarin*, and *Pacira* cases is that, where communications are truthful and non-misleading, they are protected speech under the First Amendment. By focusing on this and encouraging the use of relevant disclaimers and contextual information, the Joint Principles embody First Amendment freedoms while providing a means for HCPs to fully evaluate a wide range of data to make informed treatment decisions.

It is important to note that in many ways the Joint Principles are not reflective of current industry practices but instead are aspirational. Were companies to adopt them today, they do so at their peril.

Q 7.18 Has FDA taken any action to address off-label promotion after these cases?

On November 9 and 10, 2016, FDA held a two-day public hearing to obtain input on issues relating to off-label communications about approved/cleared medical products, meaning drugs, devices, biologics, and animal drugs. As explained in the *Federal Register* Notice, FDA is "engaged in a comprehensive review" of its policies and regulations governing off-label communications about approved/cleared medical products by manufacturers.[28] FDA intends to use input from the meeting to inform its policy development in this area. Although FDA opened the hearing to any commentary on the subject, it had particular interest in the following areas:

- The extent to which additional communications from manufacturers about off-label uses can provide relevant, scientifically sound information and the extent to which HCPs face impediments to obtaining such information;
- The pros and cons for public health associated with manufacturers' dissemination of off-label information and appropriate limitations or requirements to such dissemination that would protect patients from harm; and
- The impact of increased off-label communications on incentives to conduct biomedical research submitted to FDA for review and subjects' willingness to participate in such research.

Over the course of two days, industry, patients, the medical community, academia, and other interested parties presented their views, which varied drastically, on this heavily debated topic. The widely divergent views on the subject give FDA much to consider in sculpting its new off-label communication policies. In light of this, FDA opened an initial ninety-day comment period after the hearing to solicit further feedback and re-opened the comment period through April 10, 2017.

Q 7.19 What actions did FDA take after conducting the public hearing?

On January 18, 2017, FDA released two draft guidances on manufacturer communications about their products as well as a sixty-page memorandum addressing its position on recent challenges to FDA policy on First Amendment grounds.[29] The draft guidance, entitled "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities—Questions and Answers" (the "HCEI Draft Guidance"), addresses the communication of healthcare economic information by drug and device manufacturers with payors, formulary committees, and other similar entities. The other draft guidance, entitled "Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers" (the "Consistent Communications Draft Guidance"), details FDA's current thinking about manufacturers' medical product communications that include data and information outside of the label but relate to approved indications.

Q 7.20 What does the Consistent Communications Draft Guidance say?

The Consistent Communications Draft Guidance does not directly address promoting an approved medical product for an unapproved use.[30] It does, however, give companies leeway for providing certain information that is not included in the product labeling, so long as such information is consistent with the FDA-required labeling for the product. The Consistent Communications Draft Guidance applies to drugs, medical devices, biologics, and animal drugs although this discussion will focus on drugs for human use. The main takeaway from the Consistent Communications Draft Guidance is that FDA will not consider the communication of information outside the FDA-required labeling by itself to be evidence of a new intended use if the communication is consistent with the labeling.

In determining whether a communication is "consistent" with the FDA-required labeling, FDA examines three factors. If a communication fails to satisfy just one of the factors, then the communication is not consistent with the labeling. The first factor FDA examines is how the information in the communication compares to the information in the FDA-required labeling relating to indication, patient population, limitations and directions for use, and dosing/administration. To fulfill this factor, the communication must be for the same indication and patient population contained in the FDA-required labeling and must not conflict with the limitations of use, directions for use, and dosing/administration contained in the labeling. Essentially, this factor serves as a check to ensure the communication does not promote or claim an unapproved use of the product.

The second factor is whether the representations in the communication increase the potential for harm compared to the information contained in the FDA-required labeling. If the communication would increase the potential for harm, it would not fulfill this factor. An example of a communication that would fail to meet this factor is a communication that suggests using a second- or third-line therapy as a first-line treatment since this suggests use in a broader patient population than the drug's risk-benefit profile justifies. Although the guidance provides this concrete example, this factor is still perhaps the most intensive of

the factors since a manufacturer will need to evaluate whether the communication alters the risk-benefit profile of its product. A manufacturer will likely need to take a multi-disciplinary approach, involving medical, regulatory, legal, and statistics functions, to determine whether a communication would meet this factor.

The third and final factor is whether the directions for use in the FDA-required labeling permit the product to be used safely and effectively under the conditions represented in the communication. If so, this factor will be fulfilled. This factor is similar to the previous factor in that a safety and efficacy analysis must be undertaken. Therefore, determining whether this factor is satisfied would likely also require a multidisciplinary approach. All in all, the determination of whether a communication is consistent with the FDA-required labeling is a fact-specific inquiry based on the particular representations being made in a communication.

The Consistent Communications Draft Guidance provides examples of communications that could fulfill all three of these factors and, therefore, be consistent with the FDA-required labeling including the following:

- Information based on a comparison of the safety or efficacy of a drug for its approved indication to another drug with the same indication (can be a single head-to-head study);
- Information that provides additional context about adverse reactions for an approved indication of a drug;
- Information about the onset of action of the product for its approved indication and dosing regimen;
- Information about the long-term safety and/or efficacy of a drug approved for chronic use;
- Information about the effects of a drug in subgroups of its approved patient population;
- Patient-reported outcomes when using the drug for its approved indication in its approved patient population;
- Information about product convenience; and
- Information that provides additional context about the drug's mechanism of action detailed in its FDA-required labeling.

Even if a communication is consistent with the FDA-required labeling, it must still not be false or misleading in any particular and must otherwise comply with all applicable FDA requirements, such as including important safety information. In addition, a communication must have appropriate evidentiary support grounded in fact and science with appropriate context. For example, any data or studies cited should be scientifically appropriate and statistically sound to support the representations made in a communication. The evidence should also be accurately characterized and include any limitations. Of particular significance, the Consistent Communications Draft Guidance

explicitly states that "FDA would not consider representations . . . in a communication that is consistent with the FDA-required labeling to be false or misleading based only on the lack of evidence sufficient to satisfy the [approval standard]"—substantial evidence.[31] Therefore, the Consistent Communications Draft Guidance takes the extraordinary step of lowering the evidentiary standard for certain promotional claims so long as they are consistent with the FDA-required labeling. This appears to be in direct response to the First Amendment challenge in *Pacira* that "substantial evidence" is a standard for FDA approval of products to be marketed but was never intended to be the standard for promotional claims about that approved use.

Although it is a departure from FDA's previous thinking, it is important to remember that the Consistent Communications Draft Guidance does not directly address the off-label promotion of unapproved uses. While the Consistent Communications Draft Guidance gives companies some additional leeway, it will be important for companies to establish a process for determining and documenting why particular claims meet the requirements of the Consistent Communications Draft Guidance.

Q 7.21 What is the significance of FDA's memorandum?

The FDA's memorandum entitled "Public Health Interests and First Amendment Considerations Related to Manufacturer Communication Regarding Unapproved Uses of Approved or Cleared Medical Products" (the "First Amendment Memo"), sets forth FDA's justifications for regulating off-label promotion and how, in doing so, it protects and promotes public health.[32] The First Amendment Memo explains that the FDA's current regulatory and enforcement regime advances public or individual health interests by motivating the development of robust scientific data on safety and efficacy; preventing harm to the public; protecting against fraud, misrepresentation, and bias; preventing the diversion of healthcare resources to ineffective treatments; ensuring labeling is accurate and informative; protecting the integrity and reliability of promotional information; protecting human subjects receiving experimental treatments; ensuring informed consent; maintaining incentives for clinical trial participation; protecting incentives for innovation, such as grants of exclusivity; and promoting the development of products for underserved patients.

The First Amendment Memo does, however, acknowledge how communications on unapproved uses of approved or cleared medical products can also advance public or individual health interests by supporting informed decision-making for patient treatment and furthering scientific understanding and research. FDA noted, however, that various acceptable avenues already exist for such communications, such as mandatory posting of information about clinical trials assessing investigational new uses on ClinicalTrials.gov.

FDA identified various data points in support of its positions in the First Amendment Memo. For example, FDA cited a study showing that the incidence of adverse events was higher in unapproved uses than approved uses of drugs. FDA also presented, in an Appendix to the First Amendment Memo, anecdotal data about how commonly accepted unapproved uses of drugs have led to patient harm. In addition, FDA challenged the

Caronia and *Amarin* decisions by reiterating that it is constitutionally permissible to use speech as evidence of intent, citing Supreme Court precedent. Furthermore, FDA asserted that, under the test set forth in *Sorrell*, content- and speaker-based restrictions are constitutionally permissible in the context of prescription drug promotion. FDA then went on to explain why the alternative approaches proposed by the Second Circuit in *Caronia* and commentators are inadequate to advance the many interests cited in the memo. All in all, the First Amendment Memo serves as FDA's reminder to critics, industry, commentators, and the public of its mission to protect public health, the complicated web of interests it must consider when enforcing its rules and regulations, and its belief that regulating off-label promotion furthers its mission and minimizes patient harm.

Q 7.22 How does the 21st Century Cures Act impact off-label communications by pharmaceutical companies?

Although the 21st Century Cures Act (the "Cures Act"), signed into law on December 13, 2016, does not overhaul the means by which pharmaceutical manufacturers may disseminate off-label information, the Cures Act clarifies the scope of providing health care economic information (HCEI), which may include certain information not contained within the FDA-approved labeling of a drug, to certain audiences. Section 3037 of the Cures Act amends provisions of the FDCA, enacted under FDAMA § 114, on sharing HCEI with formulary committees and other similar entities. The Cures Act effectively broadens the types of recipients who may receive HCEI and what information constitutes HCEI.

Under FDAMA § 114, HCEI provided to "a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading [for purposes of the misbranding provisions of the FDCA] if the health care economic information directly relates" to an approved indication and is "based on competent and reliable scientific evidence."[33] FDAMA § 114 goes on to define HCEI as "any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention."[34]

As modified by the Cures Act, HCEI can now be provided to "a payor, formulary committee, or other similar entity, with knowledge and expertise in the area of health care economic analysis carrying out its responsibilities for the selection of drugs for coverage or reimbursement."[35] This provision now explicitly references payors, such as private insurers, and simply requires that the entity receiving HCEI carries out its responsibilities for the coverage and reimbursement of drugs.

Most significantly for purposes of off-label communications, the Cures Act no longer requires HCEI to "directly relate" to an approved indication as it can now simply "relate" to one. If the HCEI contains any off-label information, however, a "conspicuous and prominent statement describing any material differences between the [HCEI] and the

[approved labeling]" must be included.[36] Importantly, HCEI cannot, however, "relate only to an indication that is not approved."[37] The act, therefore, explicitly acknowledges that HCEI may contain off-label information, and, if disseminated in accordance with the act, such HCEI would not, on its face, violate the FDCA.

In addition, the Cures Act further details what information constitutes HCEI and removes the requirement that HCEI be a comparative analysis. HCEI is now defined as any "analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug. Such analysis may be comparative to the use of another drug, to another health care intervention, or to no intervention." All in all, the Cures Act clarifies how and to whom HCEI may be disseminated, which is supplemented by the HCEI Draft Guidance mentioned above.

The HCEI Draft Guidance provides recommendations to manufacturers on how to communicate HCEI under the Cures Act.[38] Specifically, the HCEI Draft Guidance addresses providing HCEI to payors regarding approved drugs and communications to payors about investigational products. Regarding the communication of HCEI, the HCEI Draft Guidance explains that HCEI may be presented in various forms, including an evidence dossier, a reprint, a software package comprising a model, or a budget impact model. Additionally, companies may provide HCEI to a range of entities provided such entities are constituted to consider HCEI through a deliberative process and have appropriate knowledge and expertise in the area of health care economic analysis needed to properly interpret HCEI. Significantly, in the HCEI Draft Guidance, FDA again acknowledges that HCEI may contain off-label information and it does not intend to use HCEI disseminated in accordance with the guidance as evidence of a new intended use.

The HCEI Draft Guidance also clarifies the requirement that HCEI relate to an approved indication. To relate to an approved indication, HCEI should relate to the disease or condition or the manifestation or symptoms of the disease or condition in the approved patient population.

Examples of HCEI that relate to an approved indication include duration of treatment (when the approved indication does not limit duration of use), practice settings that differ from the settings in which the clinical trials took place, burden of illness, data on dosing regimens that vary from the labeling, treatment effects in patient subgroups that are part of the approved population, length of hospital stay, validated surrogate endpoints, health outcome measures, patient persistence, and comparative studies. The HCEI Draft Guidance also provides examples of HCEI that would not relate to an approved indication, such as HCEI concerning disease course modification for a drug that is only approved to treat symptoms of the disease and HCEI derived from studies in unapproved patient populations.

The HCEI Draft Guidance also explains the evidentiary standard for HCEI—that it is based on competent and reliable scientific evidence (CARSE). To be based on CARSE, HCEI must be "developed using generally-accepted scientific standards, appropriate for the

information being conveyed, that yield accurate and reliable results."[39] In evaluating whether HCEI is based on CARSE, FDA will consider existing current good research practice for substantiation developed by authoritative bodies. Additionally, FDA clarified that the CARSE standard applies to all components of HCEI, such as any inputs and assumptions. The HCEI Draft Guidance also mandates that certain information accompany HCEI, including, as applicable, study design and methodology, generalizability, limitations, sensitivity analysis, conspicuous and prominent statement describing material differences between the approved labeling and HCEI, FDA-approved labeling, disclosure of omitted studies or data sources, risk information, and potential financial or affiliation biases.

The HCEI Draft Guidance also explains the type of information that companies can share with payors about investigational products. As a threshold matter, the information must be unbiased, factual, accurate, and non-misleading and must be presented with certain contextual information. Under the guidance, companies may share product information (e.g., drug class), information about the sought-after indication, factual presentations of results from preclinical or clinical studies without conclusory statements regarding the product's safety or efficacy, anticipated timeline for possible approval, pricing information, targeting and marketing strategies, and product-related programs or services, such as patient support programs, with payors. When sharing this information, companies must also provide a clear statement that the product is investigational and its safety and effectiveness have not been established and information related to the stage of product development. FDA also recommends that companies provide follow-up information to payors if information they had previously provided becomes outdated. As with all pre-approval communications, statements that represent an investigational product is approved or safe and effective are inappropriate.

Q 7.23 What is the potential effect of the FDA's proposed Final Rule regarding the scope of "intended use" on off-label promotion?

Notwithstanding the outcome of the litigation in the Second Circuit, the FDA has continued to express the opinion that a pharmaceutical company's dissemination of truthful, non-misleading statements regarding off-label use can constitute evidence of an "intended use" beyond the approved labeling. In 2015, the FDA proposed a rule regarding the scope of intended use that included a statement that FDA would "not regard a firm as intending an unapproved new use for an approved or cleared medical product based solely on that firm's knowledge that such product was being prescribed or used by doctors for such use." Nonetheless, the FDA issued a Final Rule in 2017 that retained the right of the agency to consider evidence of a company's knowledge of off-label use as part of a "totality of the evidence" standard regarding intended use. If implemented, the revision of the concept of "intended use" would perhaps indicate a renewed intention by the FDA to take further action against manufacturers for off-label promotion.

Vigorous objections filed in response to the proposed Final Rule resulted in the FDA

postponing the effective date. On January 12, 2018, FDA posted a notice in the *Federal Register* on its decision "to seek additional time to reassess [the] rule that would have changed longstanding practices for how the agency determined the 'intended use' of medical products."[40] Although action was expected in March 2018, no further indication regarding possible implementation of the Final Rule has been released.

Q 7.24 Have any state or federal legislative initiatives been undertaken regarding the issue of off-label promotion?

There are two initiatives of note in this area. On March 21, 2017, Governor Doug Ducey of Arizona signed Arizona HB 2382 (the "Free Speech in Medicine Act") lifting off-label promotion restrictions and permitting drug industry members to share truthful research and scientific information regarding safe and effective alternative uses for approved prescription pharmaceuticals with health care providers.

The Goldwater Institute in Arizona, responsible for drafting the legislation, has announced plans to have the model bill introduced in other state legislatures.

The second initiative was undertaken by Rep. Morgan Griffith (R-VA) who introduced a bill (H.R. 1703) in March 2017 (the "Medical Product Communications Act of 2017") seeking to limit FDA's authority to take action against a pharmaceutical manufacturer for discussing off-label indication with healthcare providers. As of March 2018, no further action has been taken regarding the legislation.

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1. Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y., 447 U.S. 557, 561)).
2. *Id.* at 566.
3. Wash. Legal Found. v. Henney, 56 F. Supp. 2d 81 (D.D.C. 1999).
4. *Id.* at 87.
5. *Id.* at 86–88.
6. Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011).
7. 21 C.F.R. § 312.7(a).
8. U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY)OD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON .PPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED)ICAL DEVICES, www.fda.gov/regulatoryinformation/guidances/ucm125126.htm.
9. *Id.*
10. FDA GUIDANCE FOR INDUSTRY: DISTRIBUTING SCIENTIFIC AND)ICAL PUBLICATIONS ON UNAPPROVED NEW USES—RECOMMENDED CTICES (Draft) (Feb. 2014) [hereinafter 2014 Draft Guidance], .fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
11. Although not referenced in the 2014 Draft Guidance, any internal review process red by a company for approval of any CPGs prior to dissemination should consider the

if any, played by the company in producing the CPGs in question and to require parency as to company participation and funding.

12. 2014 Draft Guidance, *supra* note 10. This comment appears to address both criticism of 009 Guidance as well as concerns raised in the wake of the Second Circuit opinion in ed States v. Caronia, 703 F.3d 149 (2d Cir. 2012).

13. For a further description of the Washington Legal Foundation comments, see Gretchen , *WLF: FDA's Revised Reprint Draft Guidance Violates Injunction and First Amendment*, LITION FOR HEALTH CARE COMMC'N (May 19, 2014 8:08 PM), .cohealthcom.org/2014/05/19/wlf-fda%E2%80%99s-revised-reprint-draft-guidance-es-injunction-and-first-amendment/.

14. United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).

15. 18 U.S.C. § 371 and 21 U.S.C. § 331(a).

16. *Caronia*, 703 F.3d at 160.

17. *Id.* at 166–69.

18. *Id.* at 169.

19. Allergan, Inc. v. United States, No. 09-1879 (D.D.C. Oct. 2, 2009).

20. United States *ex rel.* Matthew Cestra v. Cephalon, Inc., 10 Civ. 6457 (SHS) (S.D.N.Y.).

21. *See* Statement of Interest of the United States of America, at 4, United States v. Caronia, .3d 149 (2d Cir. 2012).

22. Cestra v. Cephalon, Inc., No. 2:14-cv-01842-TON (E.D. Pa. 2014).

23. Complaint for Declaratory and Injunctive Relief Par Pharm., Inc. v. United States, No. cv-01820 RWR (D.D.C. Oct. 14, 2011).

24. Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015).

25. Pacira Pharm., Inc. v. FDA, 1:15-cv-07055-RA (S.D.N.Y. 2015).

26. Press Release, PhRMA, PhRMA & BIO Release Joint Principles on Communications Health Care Professionals and Payers (July 26, 2016), http://catalyst.phrma.org/phrma-bio-e-joint-principles-on-communications-with-health-care-professionals-and-payers.

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29. FDA, FDA Statement, Statement from FDA Commissioner Robert Califf, M.D. uncing New Draft Guidances on Medical Product Communications (Jan. 18, 2017), .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm537371.htm.

30. FDA, Guidance for Industry—Medical Product Communications That Are Consistent the FDA-Required Labeling–Questions and Answers (Draft) (Jan. 2017), .fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-locuments/document/ucm537130.pdf.

31. *Id.*

32. FDA, Memorandum, Public Health Interests and First Amendment Considerations ed to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared cal Products (Jan. 2017), www.regulations.gov/document?D=FDA-2016-N-1149-0040.

33. Food and Drug Administration Modernization Act (FDAMA), 21 U.S.C. 301 (1997) ł.

34. *Id.*

35. 21st Century Cures Act, Pub. L. No. 114-255, § 3037.

36. *Id.*

37. *Id.*

38. FDA, Guidance for Industry and Review Staff—Drug and Device Manufacturer munications with Payors, Formulary Committees, and Similar Entities–Questions and ers (Draft) (Jan. 2017), www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-locuments/document/ucm537347.pdf.

39. *Id.*

40. 83 Fed. Reg. 2092 (Jan. 16, 2018), ://www.federalregister.gov/documents/2018/01/16/2018-00555/clarification-of-when-ıcts-made-or-derived-from-tobacco-are-regulated-as-drugs-devices-org.

Food and Drug Administration Amendments Act of 2007 and the Growth of FDA Enforcement Authority

Scott M. Lassman

The Food and Drug Administration Amendments Act of 2007 (FDAAA) was signed into law by the President on September 27, 2007.[1] Although it originally was intended simply to reauthorize the Prescription Drug User Fee Act (PDUFA) for the fourth time, in the wake of concerns about drug safety following the withdrawal of a well-known pain medication and questions about the use of antidepressants in children, Congress used PDUFA reauthorization as a vehicle to enact sweeping changes to the Food and Drug Administration's (FDA's) authority over prescription drug products, particularly with respect to post-market safety. In fact, FDAAA represented perhaps the most significant piece of FDA reform legislation in nearly fifty years.

Among other things, the legislation provides FDA with additional authority to (1) require companies to conduct post-market studies and clinical trials assessing drug safety, (2) order revisions to drug labeling to reflect new safety information, and (3) impose Risk Evaluation and Mitigation Strategies (REMS), including distribution and use restrictions, on certain drugs. Congress also sought to address drug safety by placing new requirements and restrictions on direct-to-consumer (DTC) advertising, including, among other things, granting FDA authority to require pre-review of DTC television advertisements under certain circumstances and imposing disclosure requirements for DTC print advertisements to help facilitate the reporting of adverse events. Finally, Congress sought to ensure that physicians and patients have access to all relevant information about the drug products they might prescribe or use by requiring companies to publicly disclose a wide variety of information about ongoing and completed clinical trials, including information that many companies considered to be confidential commercial information.

FDAAA is significant not only because of the numerous regulatory obligations it created, but also because Congress provided FDA with tough new

enforcement tools in order to ensure compliance with these new obligations. For example, FDA now has authority to impose civil money penalties (CMPs) for certain violations of the rules governing DTC advertising. Likewise, failure to comply with the requirements pertaining to post-market studies, safety labeling changes, REMS, or disclosure of information about clinical trials may result in hefty CMPs, some of which can reach $10 million, or may be grounds for FDA to seek seizure, injunction, or criminal penalties. As a result of FDAAA, FDA has a varied and potent set of new tools in its arsenal to ensure compliance with the federal Food, Drug, and Cosmetic Act (FDCA).

Post-Market Studies and Post-Market Clinical Trials

Q 8.1 Can prescription drug manufacturers be required to conduct studies or clinical trials of a drug product after its approval?

Yes. Pursuant to a new provision of the FDCA added by FDAAA, FDA may require a "responsible person" to conduct one or more post-market studies or post-market clinical trials if certain requirements are met.[2] The term "responsible person" is defined as the holder of an approved or pending new drug application (NDA) for a prescription drug or the holder of an approved or pending biologics license application (BLA) for a biological product.[3] The decision to require post-market studies or post-market clinical trials can be made either before or after approval of a drug product.

Q 8.2 Is there a difference between a post-market "study" and a post-market "clinical trial"?

Yes. FDA defines the term "clinical trials" for purposes of this provision as "any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects."[4] By contrast, FDA defines the term "studies" as "all other investigations, such as investigations with humans that are not clinical trials as defined above (for example, observational epidemiologic studies), animal studies, and laboratory experiments."[5] Accordingly, FDA can require sponsors to conduct a broad range of studies and clinical trials under its FDAAA authority, including laboratory experiments, preclinical animal studies, observational studies, and well-controlled, prospective clinical trials.

Q 8.3 When is FDA authorized to require post-market studies or post-market clinical trials?

FDA may require one or more post-market studies or post-market clinical trials, either before or after approval, for any or all of the following purposes:

- to assess a known serious risk related to use of the drug;
- to assess signals of serious risk related to use of the drug; or
- to identify an unexpected serious risk when available data indicate the potential for serious risk.[6]

The FDA's request must be based on "scientific data deemed appropriate by [FDA]"[7] and, for previously approved drugs, must be based upon "new safety information."[8] The statute does not specify the types of scientific data that may be "deemed appropriate" by FDA, but such data likely would include information contained in the NDA or BLA for the drug, any available data in scientific or medical journals, and information about other

approved or unapproved drugs that are chemically or pharmacologically related to the drug in question, including adverse event reports.

Before requiring a post-market *study*, FDA must determine that routine adverse event reporting and active surveillance would not be sufficient to meet the safety-related purpose or purposes for which FDA would require the study's completion.[9] Before requiring a post-market *clinical trial*, FDA first must determine that a post-market study or studies will not be sufficient to meet the specified safety-related purpose or purposes.[10] Accordingly, Congress intended FDA to implement its new authority in a stepwise fashion and to require post-market studies or post-market clinical trials only when open safety issues cannot be addressed through less burdensome avenues, such as adverse event reporting or active surveillance.

Q 8.4 What is a "serious risk," a "signal of a serious risk," and an "unexpected serious risk"?

A "serious risk" is defined as a "risk of a serious adverse drug experience."[11] A "serious adverse drug experience," in turn, is defined as an adverse drug experience that results in death (or places the patient at immediate risk of death), an inpatient hospitalization or the prolongation of an existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or a condition that may jeopardize the patient and may require a medical or surgical intervention to prevent one of the above outcomes.[12]

A "signal of a serious risk" is defined as information related to a serious adverse drug experience that is derived from a clinical trial, adverse event reports, a post-market study, peer-reviewed biomedical literature, a post-market risk identification and analysis system under development by FDA, or other scientific data deemed appropriate by FDA.[13]

Finally, the term "unexpected serious risk" means "a serious adverse drug experience that is not listed in the labeling of a drug, or that may be symptomatically and pathophysiologically related to an adverse drug experience identified in the labeling, but differs from such adverse drug experience because of greater severity, specificity, or prevalence."[14]

Consequently, FDA may order a company to conduct a post-market study or post-market clinical trial only if the study or clinical trial is intended to assess or identify a known or suspected *serious* risk. FDA does not have authority under this provision to order studies or clinical trials to assess or identify non-serious risks or to assess the effectiveness of a drug product.

Q 8.5 What does the term "new safety information" mean for purposes of requiring post-market studies or post-market clinical trials after approval of a drug product?

As mentioned above, FDA is authorized to require post-market studies or post-market clinical trials for previously approved drug products only if the request is based upon "new

safety information." The term "new safety information" is defined in the statute as information about (1) a serious risk or unexpected serious risk associated with a drug that FDA has become aware of since the drug was approved, since a REMS was required, or since the last assessment of an approved REMS, or (2) the effectiveness of an approved REMS for the drug obtained since its last assessment.[15] Furthermore, the above information must be derived from a clinical trial, an adverse event report, a post-approval study, peer-reviewed biomedical literature, data derived from a post-market risk identification and analysis system under development by FDA, or other scientific data deemed appropriate by FDA.[16]

Q 8.6 Are there circumstances under which FDA will request a sponsor to voluntarily agree to conduct post-market studies or clinical trials rather than require them to do so under the new FDAAA provisions?

Yes. Prior to FDAAA, FDA often requested sponsors to conduct post-market studies or clinical trials on a voluntary basis, and most sponsors agreed to do so.[17] These studies often were intended to further refine the safety, efficacy, or optimal use of a product or to ensure consistency and reliability of product quality.[18] This practice will continue for studies or clinical trials that do not fall within the scope of the FDAAA provisions because, for example, they focus on drug quality or effectiveness rather than safety.[19] Post-market studies and clinical trials that a sponsor has agreed to conduct voluntarily are referred to by FDA as "post-marketing commitments," or PMCs.[20] Post-market studies or clinical trials that are required under FDAAA or another statutory or regulatory provision (for example, deferred pediatric studies, Subpart H studies) are referred to by FDA as "post-marketing requirements," or PMRs.[21]

Q 8.7 What is the process for FDA to require a post-market study or post-market clinical trial under FDAAA?

FDA generally seeks to notify the responsible person of the planned target date for discussions regarding PMRs and PMCs within fourteen days of the sixty-day filing date for the NDA or BLA application.[22] FDA has indicated that generally the planned target date for discussions should be no later than one month prior to the PDUFA goal date.[23] This time frame was designed to facilitate earlier discussions and help ensure that required post-market studies and post-market clinical trials are appropriate and necessary, and are well designed to answer legitimate scientific and medical questions regarding the safety of a drug product.[24] One criticism of the prior system was that discussions regarding post-market commitments often did not occur until late in the review process, resulting in rushed decisions and the requirement to conduct many ill-designed post-market studies of questionable scientific or medical relevance. It is not clear at this time, however, whether the process for requesting and discussing PMRs and PMCs has improved significantly since passage of FDAAA in 2007.

The decision to require a post-market study or post-market clinical trial must be made at or above the level of the person empowered to approve the NDA or BLA for the drug product in question.[25] Generally, this will be the division director, but in some cases it may be the office director. Appeals are available through the normal dispute resolution channels.[26] The appeals process is important because many of these studies are time-consuming and expensive. Unless discussions begin early in the review process, however, the dispute resolution process may not be useful as a practical matter because of pressure to obtain timely approval of the drug product.

For each PMR or PMC intended to investigate a safety issue, the responsible person must submit a timetable for completion of the study or clinical trial.[27] The timetable should include a schedule for "milestone submissions," such as final protocol submission, study completion date, and final report submission.[28]

Q 8.8 How does FDA determine whether post-market studies or post-market clinical trials are proceeding in accordance with the established timetable?

Companies subject to PMRs and PMCs investigating a safety issue are required to "periodically report" to FDA on the status of the post-market study or clinical trial.[29] FDA has indicated that companies typically can satisfy this obligation by submitting annual status reports pursuant to 21 C.F.R. § 314.81 (for drug products) or § 601.70 (for biological products).[30] On a case-by-case basis, however, a PMR may require additional periodic reporting at specified "milestones."[31]

Periodic reports must include, at a minimum, information on the status of the study or clinical trial, including whether any difficulties in completing the study have been encountered.[32] For clinical trials, periodic reports must contain additional details, including, among other things, whether enrollment has begun, the number of participants enrolled, the expected completion date, and documentation that the clinical trial is registered in the public database administered by the National Institutes of Health (NIH), which is discussed in more detail below.[33]

Q 8.9 Are there any penalties for failing to comply with PMR requirements?

Yes. Failure to comply with a PMR established under FDAAA is a "prohibited act" under section 301 of the FDCA[34] and also constitutes misbranding under section 502 of the FDCA.[35] FDA thus can use the full complement of civil and criminal enforcement tools available under the FDCA against companies that fail to comply with a PMR, including failing to comply with a submitted timetable. These penalties can include, among other things, issuance of a Warning or Untitled Letter, seizure, injunction, and, in extreme cases, criminal prosecution.[36]

Failure to comply with a PMR also constitutes grounds for imposing substantial

CMPs.[37] Since FDA may issue CMPs also for violations of the FDAAA provisions governing safety labeling changes and REMS, they are discussed in detail below.

Significantly, the statute provides that no violation will be found if the responsible person can demonstrate "good cause" for the non-compliance or violation.[38] This provision is important because many studies are delayed due to circumstances beyond the sponsor's control, such as difficulties recruiting subjects. FDA is charged with determining what constitutes "good cause" for noncompliance.[39] The agency, however, has not yet defined what constitutes "good cause" for purposes of this provision.

Authority to Mandate Safety Labeling Changes

Q 8.10 Can FDA require companies to revise the approved labeling of their marketed drug and biological products?

Yes. FDAAA provides FDA with sweeping authority to require labeling changes if it becomes aware of "new safety information" that it believes should be reflected in the approved labeling.[40] As discussed above, the term "new safety information" is defined as information derived from a clinical trial, an adverse event report, a post-approval study, peer-reviewed biomedical literature, or active surveillance about either: (a) a serious risk or unexpected serious risk associated with use of the drug that FDA has become aware of since the drug was approved, a REMS was required, or the last assessment of the REMS; or (b) the effectiveness of the approved REMS for the drug since its last assessment. FDA's authority, therefore, is not all-inclusive but rather is limited to revisions to labeling based upon *new* information about *serious* adverse events.

Q 8.11 Does FDA's authority to require safety labeling changes apply to all drug and biological products?

No. FDA's authority extends to (1) prescription drug products with an approved NDA, (2) biological products with an approved BLA, and (3) prescription drug products with an approved Abbreviated New Drug Application (ANDA) if the reference listed drug (RLD) upon which ANDA approval was based is not currently marketed.[41] FDA's authority does not extend to non-prescription (over-the-counter) drugs, even those approved under an NDA, or to marketed unapproved drugs.[42]

Q 8.12 Can FDA order changes to any portion of a covered product's approved labeling?

The statute does not limit the changes that may be required to any particular section of the approved labeling, although it specifically states that labeling revisions may include changes to "boxed warnings, contraindications, warnings, precautions, or adverse reactions."[43] Since mandatory changes must be based upon new information regarding *serious* risks, the portions of labeling that typically communicate such risks are most likely to be subject to mandatory safety labeling changes. These include boxed warnings, contraindications, warnings and precautions, drug interactions, and adverse reactions. If new information would require a change only to the adverse reactions section of labeling, it likely would not trigger the safety labeling change provisions of FDAAA because the change likely would not communicate a serious risk.[44]

There is some debate as to whether FDAAA authorizes FDA to require changes to the "Indications and Usage" section of labeling. Arguably, the "Indications and Usage" section

is unlike the labeling sections specifically mentioned in the statute (for example, boxed warnings, contraindications) in that the information contained therein does not relate solely to safety; rather, it is the product of a risk/benefit analysis that describes those uses for which FDA has approved the therapy. Any decision to change the "Indications and Usage" section thus arguably would require a new risk/benefit assessment and consideration of efficacy data beyond the scope of an inquiry under FDAAA, which is triggered by receipt of, and is limited to consideration of, new safety information. Nevertheless, in some cases, FDA specifically has mandated revisions to the "Indications and Usage" section of labeling.[45]

Q 8.13 What is the process for FDA to require safety labeling changes?

The statute establishes a streamlined process designed to resolve safety labeling issues in a rapid manner. Under FDAAA, if FDA becomes aware of "new safety information" that it believes should be included in the labeling, it must promptly notify the sponsor.[46] FDA may become aware of new safety information from a variety of sources, including adverse event reports, safety-related data in NDAs and BLAs, inspections, medical literature, meta-analyses of safety information, or new analyses of previously submitted information.[47] FDA typically utilizes a multidisciplinary team to evaluate whether new safety information should be incorporated into labeling.[48] FDA's notification will be sent to the holder of the approved NDA or BLA and will include: (a) the source of the new safety information; (b) a brief description of the serious risk implicated by the new information; (c) proposed labeling changes; and (d) instructions for responding to FDA's notice.[49]

After receiving FDA's notification, the sponsor must respond within thirty days by either submitting a supplement with proposed labeling changes or submitting a written statement detailing the sponsor's justification for not proposing a labeling change, which is referred to as a "rebuttal statement."[50] The FDA must promptly review and act upon any submitted supplement, and, if the agency disagrees with either the proposed changes in the supplement or the sponsor's rebuttal statement, the agency must initiate discussions with the sponsor.[51] These discussions may not extend more than thirty days from the date the sponsor's response was due unless FDA determines that an extension is warranted.[52]

If FDA and the sponsor cannot agree on safety labeling changes, within fifteen days of the conclusion of discussions, FDA may issue an "order" requiring the sponsor to make any labeling changes that FDA "deems appropriate to address the new safety information."[53] This order must be issued by an official at or above the level of the person empowered to approve the NDA, BLA, or ANDA for the drug product (that is, division director or above).[54] Appeals are available and must be requested within five days of receiving an order.[55] If the sponsor fails to submit a supplement containing the required labeling changes within fifteen days of receiving the order (or fifteen days after the conclusion of any appeal), the sponsor could be in violation subject to potential misbranding charges and CMPs (discussed further below).[56]

Q 8.14 If a sponsor intends to propose a safety labeling change, what type of supplement should be submitted?

FDA recommends that sponsors submit changes-being-effected, or CBE, supplements if they propose changes that are identical to those recommended by FDA in its notification letter.[57] In all other cases, FDA directs sponsors to submit prior approval supplements.[58]

Submitting a labeling change via a CBE, however, arguably is inconsistent with FDA's regulations governing supplements for labeling changes. FDA interprets its regulations as requiring use of a prior approval supplement whenever an application holder seeks to make changes affecting the "Highlights" section of a drug's labeling.[59] The types of changes to which FDAAA applies—those related to "serious" risks—would typically be expected to require changes to the "Highlights" section, and, therefore, submission of a prior approval supplement. It is thus unclear how FDA will reconcile its recommendation to submit a CBE in cases where the proposed labeling changes affect the "Highlights" section of labeling.

Q 8.15 Is FDA subject to any deadlines for responding to a sponsor's supplement or rebuttal statement?

The statute does not impose any deadlines on FDA to respond to a sponsor's supplement or rebuttal statement. The statute requires FDA to "promptly" review all supplements and contemplates that, in most cases, FDA will conduct its review and the parties will complete discussions about outstanding issues within thirty days of FDA's receipt of the supplement or rebuttal statement.[60] FDA has indicated that it intends to take action within thirty calendar days on supplements that "propose acceptable wording."[61] FDA, however, has not provided any commitment or timing goals regarding responding to rebuttal statements or supplements proposing changes that FDA rejects.

Without clear deadlines for FDA review, the compressed thirty-day time frame for "discussions" may not permit a real opportunity for FDA and the sponsor to conduct discussions about the available scientific information and the need for and content of safety labeling changes. For example, if FDA takes thirty days to review a supplement or rebuttal statement, there would be no time left for any discussions prior to the possible issuance of FDA's "order." While FDA may extend this thirty-day time limit, the decision to do so is left entirely to FDA's discretion.[62] Companies thus may face increased pressure to accept FDA's suggested labeling revisions "voluntarily" in order to avoid issuance of an order, which may have negative evidentiary ramifications in product liability litigation.

Q 8.16 What happens if FDA and the sponsor cannot agree on labeling language?

If FDA and the sponsor cannot agree on acceptable labeling language following the thirty-day discussion period (including any extensions), within fifteen days of the conclusion of the discussion period, FDA may issue an order directing the application

holder to "make such a labeling change as [FDA] deems appropriate to address the new safety information."[63] FDA's order letter generally will include: (1) approval of any sections of labeling on which agreement has been reached; (2) a Complete Response action for the sections of labeling on which there is no agreement; (3) a brief explanation regarding why the application holder's proposed labeling changes or rebuttal do not adequately address the new safety information; and (4) an order to submit a CBE supplement within fifteen calendar days of the date of the order containing the specific wording directed by FDA.[64] FDA expects to review and approve such supplements within fifteen calendar days of receipt.[65]

If the application holder continues to disagree with FDA's safety labeling change order, it may file an appeal within five calendar days of the date of the order in lieu of submitting a CBE supplement.[66] The appeal is handled using FDA's usual dispute resolution procedures for appeals above the division level.[67] We note that, although a dispute resolution process is available, it may be of only limited utility since it is not available until *after* the issuance of an "order" by FDA. Companies making use of the dispute resolution process thus would have to be willing to accept the issuance of an order as a prerequisite to taking their dispute higher up the FDA chain of command. In addition, it is unclear whether an application holder has the option of complying with a safety labeling change order while an appeal is pending or whether interim compliance will be considered a waiver of appeal rights. Given the constant threat of product liability claims, application holders may find it unduly risky to appeal a safety labeling change order if they cannot simultaneously comply with the order during the pendency of the appeal.

Q 8.17 Should the FDAAA process be used if the sponsor, rather than FDA, first becomes aware of "new safety information"?

It is not clear whether an application holder may voluntarily trigger the FDAAA process if it becomes aware of new safety information that should be included in the approved labeling. The safety labeling changes provision includes a "rule of construction," which states that FDAAA "shall not be construed to affect the responsibility of the [sponsor] to maintain its label in accordance with existing requirements," including 21 C.F.R. §§ 314.70 and 601.12.[68] Sections 314.70 and 601.12 contain the FDA's regulations on CBE supplements. The ultimate impact of this provision remains unclear.

FDA has stated that the labeling change process available under 21 C.F.R. §§ 314.70 and 601.12 continues to apply in situations in which the application holder is aware of newly acquired information.[69] In some cases, however, an application holder may find it advantageous to trigger the streamlined FDAAA safety labeling change process. At this time, however, it is not clear whether that option is available.

Q 8.18 Are there penalties for failing to comply with a safety labeling change order?

Yes. Failure to comply with a safety labeling change order is a "prohibited act" under

section 301 of the FDCA[70] and also constitutes misbranding under section 502 of the FDCA.[71] These violations occur when an application holder fails to submit a supplement containing the required labeling changes within fifteen days of receiving the order or fifteen days after the conclusion of any appeal.[72] FDA can use all of the civil and criminal enforcement tools at its disposal under the FDCA against companies that fail to comply with a safety labeling order, including (among other things) issuance of a Warning or Untitled Letter, seizure, injunction, and, in extreme cases, criminal prosecution. Moreover, failure to comply with a safety labeling order constitutes grounds for imposing substantial CMPs, which are discussed in more detail below.

Risk Evaluation and Mitigation Strategies

Q 8.19 What is a REMS?

REMS, which stands for Risk Evaluation and Mitigation Strategy, refers to a set of requirements that FDA can impose either upon or after approval of a new drug or biological product to ensure that the benefits of the drug outweigh its risks.[73] A REMS is typically required if FDA determines that standard risk management tools, such as approved labeling and adverse event reporting, are not adequate to ensure the safe use of a particular drug or biological product. In such cases, a REMS may require the application of additional risk management tools, such as specific risk communications to physicians or distribution and use restrictions. The below questions and answers provide an overview of FDAAA's REMS provisions. For more detailed information on the REMS process, please see chapter 9.

Q 8.20 What are the standards for imposing a REMS?

Under FDAAA, FDA may require a company to submit a REMS if FDA determines that a REMS is necessary to "ensure that the benefits of the drug outweigh the risks of the drug."[74] FDA must consider several factors in making this determination, including: the size of the population likely to take the drug; the seriousness of the disease or condition; the expected benefit of the drug; and the expected or actual duration of use of the drug.[75] If a drug is approved without a REMS, FDA subsequently may impose a REMS if the agency becomes aware of "new safety information" and makes a determination that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[76] The decision to impose a REMS either before or after approval must be made by an official at or above the level of the person empowered to approve the NDA or BLA for the drug product (that is, division director or above)[77] and only after consultation with the office responsible for post-approval safety (that is, Office of Safety and Epidemiology (OSE)).[78]

Q 8.21 If FDA decides to impose a REMS, what specific risk management tools can it require to be used?

A REMS must contain, at a minimum, a timetable for the submission of assessments, including required assessments at eighteen months, three years and seven years after approval.[79] A REMS assessment is intended to evaluate the extent to which each of the REMS elements is meeting the goals and objectives of the REMS and whether those elements, goals, or objectives should be modified. The REMS also may include the following additional elements:

- a Medication Guide, as provided for in 21 C.F.R. Part 208;

- a patient package insert, if FDA determines that it may help mitigate a serious risk;
- a communication plan to healthcare providers, if FDA determines that such a plan "may support implementation of an element of the REMS"; and
- such other elements "as are necessary to assure safe use of the drug."[80]

Although FDA initially required all drug and biological products with a Medication Guide to have a REMS, it has since recognized that this is unduly burdensome for both the sponsor and the agency and thus has taken the position that, in most cases, a drug or biological product with only a Medication Guide (and no other REMS element) does not need to have a REMS.[81]

With respect to the "communication plan to health care providers," FDA may require the responsible person to (a) send letters to healthcare providers, (b) disseminate information about the elements of the REMS to encourage implementation by healthcare providers, or (c) disseminate information to healthcare providers through professional societies.[82]

With respect to an element to assure safe use of the drug, also known as an ETASU, FDA may impose a number of distribution and use restrictions. These may include: (1) required training or certification for healthcare providers; (2) special certification for dispensing sites; (3) limitations on where the drug may be dispensed (for example, hospitals only); (4) permitting dispensing only upon evidence of safe use conditions (for example, certain laboratory test results); (5) patient monitoring requirements; and (6) requirements to enroll patients in patient registries.[83] For elements described in (2), (3), and (4) above, the FDA also may require the company to adopt an implementation system to help track and improve compliance.[84]

Q 8.22 Under what circumstances can FDA impose a distribution or use restriction as an ETASU?

FDA may require distribution and use restrictions under an ETASU only if it determines that the drug or biological product could not be approved, or approval would be withdrawn, unless such elements were required.[85] For drugs initially approved without such elements, FDA also must make a determination that other REMS elements (such as a patient package insert or communication plan) are not sufficient to mitigate the serious risk.[86]

Moreover, any distribution or use restrictions imposed under an ETASU must be commensurate with the specific labeled risk sought to be addressed, must not be unduly burdensome on patient access to the drug, must be consistent with elements for other drugs with similar safety issues, and must be compatible with established distribution, procurement, and dispensing systems.[87] Each year, FDA must evaluate the distribution and use restrictions imposed on one or more drug products to determine whether such elements are working effectively to assure safe use, are not unduly burdensome on patient access, and minimize the burden on the healthcare delivery system.[88] FDA also must seek input from

patients, physicians, pharmacists, and other healthcare providers about how elements for one or more drugs can be standardized so as not to be unduly burdensome on patient access or the healthcare delivery system as a whole.[89] Within thirty days after imposing a distribution or use restriction, FDA must post a public notice explaining how the element will mitigate the observed risk.[90]

Q 8.23 Can a REMS be modified?

Yes. A company may seek to modify a REMS at any time on a voluntary basis.[91] In addition, an assessment of a REMS must be filed: (1) when submitting a supplemental application for a new indication for use (unless the drug is intended for over-the-counter use only and the REMS includes only a timetable); (2) when required by the REMS timetable (for example, eighteen months after approval); or (3) when required by FDA because of new safety or effectiveness information indicating that a REMS element should be modified or added.[92] The assessment should include an appraisal of the extent to which required elements are meeting their goals and whether one or more goals or elements should be modified.[93] A required assessment also can propose a modification to any element of the approved REMS.[94]

Q 8.24 How does FDA process proposed REMS and REMS assessments?

FDA must promptly review a proposed REMS, assessment, or modification and, if necessary, initiate discussions with the sponsor.[95] Unless the sponsor initiates the dispute resolution process during discussions, FDA must review and act upon a proposed REMS, assessment, or modification within 180 days (or sixty days for minor modifications and modifications due to safety labeling changes).[96] Such action letters must be made publicly available.[97]

If there is a dispute regarding a proposed REMS submitted in an application for initial approval of a drug or biological product, the existing major dispute resolution procedures must be followed.[98] In all other cases, the responsible person can trigger the dispute resolution process after making a required REMS submission.[99] The dispute will be referred to the Drug Safety Oversight Board (DSOB), which must hold a meeting and provide its recommendation on resolving the dispute to FDA within five days of such meeting.[100] The FDA then has seven days (or until the deadline for the action letter) to issue an order or action letter resolving the dispute.[101]

Q 8.25 Do the REMS provisions apply to generic drugs?

Yes, at least to some extent. Generic drugs approved under ANDAs are subject to special requirements under the REMS provisions. First, they can be required to comply with only a subset of available REMS requirements, including Medication Guides, patient package inserts, and distribution and use restrictions.[102] FDA is required to undertake any required communication plan on behalf of the generic applicant.[103] With respect to distribution and

use restrictions, such generic drugs generally must use a "single, shared system" with the listed innovator drug.[104] FDA may waive this requirement if it determines that (1) the burden of creating a single, shared system outweighs its benefits, or (2) an aspect of the system is subject to intellectual property protections and the ANDA applicant certifies it was unable to obtain a license from the owner.[105] In the latter case, FDA may seek to negotiate a voluntary agreement for a license with the owner of the intellectual property.[106] Finally, innovator companies may not use any element required by FDA to assure safe use of the drug to block or delay approval of an ANDA or FDCA section 505(b)(2) application.[107]

At this time, the scope of some of the provisions governing ANDAs is unclear. For example, it is not clear to what extent FDA has authority to intervene in private disputes between commercial entities with respect to license agreements for REMS elements. Moreover, the provision prohibiting the use of any REMS element to block or delay approval of an ANDA or 505(b)(2) application does not focus on the FDA's actions in approving (or not) a generic application but rather proscribes the NDA/BLA holder's use of any required ETASU to block or delay. As such, it is unclear whether this provision is intended to limit administrative action in this specific area (for example, to the filing of a citizen petition) or even to foreclose judicial action aimed at protecting intellectual property.

Q 8.26 How is a REMS applied when a safety issue affects a class of products?

FDA may defer assessments of an approved REMS if it determines that a serious risk of a drug may be related to the pharmacological class of the drug.[108] In such a case, FDA may convene one or more public meetings and publish in the *Federal Register* a planned regulatory action, including modifying the REMS for each drug in the pharmacological class.[109] Following public comments, FDA may issue an order addressing the regulatory action.[110]

Q 8.27 Are there penalties for failing to comply with a REMS requirement?

Yes. Failure to comply with a REMS requirement is a "prohibited act" under section 301 of the FDCA[111] and also constitutes misbranding under section 502 of the FDCA.[112] Accordingly, FDA can use all of the civil and criminal enforcement tools at its disposal under the FDCA against companies that fail to comply with a REMS, including (among other things) issuance of a warning or untitled letter, seizure, injunction, and, in extreme cases, criminal prosecution. Moreover, failure to comply with a safety labeling order constitutes grounds for imposing substantial CMPs, which are discussed in more detail below.

Civil Money Penalties for REMS and Other Post-Market Safety Violations

Q 8.28 Can FDA impose CMPs for violations of the FDAAA provisions discussed above governing post-approval drug safety?

Yes. FDAAA gives FDA authority to impose sizeable CMPs against any responsible person who violates a requirement of the FDAAA's provisions governing post-market studies and post-market clinical trials, safety labeling changes, and REMS.[113] The maximum penalty is approximately $290,000 per violation and approximately $1.15 million for all violations adjudicated in a single proceeding.[114] These maximum amounts, however, increase significantly if the violations continue after FDA provides written notice to the responsible person. In such cases, the maximum penalty increases to approximately $290,000 for the first thirty-day period the violation continues, doubling each thirty-day period thereafter to a maximum of approximately $1.15 million per thirty-day period, not to exceed $11.60 million for all such violations adjudicated in a single proceeding.[115] The statute does not define the term "written notice" so it is possible that a Warning Letter or less formal administrative letter could trigger the higher, post-notice CMPs. In determining the amount of a civil penalty in the case of a continuing violation, FDA must take into consideration the responsible person's efforts to correct the violation.[116] These are by far the largest CMPs available under the FDCA.

Selected Advertising Provisions of FDAAA

Pre-Review of Television Advertisements

Q 8.29 Can FDA require companies to submit advertisements for review prior to dissemination?

Yes. FDAAA grants FDA broad authority under new section 503C of the FDCA to require the submission of any television advertisement for a drug forty-five days prior to broadcast.[117] This authority is specifically limited to *television* advertisements for drugs. The legislation does not include standards guiding when FDA may or should exercise its authority to require pre-review of television advertisements.[118] It is not clear whether or to what extent this provision, or FDA's implementation of it, would run afoul of the First Amendment's free speech guarantee. It does not appear that FDA has ever exercised its authority under this provision.

Q 8.30 Can FDA require modifications to television advertisements submitted for pre-review?

Yes, FDA is authorized to require certain mandatory disclosures in DTC television advertisements submitted for pre-review under this provision. In particular, if the agency determines that a television advertisement otherwise would be false or misleading, it may require the company to include (a) a specific disclosure about a serious risk listed in the labeling of the drug, or (b) the date of approval of the drug (for a period not to exceed two years from the date of approval).[119] Failure to comply with this provision is considered to be a prohibited act under section 301 of the FDCA.[120]

As part of the pre-review process, FDA also may make non-binding recommendations "with respect to information included in the label of the drug" on: (1) changes necessary to "protect the consumer good and well-being"; (2) changes to make the advertisement consistent with prescribing information for the product; and (3) if appropriate and if information exists, including statements to address the efficacy of the drug in specific population groups (for example, the elderly, children and racial and ethnic groups).[121] The FDA, however, may not require the sponsor of the advertisement to accept any of these suggestions. Nevertheless, failure to incorporate FDA's comments is one factor FDA can consider when determining the amount of any CMPs imposed against the company for disseminating false or misleading advertising.

The scope of FDA's authority to "recommend" changes under this section is unclear. As noted above, such changes must be made "with respect to information included in the label of the drug." The term "label,"[122] however, has a very specific meaning under the FDCA and typically does not include the approved package insert, which is considered to be

"labeling."[123] Moreover, the information included on a drug's label (as opposed to its labeling) is usually very circumscribed and is limited to such information as the name of the drug, the quantity of contents, and the name of the manufacturer or distributor. As a practical matter, it is not clear how or why FDA's recommendations would be limited to the information on a drug's label.

Major Statement in Radio and Television Advertisements

Q 8.31 Does FDAAA affect how risk information is communicated in DTC advertisements?

Yes. FDAAA revises section 502(n) of the FDCA to require DTC advertisements in radio and television format (other than reminder advertisements) to present the major statement relating to side effects and contraindications "in a clear, conspicuous, and neutral manner."[124] The major statement is the portion of a broadcast advertisement that presents information relating to the major side effects and contraindications of the advertised drug. This requirement is designed to address concerns that background distractions undercut the communication of safety information in DTC broadcast advertisements.

Q 8.32 Has FDA provided guidance on what "clear, conspicuous, and neutral" means?

Yes, although its guidance is only preliminary. The statute required that, within thirty months of FDAAA's enactment, FDA issue regulations establishing standards for determining whether a major statement is presented in a "clear, conspicuous and neutral manner."[125] On March 29, 2010, FDA issued proposed regulations,[126] but as of the date of this writing has not yet issued final regulations. According to FDA's proposed regulations, a major statement is "clear, conspicuous, and neutral" if: (1) information is presented in language that is readily understood by consumers; (2) audio information is understandable in terms of the volume, articulation, and pacing used; (3) textual information is presented in a manner that is easily read; and (4) the advertisement does not include distracting representations that detract from the communication of the major statement.[127] There is some concern that FDA's fourth criterion could require advertisers to utilize a "tombstone" approach to the communication of risk information. Until FDA finalizes the regulations or interprets them after implementation, however, the actual effect will remain unclear.

Other Advertising Provisions

Q 8.33 Did FDAAA include other provisions applicable to drug advertising?

Yes, FDAAA included a number of provisions affecting drug advertising. For example, FDAAA requires "published" DTC advertisements to include a statement about how consumers can report side effects to FDA.[128] The statute also required FDA to conduct a study to determine whether the statement is appropriate for inclusion in DTC television advertisements and, if so, to issue regulations requiring the statement's inclusion. When issuing these regulations, FDA must also determine what constitutes a reasonable length of time for displaying the statement in such advertisements.[129] FDA has not issued any such regulations.

FDAAA also revised section 502(n) of the FDCA to permit FDA to revise its advertising regulations without following the public hearing procedures set forth at 21 C.F.R. Part 15.[130] The Part 15 hearing procedures are quite onerous and may have dissuaded FDA from revising its advertising regulations in the past, particularly with respect to DTC advertising. This change will likely make it easier for FDA to promulgate revised regulations governing DTC and other drug advertising issues.

Civil Money Penalties for DTC Advertising Violations

Q 8.34 Can FDA impose CMPs for advertising violations?

Yes. FDAAA gave FDA new authority to impose CMPs against the holder of an approved NDA or BLA (but not an advertiser or advertising agency) who disseminates any DTC advertisement, including a print advertisement, that is "false or misleading."[131] The maximum penalty is approximately $290,000 for the first violation in any three-year period and approximately $580,000 for each subsequent violation in any three-year period.[132] Prior to written notification that FDA intends to seek CMPs, repeated dissemination of the same or similar advertisement constitutes a single violation.[133] After such written notice, however, each day an application holder disseminates one or more violative advertisements constitutes a separate violation, except that, for print advertisements in publications that are published less frequently than daily, each issue date (for example, weekly, monthly) is considered a single violation.[134] FDA may not assess CMPs for FDCA violations involving DTC advertising except under its FDAAA authority.[135]

Q 8.35 What are the procedures for imposing CMPs for advertising violations?

FDA may impose CMPs only after providing the company written notice and an opportunity for a hearing.[136] No CMP may be imposed if the company submits the advertisement to FDA prior to dissemination and incorporates each comment received from FDA.[137] FDA may retract or modify any prior comments based on new information or changed circumstances as long as it provides written notice to the person and provides a reasonable time for modification or correction of the advertisement prior to seeking any CMP.[138]

In determining the amount of any penalty, FDA must take into account the "nature, circumstances, extent and gravity" of the violation(s).[139] Factors that must be considered include: whether the advertisement was submitted for advisory review (either voluntarily or as required); whether the advertisement was disseminated prior to the expiration of FDA's forty-five-day review period; whether the creator or disseminator incorporated any FDA comments or pulled the advertisement after receiving written notice of FDA's intent to assess a CMP; whether the advertisement was reviewed by qualified medical, regulatory, and legal reviewers prior to its dissemination; whether the violations were material; whether the advertisement's creator or disseminator acted in good faith; whether such person has been subject to a DTC advertising CMP within the previous year; and the scope and extent of any voluntary remedial actions.[140]

Q 8.35.1 Has FDA ever used its new authority to impose CMPs for

advertising violations?

We are not aware of any instance in which FDA has exercised its new authority to impose CMPs for advertising violations. FDA has not extensively used CMPs in other similar contexts in which they are authorized, such as for violations of medical device requirements. This may be due, in part, to the resource-intensive nature of the administrative process required to impose CMPs, including the hearing process.

Clinical Trial Registries and Results Databases

Overview

Q 8.36 Are prescription drug manufacturers subject to requirements for registering clinical trials on a publicly accessible, government database?

Yes. NIH maintains a publicly accessible website (CT.gov) to which companies are required to submit information about certain clinical trials involving drugs and devices, including results information.[141] Prior to 2007, this submission requirement applied solely to clinical investigations of drugs intended to treat serious or life-threatening diseases or conditions; it did not apply to clinical investigations of medical devices or of drugs intended to treat non-serious diseases or conditions.

In 2007, as part of FDAAA, Congress substantially expanded the federal clinical trial disclosure requirements. In particular, Congress (a) required drug companies to submit more information about a broader group of drug trials during the registration phase, and (b) created for the first time a clinical trial results database.[142] In addition, Congress subjected medical device manufacturers and researchers to most of the same clinical trial reporting requirements as pharmaceutical manufacturers and researchers.[143]

Q 8.37 What is the clinical trial registry database?

The clinical trial registry database is the portion of CT.gov that provides basic information about the scope and status of *ongoing* clinical trials. It is intended to enhance patient enrollment in clinical trials by providing patients and healthcare providers with real-time information about available and ongoing trials, including eligibility criteria, recruitment status and location, and contact information. It also is intended to provide a mechanism for interested parties to track the subsequent progress of clinical trials, including the publication of results.

Q 8.38 What is the clinical trial results database?

The clinical trials results database is the portion of CT.gov that provides summary information about the results of *completed* clinical trials. Like the other portions of CT.gov, it is publicly accessible and searchable by, among other things, the name of the sponsoring company, the name of the intervention (drug or device), or the name of the disease or condition studied.

Q 8.39 Who is responsible for submitting clinical trial information to CT.gov in accordance with the FDAAA requirements?

The "sponsor" of a clinical trial generally is responsible for complying with the clinical trial reporting requirements under FDAAA.[144] NIH considers the "sponsor" to be the person or entity who initiates the clinical trial.[145] For studies conducted under an Investigational New Drug application (IND), the IND holder will be considered the sponsor regardless of how the study is funded.[146] For studies conducted without an IND, NIH will examine the specific funding arrangement to determine who initiated the trial and thus who is the sponsor (for example, for studies funded through a research grant, the funding recipient generally will be considered the sponsor).[147] The term "sponsor" refers to both sponsoring companies and individual researchers who both initiate and conduct clinical trials (that is, sponsor-investigators).[148] In rare cases, the principal investigator (PI) of a clinical trial sponsored by another entity will be held responsible for complying with the clinical trial reporting requirements under FDAAA.[149] The sponsor may shift this responsibility to the PI, however, only when the PI "is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements [under FDAAA] for the submission of clinical trial information" to http://CT.gov.[150] In most cases, the sponsor, rather than the PI, will be responsible for posting clinical trial information to CT.gov.

Q 8.40 Do the federal reporting requirements for clinical trial registries and results databases apply to *all clinical trials involving a pharmaceutical or biological product?*

No. The FDAAA requirements apply only to trials that are considered to be "applicable drug clinical trials" and that were initiated after the enactment date of FDAAA (September 27, 2007) or were ongoing as of December 26, 2007.[151] An "applicable drug clinical trial" is defined as "a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of [the Public Health Service Act]."[152] Accordingly, NIH considers a trial to be an "applicable drug clinical trial" if it meets the following four criteria:

1. It is "controlled" (which NIH has interpreted to mean most interventional trials, even if they are single arm);
2. It is a "clinical investigation";
3. It is not a Phase I clinical investigation; and
4. It involves a drug that is subject to section 505 of the FDCA or section 351 of the PHS Act.[153]

Foreign Clinical Studies

Q 8.41 If a drug trial is being conducted in a foreign country, is the sponsor

required to submit information about it to CT.gov?

It depends. If the clinical trial is conducted entirely outside the United States (including its territories) and does not use a drug that is manufactured in the United States, then the clinical trial would be exempt from the FDAAA clinical trial reporting requirements because it would not involve a drug subject to section 505 of the FDCA or to section 351 of the PHS Act.[154]

However, if the clinical trial uses a drug that is manufactured in the United States (and exported to the foreign sites) or includes both foreign and domestic clinical trial sites, then information about the trial would need to be submitted to CT.gov in accordance with FDAAA (assuming the other requirements are satisfied).[155]

Applicable Drug Clinical Trials

Q 8.42 Does information about observational studies need to be submitted to CT.gov?

Generally, information about observational studies would not need to be submitted to CT.gov. The clinical trial reporting requirements apply solely to "controlled clinical investigation[s]."[156] The term "clinical investigation" is defined as "any experiment in which a drug is administered, dispensed to, or used involving one or more human subjects."[157] Relying upon FDA's regulations applicable to drug trials, NIH further defines an "experiment" as "any use of a drug except for the use of a marketed drug in the course of medical practice."[158] Because most observational studies are designed to collect data or conduct analyses on patients who have already received a drug intervention in the course of routine medical practice, such studies are not "experiments" under this definition and thus are not "applicable drug clinical trials" subject to the FDAAA clinical trial reporting requirements.

Q 8.43 If the FDAAA requirements apply, when must a sponsor submit information about a drug trial to the clinical trial registry database?

Clinical trial information must be submitted to the registry databank portion of CT.gov no later than twenty-one days after the first patient is enrolled in the trial.[159] Because the International Committee of Medical Journal Editors (ICMJE) has announced that their members will refuse to publish any study that was not registered at or before the onset of patient enrollment, many companies voluntarily register clinical studies prior to the FDAAA deadline.[160]

Q 8.44 What type of information must be submitted to the clinical trial registry for each "applicable drug clinical trial"?

FDAAA requires sponsors to submit detailed information about each drug clinical trial subject to the reporting requirements. In particular, sponsors must submit:

1. Descriptive information, including a summary of the trial, the study design, the primary disease or condition being studied, the intervention name and type, the primary and secondary outcome measures, the target number of subjects, and the estimated completion date;
2. Recruitment information, including eligibility criteria, age limits, and overall recruitment status;
3. Location and contact information, including the name of the sponsor, the responsible party, and the facility name and contact information; and
4. Administrative data, including the unique protocol identification number and the IND number.[161]

In addition, recently adopted regulations impose additional data requirements for clinical trials initiated after January 18, 2017, such as the creation of an Expanded Access Record.[162]

Public Availability of Registry and Results Information

Q 8.45 Does NIH make registry information publicly available at or near the time it is submitted to CT.gov?

Yes. Under FDAAA, NIH must make information about drug trials publicly available no later than thirty days after such information is submitted.[163] As a result, CT.gov provides information about ongoing clinical trials that not only is useful to physicians and patients but also may be extremely valuable to a company's competitors.

Q 8.46 Does FDAAA require a sponsor to submit results information for each drug study for which registry information has been submitted to CT.gov?

It depends on when the study is completed. For studies completed prior to January 18, 2017, results information is required only for clinical studies involving drugs and biological products that have received NDA, BLA, or ANDA approval.[164] Consequently, there may be some studies for which registry information must be submitted to CT.gov (that is, because the study is an "applicable drug clinical trial" initiated after September 27, 2007) but for which results information is not required (that is, because the drug is never approved by FDA).

Under new NIH regulations, for studies completed after January 18, 2017, results information must be submitted for all "applicable" clinical trials, regardless whether the study drug is ever approved.[165]

Timing of Submissions

Q 8.47 If results information is required, when must it be submitted to CT.gov and by whom?

As with registry information, results information must be submitted by the sponsor of the clinical trial or, in the rare cases described above, the PI.[166] Generally, results information must be submitted within one year of the estimated or actual completion date of the trial, whichever is earlier.[167] For purposes of CT.gov, the term "completion date" is defined as "the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome . . . ."[168] Consequently, some trials may have a "completion date" and, concomitantly, a one-year deadline for submission of results, even though the trial activities continue for the collection of data for one or more *secondary* outcomes. In such cases, it may be difficult or impossible to meet the statutory one-year deadline.

Q 8.48 Are there any mechanisms to delay the deadline for submission of results information?

Yes. FDAAA allows a sponsor to delay the submission of results information in three situations: (1) when seeking initial approval of a drug; (2) when seeking approval of a new use of a drug; or (3) when NIH grants an extension for "good cause." First, if an applicable drug clinical trial is completed before the studied drug is initially approved for any use (and the study is completed after January 18, 2017), the sponsor may submit a certification to NIH, which automatically delays the deadline for submitting results information to no later than thirty days after initial approval.[169] However, this extension only applies if the sponsor is continuing to develop the drug and lasts for a maximum of two years.[170]

Second, if the sponsor submits a certification that it has filed, or will file within one year, an application seeking NDA, BLA, or ANDA approval for a new use studied in a clinical trial, then the one-year deadline for submitting results information on that trial is automatically delayed to no later than thirty days after the earlier of: (a) FDA approval of the new use; (b) issuance by FDA of a letter not approving the new use (for example, a Complete Response Letter); or (c) 210 days after withdrawal of the NDA, BLA, or ANDA seeking approval for the new use.[171] However, the maximum delay under this second option is two years from the date of the certification.[172] Moreover, if a sponsor takes advantage of this second option, it must make the same certification (and thus delay the posting of results information for the same amount of time) for each clinical trial that is required to be submitted in the application seeking clearance or approval of the new use.[173] This requirement is designed to prevent cherry-picking of positive results.

Finally, FDAAA provides for a catch-all "good cause" extension of the one-year deadline.[174] This extension, however, is not automatic and instead requires an affirmative decision by NIH.[175] NIH has indicated in informal guidance that seeking publication of a study in a peer-reviewed journal will *not* be considered "good cause" for an extension.[176]

Results Information and Reporting Requirements

Q 8.49 If required, what type of results information must be submitted to CT.gov for each applicable drug clinical trial?

Results information currently must be submitted to CT.gov in tabular format. Sponsors must provide, among other things:
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1. A table of demographic and baseline data describing the studied patient population;
2. A table of values for each of the primary and secondary outcome measures for each arm of the trial;
3. A table of anticipated and unanticipated serious adverse events, grouped by organ system, for each arm of the trial; and
4. A table of anticipated and unanticipated non-serious adverse events that exceed a frequency of 5% within any arm of the trial, grouped by organ system.[177]

In addition, sponsors must provide a point of contact for scientific information about the clinical trial results and information on whether it has any agreements with the PI restricting the PI's ability to discuss or publish the results of the study.[178]

Moreover, under new regulations, expanded results information must be submitted for clinical studies completed after January 18, 2017.[179] Most notably, responsible parties must submit a copy of the study protocol and statistical analysis plan.[180]

Q 8.50 Are sponsors required to update their submissions to CT.gov?

Yes. FDAAA requires sponsors to submit updates to CT.gov no less than once every twelve months, unless there were no changes during that time period.[181] In addition, updates to the recruitment status and completion date information must be submitted within thirty days of the change.[182]

Q 8.51 Are there any state clinical trial reporting requirements?

No. The State of Maine previously had requirements for reporting clinical trial information that were similar but not identical to the FDAAA requirements. In 2011, however, these Maine requirements were repealed. While other states have considered enacting clinical trial reporting requirements, at present, none have done so.

Compliance and Enforcement

Q 8.52 What are the consequences for failure to comply with the clinical trial reporting requirements under FDAAA?

FDAAA authorizes several sanctions against companies that, or individuals who, fail to comply with federal clinical trial reporting requirements. First, NIH can make use of a public shaming provision by issuing a notice on CT.gov that a company has failed to submit required information or has submitted information that is false or misleading.[183] This compliance information must be publicly searchable and undoubtedly will be used as a rich source of evidence by prosecutors and plaintiffs' lawyers alike.[184] Second, it is now a "prohibited act" under section 301 of the FDCA for a person to fail to submit required information to CT.gov or to submit information that is false or misleading.[185] This means that FDA can apply most of the enforcement tools at its disposal under the FDCA, including injunction and criminal prosecution, against those who violate the FDAAA clinical trial reporting requirements. Third, FDA can impose civil money penalties of up to $11,500 per day (with no maximum) for ongoing violations.[186] Finally, if a clinical trial is funded in whole or in part by a grant from the Department of Health and Human Services (HHS) or one of its constituent agencies, any remaining grant funds and any future grant funds to the grantee may be withheld for non-compliance with the FDAAA requirements.[187]

Q 8.53 How does the government monitor compliance?

NIH and FDA have established a pilot quality control project to determine the optimal method of verifying the accuracy of submitted information to help ensure that such information is not promotional, false, or misleading.[188] In addition, FDAAA requires companies to submit a certification that all applicable clinical trial reporting requirements have been met at the time of submission of an NDA, BLA, or ANDA.[189] FDA has created a special form for this certification—Form FDA 3674[190]—and has clarified in a guidance document that the certifications should be submitted for all NDAs, BLAs, ANDAs, INDs, efficacy supplements to approved NDAs and BLAs, and new clinical protocols submitted to an IND.[191]

If required, the failure to submit this certification, or the knowing submission of a false certification, is considered to be a "prohibited act" under section 301 of the FDCA that can give rise to both civil and criminal liability, including civil money penalties.[192]

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1. Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-
21 Stat. 823 (2007).

2. *See* 21 U.S.C. § 355(o)(3).

3. *See* 21 U.S.C. § 355(o)(2)(A), (B).

4. U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY:
ΓMARKETING STUDIES AND CLINICAL TRIALS—IMPLEMENTATION OF
ΓION 505(O)(3) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (Apr.
) [hereinafter FDA GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES
) CLINICAL TRIALS], at 4.

5. *Id.*
6. 21 U.S.C. § 355(o)(3)(B).
7. 21 U.S.C. § 355(o)(3)(A).
8. 21 U.S.C. § 355(o)(3)(C).
9. 21 U.S.C. § 355(o)(3)(D)(i).
10. 21 U.S.C. § 355(o)(3)(D)(ii).
11. *See* 21 U.S.C. §§ 355(o)(2)(C), 355-1(b)(5).
12. 21 U.S.C. § 355-1(b)(4).
13. 21 U.S.C. § 355-1(b)(6).
14. 21 U.S.C. § 355-1(b)(8).
15. 21 U.S.C. § 355-1(b)(3).
16. *Id.*
17. *See* FDA GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND NICAL TRIALS, *supra*note 4, at 2–3.
18. *Id.* at 2.
19. *See id.* at 3 (discussing post-FDAAA requirements for PMCs).
20. *See id.* at 2.
21. *See id.* at 7.
22. *See id.* at 11.
23. *Id.*
24. *See id.* at 11–12.
25. 21 U.S.C. § 355(p)(5).
26. *See* 21 U.S.C. § 355(o)(3)(F).
27. *See* 21 U.S.C. § 355(o)(3)(E)(ii).
28. *See* FDA GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND NICAL TRIALS, *supra* note 4, at 12 & n.18.
29. 21 U.S.C. § 355(o)(3)(E)(ii).
30. FDA GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND NICAL TRIALS, *supra* note 4, at 12.
31. *Id.*
32. 21 U.S.C. § 355(o)(3)(E)(ii).
33. Id.
34. *See* 21 U.S.C. §§ 331(d), 355(o)(1).
35. *See* 21 U.S.C. § 352(z).
36. *See, e.g.*, 21 U.S.C. § 333(a) (discussing the criminal penalties imposable for "prohibited).
37. *See* 21 U.S.C. § 333(f)(4).
38. 21 U.S.C. § 355(o)(3)(E)(ii).
39. *Id.*
40. *See* 21 U.S.C. § 355(o)(4).

41. *See* 21 U.S.C. § 355(o)(4)(A); *see also* U.S. FOOD AND DRUG
MINISTRATION, GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES—
LEMENTATION OF SECTION 505(O)(4) OF THE FEDERAL FOOD, DRUG, AND
METIC ACT (July 2013) [hereinafter FDA GUIDANCE FOR INDUSTRY: SAFETY
ELING CHANGES], at 1.

42. *See id.* at 2 & n.2.

43. 21 U.S.C. § 355(o)(4)(B)(i).

44. *See* FDA GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* 41, at 6 ("FDA expects that information that results in changes made only to the ERSE REACTIONS section, but does not warrant inclusion in other sections of labeling would not normally trigger required safety labeling changes under section 505(o)(4).").

45. *See* U.S. FOOD AND DRUG ADMINISTRATION, COMPLETE RESPONSE AND ETY LABELING CHANGE ORDER ISSUED TO AMGEN, INC. (undated), .fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandPr rs/ucm110268.pdf.

46. 21 U.S.C. § 355(o)(4)(A).

47. *See* FDA GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* 41, at 16.

48. *Id.* at 4.

49. *Id.* at 6.

50. *See* 21 U.S.C. § 355(o)(4)(B); FDA GUIDANCE FOR INDUSTRY: SAFETY ELING CHANGES, *supra* note 41, at 7.

51. 21 U.S.C. § 355(o)(4)(C).

52. 21 U.S.C. § 355(o)(4)(D).

53. 21 U.S.C. § 355(o)(4)(E).

54. 21 U.S.C. § 355(p)(5).

55. 21 U.S.C. § 355(o)(4)(F).

56. *See* 21 U.S.C. § 355(o)(4)(G).

57. FDA GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* note t 7.

58. *Id.*

59. *See* U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR USTRY: LABELING FOR HUMAN PRESCRIPTION DRUGS AND BIOLOGICAL DUCTS—IMPLEMENTING THE PLR CONTENT AND FORMAT UIREMENTS, at 20 (Feb. 2013).

60. 21 U.S.C. § 355(o)(4)(C), (D).

61. FDA GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* note t 9.

62. *See* 21 U.S.C. § 355(o)(4)(D).

63. 21 U.S.C. § 355(o)(4)(E).

64. FDA GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* note

t 12.

65. *Id.* at 9–10.

66. 21 U.S.C. § 355(o)(4)(F).

67. *See* FDA GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* 41, at 12.

68. 21 U.S.C. § 355(o)(4)(I).

69. FDA GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* note t 7.

70. *See* 21 U.S.C. §§ 331(d), 355(o)(1).

71. *See* 21 U.S.C. § 352(z).

72. *See* 21 U.S.C. § 355(o)(4)(G).

73. *See* 21 U.S.C. § 355-1(a)(1), (2)(A).

74. *Id.*

75. *See* 21 U.S.C. § 355-1(a)(1).

76. *See* 21 U.S.C. § 355-1(a)(2)(A).

77. 21 U.S.C. § 355-1(a)(4).

78. 21 U.S.C. § 355-1(a)(1), (a)(2)(A).

79. 21 U.S.C. § 355-1(d).

80. *See* 21 U.S.C. § 355-1(e), (f).

81. *See* U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR USTRY: MEDICATION GUIDES—DISTRIBUTION REQUIREMENTS AND LUSION IN RISK EVALUATION AND MITIGATION STRATEGIES (REMS), at 8 . 2011).

82. 21 U.S.C. § 355-1(e)(3).

83. 21 U.S.C. § 355-1(f)(3).

84. 21 U.S.C. § 355-1(f)(4).

85. 21 U.S.C. § 355-1(f)(1)(A).

86. 21 U.S.C. § 355-1(f)(1)(B).

87. *See* 21 U.S.C. § 355-1(f)(2)(A), (C), (D).

88. 21 U.S.C. § 355-1(f)(5)(B).

89. 21 U.S.C. § 355-1(f)(5)(A).

90. 21 U.S.C. § 355-1(f)(2)(B).

91. 21 U.S.C. § 355-1(g)(4).

92. 21 U.S.C. § 355-1(g)(2).

93. 21 U.S.C. § 355-1(g)(3).

94. 21 U.S.C. § 355-1(g)(2).

95. 21 U.S.C. § 355-1(h)(1).

96. *See* 21 U.S.C. § 355-1(h)(2)(A).

97. 21 U.S.C. § 355-1(h)(2)(C).

98. 21 U.S.C. § 355-1(h)(3).

99. 21 U.S.C. § 355-1(h)(4)(A)(i).
100. *See* 21 U.S.C. § 355-1(h)(4)(B), (F).
101. 21 U.S.C. § 355-1(h)(4)(G).
102. 21 U.S.C. § 355-1(i)(1).
103. 21 U.S.C. § 355-1(i)(2)(A).
104. 21 U.S.C. § 355-1(i)(1)(B).
105. *Id.*
106. *Id.*
107. 21 U.S.C. § 355-1(f)(8).
108. 21 U.S.C. § 355-1(h)(6)(A).
109. 21 U.S.C. § 355-1(h)(6)(A), (D)(i).
110. 21 U.S.C. § 355-1(h)(6)(D)(iii).
111. *See* 21 U.S.C. §§ 331(d), 355(p)(1).
112. 21 U.S.C. § 352(y).
113. *See* 21 U.S.C. § 333(f)(4).
114. 21 U.S.C. § 333(f)(4)(A)(i); 21 C.F.R. § 17.2.
115. 21 U.S.C. § 333(f)(4)(A)(ii); 21 C.F.R. § 17.2.
116. 21 U.S.C. § 333(f)(4)(B).
117. *See* 21 U.S.C. § 353c(a). Subsequently moved under 2013's Drug Supply Chain Security his provision originally appeared at section 503B of the FDCA.
118. In March 2012, FDA issued a draft guidance document identifying six categories of advertisements for which it intended to exercise its authority to require pre-dissemination ission (for example, the initial television ad for a new or expanded approved indication for prescription drug, all ads for Schedule II controlled substances). *See generally* U.S. FOOD DRUG ADMINISTRATION, DRAFT GUIDANCE FOR INDUSTRY: DIRECT-CONSUMER TELEVISION ADVERTISEMENTS—FDAAA DTC TELEVISION AD DISSEMINATION REVIEW PROGRAM (2012). However, FDA has not yet finalized ocument, and it therefore appears that it has not yet begun implementing the approach osed therein.
119. 21 U.S.C. § 353C(e).
120. 21 U.S.C. § 331(kk).
121. 21 U.S.C. § 353C(b).
122. The term "label" is defined as "a display of written, printed, or graphic matter upon the diate container of any article . . . ." 21 U.S.C. § 321(k).
123. The term "labeling" is defined as "all labels and other written, printed, or graphic matter pon any article or any of its containers or wrappers, or (2) accompanying such article." 21 C. § 321(m).
124. *See* 21 U.S.C. § 352(n)(3).
125. FDAAA § 901(d)(3)(B).
126. 75 Fed. Reg. 15,376 (Mar. 29, 2010).

75 Fed. Reg. at 15,387 (proposed to be codified at 21 C.F.R. § 202.1(e)(ii)).

See 21 U.S.C. § 352(n)(3).

FDAAA § 906(b).

See FDAAA § 901(d)(6).

See 21 U.S.C. § 333(g)(1).

See id.; 21 C.F.R. § 17.2.

See 21 U.S.C. § 333(g)(1).

See id.

See id.

21 U.S.C. § 333(g)(2).

21 U.S.C. § 333(g)(4)(A).

21 U.S.C. § 333(g)(4)(B).

21 U.S.C. § 333(g)(3).

Id.

NIH, CLINICAL TRIALS, www.clinicaltrials.gov.

See FDAAA § 801 (codified at 42 U.S.C. § 282(j)).

See id.

42 U.S.C. § 282(j)(1)(A)(ix)(I).

See NIH, [DRAFT] ELABORATION OF DEFINITIONS OF RESPONSIBLE
ΓY AND APPLICABLE CLINICAL TRIAL (Mar. 9, 2009) [hereinafter NIH, [DRAFT]
ɜORATION OF DEFINITIONS OF RESPONSIBLE PARTY AND APPLICABLE
ɴICAL TRIAL], at 2–3 (discussing definitions from 21 C.F.R. § 50.3(e), (f)).

Id. at 3.

Id.

Id. at 2 (discussing the "sponsor-investigator" definition from 21 C.F.R. § 50.3(f)).

42 U.S.C. § 282(j)(1)(A)(ix)(II).

Id.

See NIH, [DRAFT] ELABORATION OF DEFINITIONS OF RESPONSIBLE
ΓY AND APPLICABLE CLINICAL TRIAL, *supra* note 145, at 4; *see also* 42 U.S.C.
ʔ(j)(2)(C).

42 U.S.C. § 282(j)(1)(A)(iii)(I).

See NIH, [DRAFT] ELABORATION OF DEFINITIONS OF RESPONSIBLE
ΓY AND APPLICABLE CLINICAL TRIAL, *supra* note 145, at 7–10.

See id. at 8.

Id.

42 U.S.C. § 282(j)(1)(A)(iii)(I).

42 U.S.C. § 282(j)(1)(A)(iii)(II); 21 C.F.R. § 312.3(b); *see also* NIH, [DRAFT]
ɜORATION OF DEFINITIONS OF RESPONSIBLE PARTY AND APPLICABLE
ɴICAL TRIAL, *supra* note 145, at 9.

NIH, [DRAFT] ELABORATION OF DEFINITIONS OF RESPONSIBLE PARTY

) APPLICABLE CLINICAL TRIAL, *supra* note 145, at 9 (adopting definition used in ition of "clinical investigation" at 21 C.F.R. § 312.3(b)).

159. 42 U.S.C. § 282(j)(2)(C)(ii).

160. ICMJE, CLINICAL TRIAL REGISTRATION: A STATEMENT FROM THE ERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS (2004), .icmje.org/news-and-editorials/clin_trial_sep2004.pdf.

161. 42 U.S.C. § 282(j)(2)(A)(ii).

162. 42 C.F.R. § 11.28(a)(2) (2017).

163. *See* 42 U.S.C. § 282(j)(2)(D)(i).

164. *See* 42 U.S.C. § 282(j)(3)(C).

165. 42 C.F.R. § 11.42(b).

166. *See* 42 U.S.C. § 282(j)(3)(E)(i).

167. 42 U.S.C. § 282(j)(3)(E)(i)(I), (II).

168. 42 U.S.C. § 282(j)(1)(A)(v).

169. 42 U.S.C. § 282(j)(3)(E)(iv).

170. 42 C.F.R. 11.44(c).

171. 42 U.S.C. § 282(j)(3)(E)(v)(I).

172. 42 U.S.C. § 282(j)(3)(E)(v)(III).

173. 42 U.S.C. § 282(j)(3)(E)(v)(II).

174. 42 U.S.C. § 282(j)(3)(E)(vi).

175. *Id.*

176. NIH, CLINICALTRIALS.GOV "BASIC RESULTS" DATA ELEMENT INITIONS FOR INTERVENTIONAL AND OBSERVATIONAL STUDIES (Mar. 22,), http://prsinfo.clinicaltrials.gov/results_definitions.html ("Note that 'pending publication' lelays in data analysis for unspecified causes are not considered good cause for an sion.").

177. *Id.*

178. *Id.*

179. 42 C.F.R. § 11.48.

180. 42 C.F.R. § 11.48(a)(5).

181. 42 U.S.C. § 282(j)(4)(C)(i)(I).

182. 42 U.S.C. § 282(j)(4)(C)(i)(III), (IV).

183. 42 U.S.C. § 282(j)(5)(E)(i).

184. *See* 42 U.S.C. § 282(j)(5)(E)(vi).

185. 21 U.S.C. § 331(jj)(2), (3).

186. *See* 21 U.S.C. § 333(f)(3); 21 C.F.R. § 17.2.

187. *See* 42 U.S.C. § 282(j)(5)(A)(ii).

188. *See* 42 U.S.C. § 282(j)(5)(C)(i).

189. *See* 42 U.S.C. § 282(j)(5)(B).

190. U.S. FOOD AND DRUG ADMINISTRATION, Form FDA 3674,

.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf.

191. *See* U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR NSORS, INDUSTRY, RESEARCHERS, INVESTIGATORS, AND FOOD AND G ADMINISTRATION STAFF: CERTIFICATIONS TO ACCOMPANY DRUG, LOGICAL PRODUCT, AND DEVICE APPLICATIONS/SUBMISSIONS: MPLIANCE WITH SECTION 402(J) OF THE PUBLIC HEALTH SERVICE ACT, ED BY TITLE VIII OF THE FOOD AND DRUG ADMINISTRATION NDMENTS ACT OF 2007, at 5–6 (Jan. 2009).

192. 21 U.S.C. §§ 331(jj)(1), 333(f)(3).

Risk Evaluation and Mitigation Strategies (REMS) and Related Post-Market Safety Oversight

Linda Pissott Reig & James F. Hlavenka[1]

Prescription drugs by their nature are unavoidably dangerous products that need to be accompanied by product labeling and dispensed pursuant to a valid prescription. When a drug has significant risks, FDA may choose not to approve it for use in the United States. Such an outcome is a harsh consequence, however, for those subgroups of patients who may experience significant benefits despite the drug's major risks. For such subgroups, there may be various reasons to allow access to the drug. For example, there may be no other treatment for the disease or the drug may work far better than other less risky, but also less potent drugs. Or certain patient populations may experience higher risks, but those risks can be minimized significantly when safeguards are in place.

One example of a drug with substantial risk when taken by those of childbearing age is Thalomid® (thalidomide), a product that was not available for sale in the United States until relatively recently. Initially, the drug was thought to be extremely dangerous. Indeed, experiences with the drug in other countries revealed that pregnant women using the drug for morning sickness, later gave birth to children with severe malformations.[2]

Today, however, Thalomid is commercially available. Further research has revealed that it is extremely effective for people who have the rare condition of leprosy. It also benefits those with newly diagnosed multiple myeloma. Due to its anti-inflammatory properties, there may also be potential benefits for arthritis, some cancers, AIDS, multiple sclerosis, and many other debilitating illnesses. For these reasons, FDA decided that a complete ban on the drug no longer made sense. Instead, efforts have been made to minimize risks and fully educate healthcare providers and patients who then can decide if the potential benefits of the product warrant exposure to such serious risks. In the case of Thalomid, due to the significant risks of birth defects, all prescriptions for Thalomid are subject to a broad array of restrictions and oversight.[3] Today, such risk management programs fall under a regulatory construct referred to as

a Risk Evaluation and Mitigation Strategy (REMS).

REMS serve important purposes. They allow patients who will benefit from a drug to have access to a unique medicine that offers, in some instances, the only treatment available for a particular condition. At the same time, such drugs are subject to a wide array of safeguards tailored to help prevent the specific risks identified with these drugs. Maintenance of a patient registry to monitor outcomes; patient medication guides; informed consent from patients; and physician sign-up, training, and certifications—these are just a few of the many ways that REMS can work to manage the unavoidable and significant risks that these important drugs may have.

A few years ago, there were hundreds of drugs with REMS. Over time, some products have been released from their REMS requirement, but other products (such as Thalomid) continue to utilize a REMS. REMS help to minimize the significant safety risks of a product that some patients desperately need. The need for a REMS program can evolve over time. For example, Tysabri®, was the subject of a 2004 market withdrawal due to several reports of a rare brain disease developing in users. Patients with Multiple Sclerosis were devastated to find that they were no longer able to obtain the drug. Then, in 2006, Tysabri was reintroduced to the market along with a program to educate patients on the risks.[4] Tysabri continues to be sold in accordance with a REMS that helps to manage that product's significant safety risks.

In some instances, a REMS may apply to an entire class of products, also known as Shared System REMS, in an effort to make risk minimization efforts uniform across entire classes of products. For example, extended-release and long-acting opioid drugs are subject to a class-wide REMS program and class-wide labeling changes.[5] Recently, FDA has focused renewed attention on ways to address the misuse and abuse of prescription opioid analgesics, and developed a "high-level outline of the core educational messages" to be offered through accredited continuing education activities.[6] In addition, an updated "Opioid Analgesic REMS" is expected in the near term.[7]

Criticism of REMS from industry stakeholders and government agencies has continued to increase over the years. Industry stakeholders argue that REMS requirements add undue administrative burdens and high costs on drug sponsors and the healthcare system without measurable benefits. Similarly, a 2013 Office of Inspector General (OIG) report found that FDA lacked comprehensive data to determine whether REMS improved drug safety, and confirmed the need to identify and implement reliable methods to assess the

effectiveness of REMS.[8] In response to such criticism, FDA has held multiple public workshops and meetings to solicit feedback on a wide array of topics, including REMS development, implementation, and assessment. Additionally, all REMS for new drugs and biologics are required to include a timetable for assessments intended to gauge how effective their safety measures are.

In this chapter, we explore key aspects of REMS and related post-market safety oversight.

Basics of REMS

Q 9.1 What are REMS? When was that term first introduced?

Risk Evaluation and Mitigation Strategies (REMS) are programs designed to ensure that the benefits of particular drugs and biologics outweigh the risks they pose to patients. REMS were first introduced by the Food and Drug Administration Amendments Act of 2007 (FDAAA). FDAAA amended, in part, the Food, Drug, and Cosmetic Act (FDCA) by adding section 505-1, which authorizes FDA to require persons submitting certain drug and biologic applications to include a REMS to ensure that the benefits of the drug or biologic outweigh its risks. REMS authority became effective on March 25, 2008—180 days after enactment of FDAAA.[9]

Q 9.2 How do REMS compare to RiskMAPs?

In 2005, FDA released multiple guidances on risk management and minimization, including guidance on the development and use of Risk Minimization Action Plans (the RiskMAP guidance).[10] Risk Minimization Actions Plans (RiskMAPs) are strategic safety programs designed by FDA to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. As stated above, in 2007, FDAAA granted statutory authority to FDA to mandate REMS, which incorporate many of the principles that were included in the RiskMAP guidance. Although both RiskMAPs and REMS are similar in nature, REMS are now the primary mechanism for mitigating risks for drugs and biologics. FDAAA granted FDA statutory authority to enforce such programs, which includes: preventing the introduction of a drug or biologic into interstate commerce, or finding such drug or biologic misbranded, if a REMS is not sufficiently implemented.[11]

The RiskMAP guidance continues to apply to products that had RiskMAPs at the time FDAAA was adopted where, for example, the RiskMAPS were not viewed as constituting a REMS under the terms of the FDAAA, and to products with new RiskMAPs (for example, ANDAs for which the reference listed drug has a RiskMAP).[12]

REMS Development and Oversight

Q 9.3 What is the name of the government entity that handles REMS development and oversight?

FDA primarily handles REMS development and oversight. FDAAA authorized FDA to require persons submitting covered applications (new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs)) to submit to a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.[13] FDA can also require holders of covered applications approved without a REMS to submit to a REMS if FDA becomes aware of new safety information and determines that a REMS is necessary.

Q 9.4 When can a REMS be required and how are REMS for particular products or classes of products devised?

FDA can determine that a drug or biologic requires a REMS in three scenarios: (1) during the approval process of a drug or biologic, (2) after the product is already on the market, or (3) retroactively.[14] Section 505-1 of the FDCA lists six factors FDA must consider when determining whether a REMS is necessary:

- Estimated size of the population likely to use the drug;
- Seriousness of the disease or condition that is to be treated with the drug;
- Expected benefit of the drug with respect to the disease or condition;
- Expected or actual duration of treatment with the drug;
- Seriousness of any known or potential adverse events; and
- Whether the drug is a new molecular entity.[15]

Collectively, these factors inform whether a REMS is required and, if so, what type of REMS is necessary. In September 2016, FDA released a draft guidance clarifying the various considerations FDA may take into account within each statutory factor.[16] Interestingly, the 2016 draft guidance also expanded upon an additional consideration outside the six statutory factors: the potential burden on the healthcare delivery system and patient access. To reduce the potential burden on patients and the healthcare system, FDA takes into account existing REMS elements for other drugs with similar risks and whether the REMS under consideration can be designed to be compatible with established medical drug distribution, procurement, and dispensing systems. FDA also considers whether the REMS under consideration may impose additional access difficulties, particularly for patients in rural or medically underserved areas, and whether the REMS may result in potential treatment interruptions or delays, particularly for patients who have serious or

life-threatening conditions.[17]

Once FDA determines that a REMS is required, FDA notifies the applicant and the applicant has 120 days to develop and submit a proposed REMS to FDA.[18] A proposed REMS submission should include two parts: a proposed REMS and a REMS supporting document.[19] The proposed REMS should include the goals and proposed elements of the REMS, and the REMS supporting document should provide a thorough explanation for, and supporting information about, the content of the proposed REMS.[20] Templates for both the proposed REMS and REMS supporting document are available for download from FDA's "Postmarket Drug Safety Information for Patients and Providers" website.[21]

In response to criticism that drug-specific REMS can be difficult to locate, FDA in January 2018 launched a new REMS site with information organized by audience (that is, patients, healthcare providers and industry).[22] This new site is one step in FDA's plan to bring greater ease of accessibility to REMS programs.

Q 9.5 Are there any advantages to a company proactively suggesting REMS for a particular product to FDA?

An applicant may voluntarily submit a proposed REMS to FDA without being required to do so, such as including a proposed REMS in an original or supplemental application, or in an amendment to an existing original or supplemental application. A voluntarily submitted proposed REMS is subject to the same requirements and enforcement as a REMS originally submitted at FDA's request. If a proposed REMS is not approved, it is not subject to enforcement by FDA. If FDA determines a REMS is not required, the applicant will be notified; such applicants may voluntarily undertake risk management measures performed outside of a REMS if desired.[23]

A company may choose to proactively suggest implementation of a REMS to reduce delays in the approval of its application. For example, rather than risk non-approval, a company may suggest testing a practice REMS in Phase III clinical trials.[24] In this way, the company can demonstrate that potential risks can be appropriately managed.

Q 9.6 Who within a company is typically involved in devising a REMS plan?

Regulatory personnel bring a unique understanding of the regulatory framework and have primary responsibility for managing interactions with FDA. They often spearhead and manage REMS design, implementation, and operations within their companies. They may engage in informal discussions with FDA about REMS design and play a critical role in managing FDA submissions. In many companies, the regulatory group can lead the effort in setting up committees, overseeing training of relevant company personnel, and ensuring that there are adequate processes and procedures for REMS set-up and implementation.

Medically trained personnel are critical participants in the process. They can shed light on the type of medical risks that exist, as well as the practical considerations involved in, for

example, healthcare provider and pharmacist workflows. In addition, they may be instrumental in helping to craft adequate warnings about the relevant risks, as well as determining whether there may be ways to monitor patients using the drug, or to identify patients for whom the treatment may be particularly risky.

Legal representatives bring important perspectives on ensuring that warnings are adequate (both in terms of their content and in assessing whether warnings have sufficient prominence). They also work closely with medical personnel to identify ways to minimize product liability risks and will assist in aspects of REMS implementation such as contracting with REMS-related vendors.

The perspectives of sales and marketing personnel can also be critical to ensure that a REMS program is adequately managed and publicized. Sales representatives must be adequately trained on how the REMS works so that they can be prepared to address questions that may arise from healthcare providers. They must have an understanding of the various components of the REMS program, particularly those that may serve as a barrier to a healthcare provider being able to prescribe such products.

In addition, individuals knowledgeable about distribution channels are key participants in devising a REMS plan.[25] Such individuals may be able to identify ways to increase the likelihood that REMS-related materials actually reach their target audience. Ensuring that medication guides, for example, reach the patient can be a critical step in ensuring that patients are properly educated and, in turn, may affect whether the periodic assessments will demonstrate that the REMS program is working effectively. In addition, those who are knowledgeable about the distribution chain are uniquely situated to help work through any restricted distribution aspects of a REMS.

Q 9.7 What are some typical components of REMS?

A REMS must have a timetable for submission of assessments of the REMS (see Q 9.9 below), and may also include one or more of the following elements:

- Medication Guides: Medication guides consist of information that must be distributed to each patient when the drug is dispensed. Such guides are considered part of labeling and are thus subject to the safety labeling change provisions of section 505(o)(4) of the FDCA. It should also be noted that FDA can require a patient package insert to be distributed to each patient in lieu of a medication guide if it is determined that such an insert would help mitigate serious risks of the drug.[26]
- Communication Plans: Communication plans support implementation of various elements of a REMS and may include sending letters to physicians, pharmacists, and professional societies about the risks at issue and protocol for safe use.[27]
- Elements to Assure Safe Use (ETASU): ETASU may be required if the drug has been shown to be effective, but is associated with one or more serious adverse events and can be approved only if, or would be withdrawn unless, such elements

> are required. Such elements may restrict the distribution and use of a drug with the intent to mitigate a serious risk, and may consist of training for healthcare providers, special certification to prescribe or dispense the product, limitations on how and where the product may be dispensed, and patient monitoring and registries.[28]

Another optional component is a continuing education option for health care providers in the post-marketing, but not initial approval, time frame. Based on a newly issued report, FDA determined that including continuing education at the time of initial approval could lead to potential delays in launching a product because a company must have its REMS program fully established at the time of product launch. Introducing a continuing education component during the post-marketing time frame, however, was deemed a feasible option. In reaching this conclusion, FDA conducted an assessment of the use of continuing education within the Opioid REMS program, which (according to FDA) was the only REMS so far to include that component.[29]

Q 9.8 Are ANDA holders subject to the same requirements for REMS as NDA holders?

Unlike new drugs and biologics, ANDAs are subject to a subset of the REMS requirements for the reference drug: namely, a medication guide, patient package insert, or elements to ensure safe use.[30] The law requires FDA to undertake any communication plan required for the reference drug.[31] Note, however, that many tools previously viewed as part of a communication plan may now fall within ETASU (such as "training materials, specified procedures, patient/physician agreements or other informed consent, patient educational materials, safety protocols, medical monitoring procedures and data collection forms").[32] Both NDA holders and ANDA holders are required to implement the ETASU.

Q 9.9 Are periodic assessments necessary to determine if a REMS is working and if so, how are such assessments typically performed?

Section 505-1(d) of the FDCA requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. Such assessments must be submitted to FDA, at a minimum, eighteen months, three years, and seven years after a REMS is approved. In some cases, the assessments can be eliminated after three years.[33] These assessments allow FDA to periodically review a REMS and determine whether the REMS is meeting its stated goals. Certain factors may require more frequent assessments of a REMS and include, among others, the estimated size of the population likely to use the drug, the seriousness of known or potential risks that may be related to the drug, and knowledge about the effectiveness of REMS elements to mitigate the risks.[34] The reporting interval of each assessment should conclude no earlier than sixty days before the submission date for that assessment.

REMS assessments should include an evaluation of the extent to which each of the REMS elements are meeting the goals and objectives of the REMS, and whether or not the

goals and objectives of the REMS should be modified. Evaluation methods may include data from population- or claims-based data systems, surveys of patients and physicians, active surveillance of adverse event reporting sites, and various registries of use patterns (which may include data pertaining to use by specialty, length of therapy, patient-specific data, and indication). Rationales for the chosen methods, as well as targeted values and the time frame for achieving them should be included.[35] Assessments should also include sufficient detail to identify a need for changes to the REMS, including adverse events associated with the effectiveness of the REMS, prescriptions written by uncertified healthcare practitioners, and dispensing of the product by uncertified pharmacies.[36]

Q 9.10 Is there a defined process for modifying or revising approved REMS?

Yes. On April 7, 2015, FDA issued a Draft Guidance for industry entitled "Risk Evaluation and Mitigation Strategies: Modifications and Revisions." The Draft Guidance provides information on what types of changes to approved REMS will be considered modifications and what types of changes will be considered revisions under the FDCA. Additionally, the Draft Guidance provides information on how REMS modifications and revisions should be submitted to FDA and how FDA intends to review and act on such submissions.[37]

According to the Draft Guidance, changes to approved REMS are categorized as either *revisions* or *modifications*. Categorization hinges on the degree of the potential effect on the REMS risk message and/or other REMS requirements. Changes that FDA has determined do not affect the REMS risk message or other REMS requirements are considered REMS *revisions*. Submission of REMS revisions are not considered supplemental applications and can be implemented following receipt of the submission by FDA. FDA provides a list of changes considered to be revisions in Table 1 of section III.A.2 in the guidance.[38]

Changes that are not included in Table 1 are considered to be REMS *modifications*. REMS modifications carry a greater potential effect on a REMS risk message and/or other REMS requirements than REMS revisions and are classified as either minor or major. A minor modification is defined as a change that may nominally affect the risk message and/or nominally change the REMS requirements, and is submitted to FDA as a CBE-30 supplement. A major modification is defined as a change that may substantially affect the risk message and/or substantially change the REMS requirements, and is submitted to FDA in the form of a prior approval supplement (PAS). Tables 2 and 3 of section III.B.2 of the guidance provide examples of changes considered to be minor and major REMS modifications, respectively.[39]

Submissions containing REMS revisions or proposed REMS modifications should include a detailed description of the REMS changes. All proposed REMS modifications must also be accompanied by an adequate rationale for the proposed changes to allow the FDA to determine if the appropriate submission category was selected. Detailed submission procedures for REMS revisions and modifications can be found in paragraphs A and B, respectively, of section IV of the guidance.[40]

Post-Market Safety Oversight

Q 9.11 Can products with REMS still be subject to market withdrawal or product liability lawsuits by patients alleging harm from such drugs?

REMS do not insulate manufacturers from market withdrawal or product liability lawsuits. A product with a REMS may be considered misbranded under section 502(y) of the FDCA if the manufacturer fails to comply with a requirement of the REMS, and thus become subject to market withdrawal. Likewise, under section 505(p) of the FDCA, a product may not be introduced into interstate commerce if a manufacturer fails to maintain compliance with the requirements of an approved REMS or with other requirements under section 505-1 of the FDCA, which includes submitting periodic assessments to FDA.[41]

For example, in September 2017, Aegerion entered into a $35 million settlement of criminal and civil actions that alleged, among other things, failure to comply with a REMS. Aegerion allegedly failed to "give health care providers complete and accurate information" about the rare inherited disorder that the company's drug could help treat and "also filed a misleading REMS assessment report." As a result, the company "failed to comply with the required elements under the REMS to assure safe use" in violation of the FDCA.[42]

Similarly, in September 2017, Novo Nordisk entered into a $58 million settlement that encompassed various allegations, including failure to comply with its FDA-mandated REMS for its Type II diabetes medication Victoza. That REMS focused on the risk of a rare form of cancer (Medullary Thyroid Carcinoma (MTC)) with the drug and required the company to provide information about that risk to physicians. But sale representatives allegedly suggested to physicians that the REMS-required message "was erroneous, irrelevant or unimportant" thereby causing some physicians to be unaware of that potential risk when prescribing the drug. In fact, after a survey in 2011 revealed that 50% of primary care doctors were unaware of the MTC risk, FDA required a modification of the REMS. Thereafter, the company's sales force was allegedly given messaging that continued to "obscur[e] the risk information."[43]

There may also be product liability lawsuits alleging personal injury even though a drug has an approved REMS. Because product liability lawsuits for prescription drugs are usually based on a failure to warn, however, a REMS program may heighten awareness of a product's warnings, and thereby significantly reduce risks associated with "failure to warn" product liability claims. On the other hand, because REMS programs are viewed as necessary to ensure that the benefits of the drug outweigh the risks, if periodic assessments for the REMS program reveal that the program is not achieving its desired purpose (of ensuring that patients are fully informed of a product's most significant risks, for example), assessments findings could prove problematic to a sponsor in a product liability lawsuit. This is particularly true if prompt action is not undertaken to address any deficiencies that periodic assessments identify.

Given that FDA continues to exert control over every aspect of a REMS, including final approval of any changes suggested by manufacturers to all forms and instructions provided to HCPs and patients, it has been suggested that conforming to all FDA-mandated aspects of a REMS may provide a manufacturer with the basis of asserting a preemption defense in a product liability action brought under a failure to warn theory.[44]

Q 9.12 Can a REMS be mandated after a drug is already on the market?

Yes, a REMS may be mandated if FDA becomes aware of new safety information and determines a REMS is necessary to ensure the benefits of the drug outweigh the risks.

New safety information is defined as: "Information derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system . . . or other scientific data deemed appropriate by the Secretary about:

(A) a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the REMS was required, or since the last assessment of the approved REMS; or

(B) the effectiveness of the approved REMS obtained since the last assessment of such strategy."[45]

Once notified by FDA that a REMS is necessary, the holder must submit a proposed REMS within 120 days, or such other time as FDA specifies.[46]

Q 9.13 Are there any penalties for noncompliance with REMS?

In addition to section 505(p) of the FDCA prohibiting drugs and biologics from being introduced into interstate commerce if a manufacturer fails to comply with a required REMS, various other penalties may be imposed for noncompliance. Noncompliant products may result in civil money penalties of $250,000 per violation or $1 million for all violations adjudicated in a single proceeding. For violations that continue after FDA has given notice, a company can be fined $250,000 per thirty-day period, and double that amount for each subsequent thirty-day period.[47] Recently, FDA increased these monetary penalties to keep pace with inflation and as a result, the $250,000 per violation and $250,000 per thirty-day period amounts have been increased to $290,000.[48] See Q 9.11 for discussion of recent enforcement actions involving a drug company's alleged failure to comply with its REMS.

Q 9.14 How many REMS programs are currently in place? Where can I find information about a particular product's REMS?

According to FDA records, as of March 2018,, there are seventy-four products listed as having a REMS, down significantly from approximately 185 approved REMS in October

2011.[49] The reduction in total number of REMS currently in effect can be attributed, in part, to a November 2011 FDA Guidance that clarified requirements for medication guides and permitted applicants who had REMS consisting only of a medication guide to request termination of the REMS (if they felt the REMS was unnecessary to ensure that the benefits of the drug outweighed the risks).[50] Nonetheless, one report estimated that 40% of new drug approvals include a REMS.[51]

Those interested in finding a particular product's REMS can inquire with a product's manufacturer or search the "Drugs" section of the FDA website for the Approved Risk Evaluation and Mitigation Strategies (REMS) page.[52]

Healthcare providers who need access to REMS do not have a central location where they can access all the elements of each drug's REMS program. In addition, there is great variability in how REMS programs are implemented. FDA has recently released several new documents aimed at bringing greater uniformity and accessibility to REMS information.

For example, in September 2017, FDA released a draft Guidance entitled, "Providing Regulatory Submissions in Electronic Format—Content of the Risk Evaluation & Mitigation Strategies Document Using Structured Product Labeling". In October 2017, FDA released another draft Guidance entitled, "Format and Content of a REMS Document." Likewise, FDA has released a report entitled: "A Framework for Benefit Risk Counseling to Patients About Drugs with REMS" that encompasses four steps: Evaluate, Educate, Engage and Ensure.[53] The "REMS Platform Standards Initiative: Needs Assessment" report provides ideas for further improvements.[54]

A REMS Integration Initiative had the goal of evaluating how REMS programs are established and implemented.[55] Although that initiative began in 2011 and ended in October 2017, FDA is planning further updates to the REMS initiative in the coming year. (See Q.9.27.)

Q 9.15 Were there drugs approved before FDAAA that were later deemed to have REMS?

Yes, FDA published a list of drugs that were identified as deemed to have an approved REMS.[56] These drugs already had elements to assure safe use. Holders of approved applications for those products were required to submit a proposed REMS by September 21, 2008.

Q 9.16 If a drug has a medication guide, does this mean it is subject to REMS?

No, not all drugs with Medication Guides have REMS. FDA may approve a Medication Guide for a drug without requiring additional tools to ensure safe use of the drug. Applicants with drugs that have a REMS consisting solely of a Medication Guide may seek a REMS modification if they do not believe the REMS is necessary to ensure that the benefits of the drug outweigh the risk. The proposed REMS modification must be

accompanied by a REMS assessment. Even if the REMS is modified or eliminated, the Medication Guide may still be needed unless FDA determines it is no longer a part of the approved labeling.[57] The FDA guidance for industry entitled *Risk Evaluation andMitigation Strategies: Modifications and Revisions (April 2015)* provides further information on the process for modifications of REMS, including changes that will either revise or remove the Medication Guide element of a REMS.

Q 9.17 What other types of post-market safety oversight exist to monitor drug safety?

In addition to REMS, there are several other post-market safety oversight mechanisms to monitor drug safety, including, but not limited to, the FDA Adverse Event Reporting System (FERS), Postmarketing Drug and Biologic Safety Evaluations, and Safety Labeling Change Orders.

Q 9.18 How are spontaneous adverse event reports made? How are physicians and patients given information about how to report adverse events?

Spontaneous adverse event reports can be made to FDA and manufacturers by anyone with knowledge of such events, such as healthcare providers, pharmacists, nurses, medical personnel, patients, family members, and lawyers. These reports are voluntary, and once received by FDA, are entered into a database known as the FDA Adverse Event Reporting System (FAERS) (which was formerly known as "AERS"). FAERS is an information database used by FDA as part of its post-marketing safety surveillance program for drugs and biologics, and is used to monitor new adverse events and medication errors.[58] As required under FDAAA, FDA now reviews the FAERS database and identifies drugs on its website (on a quarterly basis) that have potential safety signals.[59]

Q 9.19 Do companies have an obligation to conduct additional clinical trials or other testing to continue to evaluate a drug's safety after FDA approval?

Sometimes approval of a drug may be accompanied by a commitment by the company to conduct additional clinical trials or other testing. Those additional clinical trials or other testing are designed to confirm a drug's safety profile. Unless such a commitment to FDA exists, however, companies typically do not have an obligation to conduct additional clinical trials or other testing after a drug is approved.

FDAAA signficantly expanded FDA's authority to mandate post-marketing studies or clinical trials. Previously, such commitments were typically limited to accelerated approval products, deferred pediatric studies and Subpart I and Subpart H Animal Efficacy Rule approvals. Section 505(o)(3) of FDAAA now authorizes FDA to require post-marketing studies or clinical trials at the time of approval *or after approval* if FDA becomes aware of new safety information.[60] FDA may require additional post-marketing studies and clinical

trials to (1) assess a known serious risk related to use of the drug; (2) assess signals of serious risk related to the use of the drug; or (3) to identify an unexpected serious risk, when available data indicates the potential for a serious risk.[61]

Patients claiming injury from using a prescription drug may allege that the drug company was negligent in failing to conduct adequate clinical trials or testing that would have uncovered a previously unidentified risk (or a risk of higher incidence than had been previously anticipated). Whether an obligation exists to conduct additional clinical trials or testing, therefore, rests in part on traditional negligence law and the question of whether a reasonable manufacturer under the circumstances would have done more to better ascertain the risks and warn about them. It is unclear how the new ability of FDA to mandate post-marketing clinical trials or studies under FDAAA will affect such claims that drug companies should have voluntarily undertaken additional research.

Q 9.20 What is a "signal" and how is a signal identified once a drug is being marketed?

A signal or safety signal represents an identified potential safety issue with a drug or biologic, but does not mean a causal relationship has been identified between the drug and the listed risk. Safety signals may be identified from aggregated adverse event report data and often warrant further inquiry as to whether a causal link exists between the drug and risk.[62]

Q 9.21 What steps must a prudent company take if a signal is identified? Will a signal of a serious adverse event result in withdrawal of the product from the market?

Companies marketing prescription drugs must be reasonably vigilant in monitoring adverse events associated with a drug's use. Prompt action may be warranted once a safety signal is identified. Such action may include an expedited report to FDA of the newly identified safety information, updating the product label, and possibly sending a Dear Doctor Letter to notify healthcare providers of the new risk information. A company may opt to update its product label through a "Changes Being Effected," in which the company notifies FDA of its intended label update and FDA has a limited time frame within which to object before the label update would take effect.

A new safety signal will not always result in product withdrawal. As with all unavoidably dangerous products, key questions remain, such as whether even with the newly identified risk, the product benefits outweigh those potential risks (at least for some group of patients).

Companies are able to proactively reach out to FDA to devise a reasonable plan of action if a safety signal is identified or strongly suspected.

Q 9.22 What challenges exist for generic drug companies when seeking to introduce products that are subject to a REMS?

Recently, generic drug companies have begun challenging the use of REMS programs to restrict access to branded drugs. In a July 23, 2014, press release,[63] the Generic Pharmaceutical Association (GPhA) criticized the "unfair trade practices" of branded companies in utilizing REMS programs to prevent purchase of branded drugs from wholesalers. The GPhA contends that such conduct results in more costly pharmaceutical options due to delays in generic drug entry to the market because generic drug companies are unable to conduct the necessary testing to show that a drug they have developed is bioequivalent to the branded drug. The Federal Trade Commission has expressed concerns and filed amicus briefs in support of the generic drug company arguments, such as in *Mylan v. Celgene*, a case involving Revlimid® and Thalomid.[64] Subsequently, the Federal Trade Commission expressed the view that the FDA has the ability to regulate REMS and it will defer to FDA to execute that authority to address REMS abuses.[65]

Branded companies have sometimes declined to make a reference listed drug (RLD) available to ANDA applicants for bioequivalence testing, arguing that it may be a violation of the RLD REMS to send that product to an ANDA applicant if the ANDA applicant cannot meet the requirements of the REMS. Hearing these concerns, in December 2014, FDA released a draft guidance that described how a prospective ANDA applicant may request a letter from FDA for sending to the RLD manufacturer stating that FDA has determined: (1) that the ANDA applicant's bioequivalence study contains safety protections comparable to those within the RLD REMS to ensure safe use of the product; and (2) that FDA will not consider it a violation of the RLD REMS for the RLD manufacturer to make the product available to the ANDA applicant for bioequivalence testing.[66]

Some commentators view FDA's latest action as not going far enough. The issuance of a statement that a drug company will not violate its REMS by releasing a drug to an ANDA holder is not nearly as strong as a provision that would "require" the manufacturer to make the drug available to the ANDA manufacturer (although it is not clear that FDA has authority to compel such an outcome). Further debate on this topic is expected until the FDA, FTC, or courts take a firm position on the issue. Recently, FDA and FTC participated in hearings about their perception that branded drug companies are using REMS programs to block generic competition.[67] In addressing ways to expedite generic drug approvals and create greater competition to lower drug prices, FDA Commissioner Scott Gottlieb, MD, said brand companies must "end the shenanigans" of using REMS to block generic companies from obtaining the drugs needed to run their studies. [68]

Recently, there has also been renewed attention by legislators on the use of REMS to block entry of generic competitors. The CREATES Act is a proposed federal law that aims to prevent brand companies from blocking generic company access to drugs based on REMS.[69]

Another tactic that may be utilized to block competition arises in how companies seek to protect systems they devise to monitor safety concerns with their drugs. For example, some companies with branded pharmaceuticals have filed patents for their REMS systems (for

example, patenting of individual REMS components or entire programs) (see Q 9.23). This can be another impediment to companies seeking to introduce generics because the existing REMS system for the branded product may not be able to be adopted in wholesale fashion. As a result, time and effort may be needed to ensure that the generic will be introduced to market with appropriate measures undertaken to satisfy the REMS requirements for that product.

Q 9.23 What other measures should be considered if a company adopts a REMS?

Some companies choose to patent their REMS. Patents may cover individual components or the REMS system as a whole. For example, the XYREM Success Program (U.S. Patent No. 7,895,059) covers the company's approach to monitoring patient access through the single pharmacy authorized to dispense the product. It also covers the approach of alerting police to doctors with high volumes of prescriptions who may be engaged in drug trafficking or other diversion.[70] "The patented system processes all prescriptions written into a central database, checks and reconciles patient and doctor information in the database, sends patient educational information, and then under strict distribution arranges for the drug to be sent to patients."[71] Companies devising REMS should consider whether patenting of REMS components or systems is warranted and can be justified.

Q 9.24 What other initiatives exist with respect to REMS?

In October 2015, FDA announced a pilot program for submission of final approved REMS and certain REMS summary information in a standard Structured Product Labeling format.[72] The goal of that pilot program was to make it easier for documents to be integrated into pharmacy and hospital information technology systems. FDA officially began accepting REMS documents in SPL format in 2016.

Q 9.25 Is there an obligation on the part of a branded drug company to share its REMS process? Can a branded company impose conditions precedent before engaging in discussions about an FDA-directed shared REMS program? How do antitrust considerations play out?

A branded drug company may be able to impose significant conditions before complying with an FDA directive to share its REMS process with generic companies. For example, in *In re Suboxone (Buprenorphine Hydrochloride and Naloxone) Antitrust Litigation*, [73] the plaintiffs (end users and direct purchasers) alleged that Reckitt Benckiser, among other things, engaged in anticompetitive conduct when it delayed and refused to engage in a shared REMS program with Actavis and Amneal. The FDA had directed the companies to work together to come up with a shared REMS but Reckitt allegedly sought to impose unreasonable conditions precedent to cooperating in a Single Shared REMS Program (SSRP). For example, Reckitt allegedly turned down numerous invitations to participate in

meetings with the generic companies, and refused to engage in substantive discussions until the generic companies agreed to, among other things, "an upfront agreement that all manufacturers would share the costs of product liability for future potential lawsuits."[74]

The District Court for the Eastern District of Pennsylvania granted Reckitt's motion to dismiss holding that Reckitt had not violated any antitrust laws in allegedly failing to cooperate with Actavis and Amneal. Under 21 U.S.C. § 355(1)(f)(8), parties are to work together in good faith and not use the SSRS process to block or delay ANDA approval. There, FDA had directed the parties to work in good faith to develop an SSRP that would ultimately lead to ANDA approval for the generics. Nonetheless, the court observed that "the Supreme Court has unequivocally stated that statutes and regulations requiring cooperation between competitors do not create an antitrust duty to deal."[75] In fact, the Supreme Court concluded that a regulatory structure requiring cooperation actually diminishes the need for antitrust scrutiny. The only exception would be if there had been a long-standing, preexisting course of dealing between Reckitt and the generics (which was not the case there).

The court distinguished two other cases (from the same circuit) that alleged antitrust violations. Specifically, the plaintiffs alleged the use of REMS to block generic company access to the drug for bioequivalent testing prevented filing of the ANDA. In contrast, in the Reckitt case, the ANDA was in fact pending when the SSRS process began. The court stated: "It would have been easier to have Reckitt provide its REMS to its competitors with no strings attached, and participation on Reckitt's part would have allowed the process to move more quickly. However, a monopolist 'certainly has no duty to deal under terms and conditions that the rivals find commercially advantageous.'"[76] Ultimately the court ruled that "[t]he antitrust laws do not impose a duty on Reckitt to aid the Generics in obtaining expeditious approval of an ANDA" and a statute provides for increased FDA oversight thereby diminishing the need for antitrust scrutiny.[77] (See also commentary about FTC's views in answer to Q 9.22.)

We may be moving toward scrutiny of generic manufacturers as potential culpable parties in product liability actions (see chapter 10, "Impact of FDA Regulatory and Compliance Oversight on Product Liability Exposure of Pharmaceutical Manufacturers"). Were this to happen, future challenges may be anticipated under theories other than antitrust violations.

Q 9.26 How many Single Shared REMS Programs exist and what types of products are subject to them? What has been FDA's position on development of such Programs?

As of March 2018, there were ten Single Shared REMS Programs listed on FDA's REMS website.[78] They are for: (1) Alosetron; (2) Buprenorphine Transmucosal Products for Opioid Dependence (BTOD); (3) Clozapine; (4) Emtricitabine/tenofovir disoproxil fumarate; (5) Extended Release and Long-Acting (ER/LA) Opioid Analgesics; (6) Isotretinoin iPLEDGE; (7) Mycophenolate; (8) Sodium Oxybate; (9) Transmucosal

Immediate-Release Fentanyl (TIRF) Products and (10) Vigabatrin.

For further details about FDA's historic views on Single Shared REMS Programs, see the October 7, 2013, Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to Prometheus Laboratories that, among other things, denies the company's request that the Agency complete notice and comment rulemaking to establish standards and processes for single shared systems.

Nonetheless, in November 2017, under new FDA Commissioner Scott Gottlieb, FDA took one step to streamline submissions when there is a Shared REMS and introduced a new Draft Guidance entitled, "Use of a Drug Master File for Shared System REMS Submissions" that aimed to streamline filings associated with shared REMS. FDA acknowledged that under current procedures, companies must coordinate submission of identical REMS-related documents for their respective submissions relating to a Shared REMS. The Draft Guidance proposes that drug companies instead submit a single Drug Master file that contains one collective set of files. In addition, FDA announced that it planned to address how and when a generic company can request a waiver from a Shared REMS, including the factors FDA intends to consider in whether to grant that waiver.[79]

Q 9.27 What further guidance can we expect from FDA about REMS requirements?

The 2018 Plan for FDA release of Draft or Final Guidances[80] includes: (1) Development of a Shared REMS; (2) REMS Assessment: Planning & Reporting; (3) Survey Methodologies to Assess REMS Goals Related to Knowledge; (4) Use of a Drug Master File for Shared Risk Evaluation & Mitigation Strategies and (5) Waivers of the Single, Shared REMS Requirement.

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1. The authors wish to acknowledge the help of Genevieve Spires of Buchanan, Ingersoll & ıey for her assistance with a prior version of this chapter

2. TRENT STEVENS & ROCK BRYNNER, DARK REMEDY: THE IMPACT OF LIDOMIDE AND ITS REVIVAL AS A VITAL MEDICINE (Basic Books Dec. 27,).

3. *See* THALOMID REMS PROGRAM, www.thalomidrems.com.

4. Duane Roth, *A Third Seat at the Table: An Insider's Perspective on Patient Representatives*, HASTINGS CTR. REPORT 29 (2011); *see also Matthew Perrone, FDA Approves Test to Screen for Risk of Rare Brain Infection in Patients Taking Tysabri*, ASSOCIATED PRESS, 20, 2012 (advising of new diagnostic test to identify patients at greatest risk for rare brain tion).

5. U.S. FOOD AND DRUG ADMINISTRATION, RISK EVALUATION AND IGATION STRATEGY (REMS) FOR EXTENDED-RELEASE AND LONG-ACTING OID ANALGESICS (REMS), .fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. An education ram for prescribers is the central component of the Opioid REMS, with sponsors to provide

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6. U.S. FOOD AND DRUG ADMINISTRATION, "FDA'S OPIOID ANALGESIC S EDUCATION BLUEPRINT FOR HEALTH CARE PROVIDERS INVOLVED IN TREATMENT AND MONITORING OF PATIENTS WITH PAIN" (Jan. 2018), ://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm594443.htm.

7. "FDA REMS Blueprint on Opioids Finalized" (Feb. 2, 2018) //www.policymed.com/2018/02/fda-rems-blueprint-on-opioids-finalized.html.

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9. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND G ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, TER FOR BIOLOGICS EVALUATION AND RESEARCH, DRAFT GUIDANCE INDUSTRY FORMAT AND CONTENT OF PROPOSED RISK EVALUATION MITIGATION STRATEGIES (REMS), REMS ASSESSMENTS, AND PROPOSED S MODIFICATIONS (Sept. 2009) [hereinafter REMS DRAFT GUIDANCE], at 2, .fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm18 .pdf.

10. *E.g.*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND G ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, TER FOR BIOLOGICS EVALUATION AND RESEARCH, GUIDANCE FOR USTRY DEVELOPMENT AND USE OF RISK MINIMIZATION PLANS (Mar.).

11. REMS DRAFT GUIDANCE, *supra* note 8, at 7.

12. *Id.* at 3.

13. 21 U.S.C. § 355-1(a)(1).

14. *REMS 2.0: Strategies for Satisfying the FDA's REMS Requirements*, FDANEWS, at 8)) [hereinafter FDANEWS].

15. 21 U.S.C. § 355-1(a)(1)(A)–(F).

16. U.S. Department of Health and Human Services, Food and Drug Administration, er for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Draft ance for Industry FDA's Application of Statutory Factors in Determining When a REMS is ssary (Sept. 2016) [hereinafter REMS Statutory Guidance], at 6, .fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM 04.pdf.

17. *Id.* at 11.
18. 21 U.S.C. § 355-1(a)(2)(B).
19. REMS Draft Guidance, *supra* note 8, at 7.
20. *Id.* at 7, 16.
21. FDA, *Postmarket Drug Safety Information for Patients and Providers*, .fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/.
22. *See* https://www.fda.gov/Drugs/DrugSafety/REMS/default.htm?.campaign=New%20REMS%20Webpages%20Launched&utm_medium=email&utm_sourloqua.
23. REMS DRAFT GUIDANCE, *supra* note 8, at 2–3.
24. FDANews, *supra* note 13, at 11.
25. Craig Kephart, How to Transform REMS into an Opportunity to Develop a More ssful Drug Launch (Jan. 2, 2011), http://pharmaceuticalcommerce.com/index.php?usiness_finance&articleid=2311.
26. FDANEWS, *supra* note 13, at 7.
27. 21 U.S.C. § 355-1(e)(3).
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29. "REMS and Continuing Education for Health Care Providers—FDA Feasbility Report" . 3, 2017), ://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM583775.tps://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM5837lf.
30. 21 U.S.C. § 355-1(i)(1).
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32. *Id.*
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10

Impact of FDA Regulatory and Compliance Oversight on Product Liability Exposure of Pharmaceutical Manufacturers

Howard L. Dorfman & Linda Pissott Reig[1]

This chapter examines a complex and intricate question. How does state tort liability co-exist with the expansive federal statutory and regulatory framework that governs the marketing of prescription drugs?

The Food and Drug Administration (FDA) and other federal agencies (particularly the Office of Inspector General (OIG) of the Department of Health and Human Services (HHS), as well as the Department of Justice (DOJ)), are charged with enforcing a complex scheme of laws. Those laws encompass many requirements for lawful marketing and sale of prescription drugs. For example, federal law defines what constitutes lawful, non-misleading promotional messaging, as well as when interactions with healthcare professionals trigger Anti-Kickback Statute violations.

Meanwhile, state tort law is designed to protect the well-being of each state's citizens. It provides additional legal standards and enables patients to recover for, among other things, injuries arising from use of pharmaceuticals.

Courts have limited a drug manufacturer's exposure to state law claims in certain instances, but not in others. Those principles, as we discuss in this chapter, are largely dependent on the federal regulatory scheme governing the pharmaceutical manufacturer. We saw this most recently in how the courts distinguished between obligations to update product labels by brand-name drug companies, as opposed to generic drug companies.

The federal government's oversight of pharmaceutical companies is significant. This is evident in the U.S. Supreme Court decisions discussed here, as well as the increasing role being played by the OIG and the DOJ in providing oversight and quasi-regulatory controls over pharmaceutical manufacturers. Nevertheless, tort law duties and liabilities under state law also remain in force, including some that are not easily reconciled with the federal legal framework.

It is not easy to make sense of this complex web of federal and state legal requirements. But a "head in the sand" approach is not an option. Companies must implement policies and procedures that minimize legal risks under both federal and state law requirements. Fail to do so and your company will face significant liability exposure, including state court jury awards for failing to respond to new drug safety concerns.

Oversight of the Pharmaceutical Industry

Q 10.1 What is FDA's regulatory regime applicable to drug manufacturers?

FDA is charged with administering the comprehensive regulatory scheme governing prescription drug distribution within the United States. FDA is a regulatory agency within the HHS. To sell drugs in the United States, a manufacturer is required to obtain approval from FDA.

Pursuant to the federal Food, Drug, and Cosmetic Act (FDCA),[2] as amended by the Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Act"), FDA has the ultimate authority to determine whether a new prescription drug is safe and effective for use. The DOJ monitors and prosecutes violations of the FDCA and other criminal and civil laws governing pharmaceutical manufacturers.

Q 10.2 How does FDA regulatory regime impact state product liability claims against drug manufacturers?

As discussed in this chapter, the different regulatory framework applicable to branded and generic drug manufacturers has major implications for potential liability under state product liability law. FDA's extensive oversight over pharmaceutical product approval, labeling, and distribution has caused courts to rule that state law design defect and/or failure to warn product liability claims are preempted in certain instances.

Despite decisions preempting state law claims, however, the courts have not yet completely determined the full scope of the tort law duties owed by brand name and generic drug manufacturers. This is true in light of new theories of liability being developed by plaintiffs seeking to recover against pharmaceutical companies for sale of their products. New cases present new facts, risks, and corresponding theories of liability. Different factual circumstances arising in new cases continue to present challenges for judges seeking to draw a line between FDA enforcement and state tort law liability.

Courts generally follow the principle, however, that state law tort suits serve a societal benefit particularly with respect to the need for companies to be vigilant in monitoring adverse drug events after FDA approval. Indeed, drug manufacturers are expected to promptly disclose safety risks. Failure to do so has resulted in settlements or verdicts, sometimes requiring payment of millions of dollars to one patient.

Some argue that state product liability law, by providing a compensatory function, incentivizes injured persons to sue, which inevitably results in a closer examination of a drug's safety risks. Some courts have concluded that FDA has limited capacity to oversee drug manufacturers and, thus, product liability law is helpful as an adjunct to the existing regulatory process.[3] Those arguing for a continuing role of litigation as part of the overall drug safety process state that manufacturers may have superior access to information about their drugs, including the information arising from the spontaneous reporting of adverse

events by healthcare practitioners and patients. This information obtained during the post-approval phase, some argue, has helped identify additional risks not observed during the extensive clinical trial phase of drug research and development.

Tension has existed for some time between the complex web of FDA regulations and the requirements that these regulations impose on pharmaceutical manufacturers and state product liability law. FDA itself has, on occasion, expressed its concern with a tort system that allows lay juries to second-guess the decisions of the agency and usurp its function as the expert arbiter on issues of drug safety and appropriate labeling. State product liability lawsuits are determined by juries comprised of laypeople, not pharmaceutical or scientific authorities or warnings experts. Thus, juries tend to analyze issues of the adequacy of warnings or designs from a completely different vantage point than FDA's experts. This dichotomy has the clear potential to result in inconsistency between FDA's expert opinions and a jury's verdict.

Another factor to consider is the increased costs incurred by manufacturers in having to satisfy FDA regulatory requirements and undertake the costly defense of state product liability litigation. These competing interests have been articulated in the various preemption decisions issued by the U.S. Supreme Court over the past several years, and are critical to understanding the basis for, and the arguments raised against, imposing limitations on pharmaceutical liability.

Q 10.3 Is oversight of the pharmaceutical industry limited to FDA regulations and authority?

No. First, in addition to FDA, there are a number of other regulatory and statutory authorities that regulate pharmaceutical and medical device manufacturers. These authorities and regulations include the OIG, the HHS, the DOJ, and the many state attorneys general, state consumer protection laws (such as unfair trade practice or consumer fraud acts), in addition to the various state product liability laws.

The U.S. Supreme Court has been careful to maintain the authority of the states to apply their product liability laws to drug manufacturers, so long as those laws are not in direct conflict with FDCA regulations. The Court has explained that while Congress enacted the FDCA "to bolster consumer protection against harmful products,"[4] the FDCA was not intended to completely preempt all state product liability law. According to the Supreme Court, "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness."[5] The Court has also reasoned that state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs, and to give adequate warnings. In addition, "the FDA traditionally regarded state law as a complementary form of drug regulation."[6]

As discussed later in this chapter, there are recent U.S. Supreme Court decisions finding that certain state product liability laws should be preempted if they conflict with the FDCA regulations. These decisions suggest that FDA is taking on a dominant role in the regulation of pharmaceutical manufacturers over state laws, but the full impact of the most

recent jurisprudence remains to be fully developed. In particular, as discussed below, the increasing FDA authority over risk identification and management during the post-approval period under the provisions of the Food and Drug Administration Amendments Act of 2007 (FDAAA) has and will continue to play a critical role in establishing appropriate manufacturers' conduct, as well as outlining the basis for a general defense in product liability litigation.

State Law Tort Claims

Generally

Q 10.4 What type of state law tort claims can be asserted against drug manufacturers by consumers of their drugs?

Generally speaking, common product liability theories involve claims for failure to warn (for example, of known risks in the drug labeling) or design defect claims (that the product's design was defective). The plaintiffs' bar continues to seek to formulate new theories of liability and expand the scope of the duty owed by drug manufacturers to consumers of prescription drugs. Plaintiffs also continue to bring claims for fraudulent misrepresentation, consumer fraud, negligence, breach of warranties and other theories.

Drug Manufacturers Failure to Warn

Q 10.5 What are the general standards for a failure to warn claim in the prescription drug context?

Manufacturers of dangerous products generally have a duty, under applicable state product liability law, to convey adequate warnings. The required warnings must not be misleading, and must be adequate to explain the possible dangers associated with the product. Although compliance with FDA warning requirements may provide a defense to manufacturers in some circumstances, it does not insulate a company from liability in all instances.

If a drug manufacturer has FDA approval for its warning, it may benefit from the laws in some states that give a certain level of deference to FDA's decisions with respect to a particular warning. For example, New Jersey allows for a rebuttable presumption of adequacy. The New Jersey Supreme Court has ruled that compliance with FDA regulations provides "compelling evidence that the manufacturer satisfied its duty to warn the physician."[7] In certain instances, however, plaintiffs may be able to overcome this presumption.

The scope of the duty to warn under state product liability law also depends on how the drug is marketed (that is, directly to consumers, over the counter, or via a physician prescription). In product liability actions involving prescription drugs, many states recognize the learned intermediary doctrine, which changes the duty owed by manufacturers.[8] Not too long ago, one court observed that at least thirty-five states have adopted some form of the learned intermediary doctrine within the prescription drug product liability context or cited favorably to it.[9]

More recently a court acknowledged that forty-eight states apply the learned intermediary doctrine.[10] That court noted that New Mexico[11] and Vermont[12] have not yet

opined either way.[13] West Virginia used to be an outlier (because they had specifically rejected the learned intermediary doctrine if a drug company had engaged in direct-to-consumer advertising) but as we address below, that is no longer the case.

Meanwhile, the Supreme Court of Arizona joined the vast majority of states in ruling that the learned intermediary doctrine applies to product liability claims involving prescription drugs. Arizona follows the *Restatement (Third) of Torts: Product Liability* approach. That approach recognizes that prescription drugs are complex products and such products are "not reasonably safe due to inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to:

(1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or

(2) the patient when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings."[14]

Q 10.5.1 What is the "learned intermediary doctrine"?

The learned intermediary doctrine stands for the proposition that:

> [A] drug "manufacturer is excused from warning each patient who receives the product when the manufacturer properly warns the prescribing physician of the product's dangers." *See Porterfield v. Ethicon, Inc.,* 183 F.3d 464, 467-68 (5th Cir.1999) (citing *Alm v. Aluminum Co. of America*, 717 S.W.2d 588, 591-92 (Tex.1986)). Hence, a drug manufacturer's duty to warn consumers about the dangers of its prescription drugs extends only to the prescribing physician or healthcare provider, who acts as a "learned intermediary" between the manufacturer and the ultimate consumer and assumes responsibility for advising individual patients of the risks associated with the drug.[15]

The learned intermediary doctrine is not applied uniformly across state lines and its application depends on the particular decisions in each state forum. Unlike most states, for example, the Supreme Court of Appeals of West Virginia had declined to follow the learned intermediary doctrine.[16] The West Virginia court reasoned that "if drug manufacturers are able to adequately provide warnings to consumers under the numerous exceptions to the learned intermediary doctrine, then they should experience no substantial impediment to providing adequate warnings to consumers in general."[17] West Virginia did, however, recognize the learned intermediary doctrine with respect to medical devices that are not direct-to-consumer advertised and are implantable.[18] Recently, however, West Virginia enacted a law that confirms that the state recognizes the learned intermediary doctrine in specified circumstances, and in effect, overturned decisions by the court that are to the contrary.[19]

Even in jurisdictions that follow the learned intermediary doctrine, there may be various exceptions to the doctrine, for example regarding (1) vaccine inoculations, (2) oral contraceptives, (3) contraceptive devices,[20] (4) drugs advertised directly to consumers, or (5) overpromoted drugs.[21] In these jurisdictions, courts have sought to ensure that consumers are protected against deceptive trade practices or misleading warnings by drug companies. Unlike prescription drugs, for example, over-the-counter products must contain a warning adequate to inform the lay purchaser of dangers. Thus, with products sold directly to consumers, courts have reasoned that the duty of the manufacturer to warn consumers of the specific risks of over-the-counter drug use derives from the basic marketing premise in the over-the-counter drug industry. Specifically, non-prescription drugs are purchased by consumers for the purpose of self-medication, which typically occurs without any intended or actual intervention by a physician.[22] The courts have imposed a duty on manufacturers to warn the consumer directly, rather than having to only warn the physician in such circumstances.

Likewise, courts have declined to follow the learned intermediary doctrine and reasoned that an exception to this doctrine exists in a direct-to-consumer sale scenario. For example, for some drugs, FDA requires warnings be given directly to the patient with the prescribed drug.[23] The manufacturer's duty to warn the consumer may not be satisfied by compliance with FDA minimum warning requirements and it is not automatically shielded from liability by properly warning the prescribing physician. Whether the state law duty to warn has been satisfied is governed by the common law (that is, court cases) of the state, not the regulations of FDA, and necessarily implicates a fact-finding process. Such factual issues may present a jury question, which means the case's outcome will turn on the particular findings made by individual jury members.

Manufacturers Drug Labeling

Q 10.6 Does FDA approval of a manufacturer's drug labeling impact a manufacturer's risks of an adverse verdict in a failure to warn claim case under state law?

Yes. FDCA labeling regulations have a direct impact on state product liability law. Because FDA's oversight capabilities are not absolute, however, courts continue to maintain that state product liability laws complement the FDA regulatory framework.

Q 10.7 How does FDA define a "label"?

By way of background, in addition to overseeing the approval process, FDA oversees virtually all product-related communication from the drug manufacturer, including the "labeling" placed on drug products. Under the FDCA, a "label" is defined as "a display of written, printed, or graphic matter upon the immediate container of any article. . . ."[24] "Labeling" means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[25] FDA also

interprets "labeling" broadly, and includes in its interpretation of labeling "Dear Doctor" letters, which are letters drug manufacturers send to healthcare providers informing them of critical newly discovered risks or side effects of a medication.[26]

NOTE: The process of drug approval for *brand name* manufacturers generally begins with an Investigational New Drug Application (IND) to FDA. The IND contains extensive disclosures regarding the drug's chemistry, manufacturing, pharmacology, and toxicology, pre-clinical data, and details on human testing.[27]
For a new brand-name drug to be approved, FDA requires a New Drug Application (NDA). The NDA process is "onerous and lengthy."[28] The NDA needs to contain "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[29]
When the patent on a brand-name drug expires, generic manufacturers may seek to replicate a generic version. Generic drug approval is different. To expedite approval for generic manufacturers, the Hatch Waxman Act allows a generic drug to be approved without the same level of clinical testing required for approval of a new brand-name drug, provided the generic drug is identical to the already approved brand-name drug in several key respects.[30] The Hatch Waxman Act provides for an Abbreviated New Drug Application (ANDA) process for the approval of generic versions of brand-name drugs. The proposed generic drug must be chemically equivalent and "bioequivalent" to the approved brand-name drug, and the labeling proposed for the new drug should be the same as the labeling approved for the approved brand-name drug. (There is, however, a Proposed Rule that would dramatically alter this long-standing expectation that labels for branded and generic prescription drugs must be identical. That Proposed Rule is discussed in further detail below in Q 10.10.) The ANDA relies on FDA's previous determination that the brand-name drug is safe and effective, which allows an applicant for a generic version of a drug to avoid the costly and time-consuming process associated with an NDA.[31] The United States is now also beginning to offer biosimilars, which follow a different approach for testing and approval. Interchangeability of biologics with biosimilars is another area that differs due to concerns about substituting a biologic particularly if a patient is doing well on the innovator biologic and no medical reason exists for a change in the biologic used.

The U.S. Supreme Court has stated that "[s]tate tort law places a duty directly on all drug manufacturers to adequately and safely label their products."[32] But the scope of the drug manufacturer's state law tort duty is still being debated, and as explained above, is at times a jury question.

The U.S. Supreme Court has recently analyzed the interplay between the FDA regulatory framework and state product liability laws. The Court's reasoning has emphasized the differences in the FDA regulations applicable to brand-name manufacturers as compared to requirements applicable to generic manufacturers. These differences have significantly impacted how the U.S. Supreme Court has analyzed and applied the traditional principles of the preemption doctrine (discussed below) to bar state law failure to warn claims against generic drug manufacturers, but not brand-name manufacturers in certain instances.

Q 10.8 Is the brand-name manufacturer responsible for updating drug labels under the FDCA?

Yes. The drug manufacturer "bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[33] Brand-name manufacturers have a duty to supply FDA with "post marketing reports," which includes reports of any serious and unexpected adverse reactions suffered by a user of a drug.[34] The brand-name manufacturer must also submit annual reports (or quarterly reports for newly approved prescription drugs) to FDA on significant information, including information that "might affect the safety, effectiveness, or labeling of the product."[35]

Recently, the Supreme Court of California significantly expanded a brand company's potential liability.[36] Plaintiff alleged that a company, *which divested a prescription drug six years earlier,* could be sued along with the successor company. Plaintiff argued that the predecessor drug company knew (or should have known) that the warnings were inadequate before the drug divestiture occurred. In an extraordinary ruling, the California Supreme Court affirmed the lower court and held that the lawsuit could proceed against *both* companies.

A later case recognized another expansive theory of innovator liability in allowing recovery for injuries caused by a generic form of a branded competitor's product.[37] In a decision issued by the Supreme Judicial Court in Massachusetts, while recognizing there was no actual basis for innovator liability under a standard product liability theory or under the state's consumer fraud statute, nevertheless held that a product liability theory could be established for conduct that can be described as "reckless" under the court's common-law authority and general tort law principles. The court stated that prescription drugs are unique in that only the innovator had the ability to institute a change in the product label to add additional safety information on its own volition while the generic manufacturer could not deviate from the approved label. The innovator could therefore be held responsible for injuries sustained by exposure to the generic form of its drug given the foreseeability of harm arising from an inadequate warning.

Q 10.8.1 What is the effect of manufacturer responsibility for updating drug labels on state product liability law?

Under usual circumstances, to change a drug label, the manufacturer needs to submit a supplemental application to FDA and obtain FDA approval for such supplemental application.[38] An FDA regulation permits a manufacturer to make certain changes to its label before receiving the agency's approval. Under this "changes being effected" (CBE) regulation, if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with FDA without waiting for FDA approval.[39] Ultimately, FDA will review any CBE modification to a label.[40]

FDA may "reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications."[41] If FDA rejects the change, it may order the manufacturer to cease distribution of the drug with the revised label.[42]

As discussed in Q 10.9 below, the CBE mechanism is not available to generic companies. This lack of availability of the CBE mechanism has directly impacted the liability of generic manufacturers under state product liability laws and limited their exposure. As discussed below, the U.S. Supreme Court expects brand-name manufacturers to be proactive in monitoring adverse events and updating the product labeling as necessary.[43] Generic manufacturers, however, are not required to undertake similar measures. Instead, the Supreme Court's *Mensing* ruling[44] essentially leaves patients who use generic drugs without a remedy even if a drug's warnings were inadequate. So long as the generic manufacturer utilizes the same label as the branded drug, the generic manufacturer has done all that the current law requires.

Now, several years later, FDA has a Proposed Rule[45] that would mandate that generic companies also engage in active monitoring of adverse events and updating of their drug labels upon notice to FDA. Both generic and branded drug companies have raised concerns about how that Proposed Rule would operate, and it remains to be seen how FDA will respond to those concerns.

Q 10.9 Is the generic manufacturer's responsibility for updating drug labels different from the brand-name manufacturer?

Yes, although this may change if the Proposed Rule from FDA[46] discussed below takes effect. Unlike a brand-name manufacturer, a manufacturer seeking generic drug approval is responsible for ensuring that its warning label is the same as the brand-name drug's label.[47] A generic manufacturer is likewise required to submit annual reports to FDA on significant information, including information that might affect the safety, effectiveness, or labeling of the product.[48] The generic drug manufacturers, however, must maintain labeling consistent with their branded counterpart, and if they fail to do so, FDA may withdraw approval for the generic manufacturer's drug.[49]

In *Mensing*, the Supreme Court adopted FDA's position that the generic manufacturer must follow the brand-manufacturer's label or FDA's instructions:

> The agency interprets the CBE regulation to allow changes to generic labels only when a generic drug manufacturer changes its label to match an updated brand-name label or to follow the FDA instructions . . . . The FDA argues that CBE changes unilaterally made to strengthen a generic drug's warning label would violate the statutes and regulations requiring a generic drug's label to match its brand-name counterpart's . . . . We defer to the FDA's interpretation of its CBE and generic labeling regulations . . . . We therefore conclude that the CBE process was not open to the [Generic] Manufacturers for the sort of change required by state law.[50]

Q 10.10 What does the FDA's Proposed Rule say and how would it alter the potential liability of generic drug companies? What about branded companies?

The FDA Proposed Rule titled, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," would arm generic drug companies with the ability to incorporate newly acquired information into their product's package insert in advance of FDA's review of the change. This ability, referred to as a "Changes Being Effected" supplement, would eliminate the disparity that exists between holders of NDAs and ANDAs. If the Proposed Rule is adopted, ANDA holders would be authorized to distribute revised product labeling (that differs from the labeling of its reference listed drug (RLD)) upon submission to FDA of the labeling change. (The NDA holder for the RLD would also receive a copy of the labeling change from the ANDA holder at the time FDA submission of the change is made.) FDA also proposes that the information it receives under a CBE be posted to an Internet webpage so that the public can promptly see the information while FDA conducts its own review.

Certain types of CBE changes require no prior notice to FDA before the labeling change is made. Such CBEs are known as CBE-0 (that is, changes being effected with zero days prior notice to FDA).[51] Another type is CBE-30 (which means that the change being proposed will automatically be made within thirty days, unless FDA objects). No response from FDA within the thirty-day time frame means the company proceeds with the proposed change in accordance with its CBE-30 notice to FDA. In either scenario, once FDA has completed its review of data, FDA can modify or reject the labeling change that the drug company proposed. In some instances, the FDA's response has occurred after more than a year! Under the Proposed Rule, once FDA has advised about the labeling change, other companies marketing that same product would have thirty days to incorporate the new language by themselves submitting a CBE-0 supplement.

There has been a significant outcry from generic and branded companies alike about the Proposed Rule. For example, the Biotechnology Industry Organization (BIO) raised the

following concerns in its comments[52] to the Proposed Rule:

(a) there is a potential enhanced product liability risk for the branded company when there are different labels for the drugs that are supposed to be interchangeable; and

(b) some adverse events may apply only to one particular generic version of the drug.

BIO has proposed that there should be notification of the proposed change to all other companies that are selling a generic of the drug, rather than only the branded drug company. In addition, BIO wants FDA to be required to send a letter to each drug company advising that they are not to change the label or post information to the Internet until FDA has completed its review of the data and rendered its decision regarding whether the labeling change is warranted.

The Generic Pharmaceutical Association (GPhA) has also objected.[53] While GPhA does not object to an expedited and open communication pathway for FDA and the generic company to assess potential new safety signals or other data, it doesn't support the CBE-0 approach. GPhA expressed concerns about the confusion that will arise if branded and generic drug labels differ despite that the drugs are supposed to be bioequivalent and interchangeable. They also argue that the new burdens that would be imposed on generic drug companies will result in deterring the introduction of new generics, thereby reducing the availability of low-cost generic drugs in the marketplace, as well as increasing the number of instances of a short supply or lack of availability of life-saving drugs. Overall, the Proposed Rule is poised to "exponentially increas[e]" litigation risk and regulatory burdens within companies.

In essence, the courts have approached product liability risk for a generic company in a very limited fashion. In most jurisdictions, the prevailing view is that generic companies (which account for over 80% of all prescriptions annually) are largely immune from product liability risks for failure to warn so long as they utilize the same label for the product as the RLD. The Proposed Rule attempts to remedy the situation by imposing new obligations on generic companies to unilaterally update their products' warnings to reflect new safety concerns in a timely manner. The Proposed Rule introduces new liability concerns *for both branded and generic companies* and injects potential confusion into the marketplace by enabling the existence of different labels for therapeutically substitutable drugs.

Whether FDA will modify the Proposed Rule remains unclear, as does the timing for when a final Rule will be released. Comments to the Proposed Rule were due March 13, 2014. On April 1, 2014, Janet Woodcock (Director of FDA's Center for Drug Evaluation & Research) defended the Proposed Rule before the House of Representatives Health Subcommittee.[54] FDA action on the Proposed Rule was expected in July 2016.[55] But final action on the Proposed Rule has not occurred and now we have the additional wild card that a new President has taken office and the Trump Administration's approach remains to be seen.

If the Proposed Rule is finalized "as is," we can expect: (a) increased product liability risk

for generic companies (because state courts will no longer dismiss claims against generic companies for simply using the label that matches the brand's label); (b) generic drug prices will increase due to the increased infrastructure needed for full-fledged pharmacovigilance departments; and (c) consolidation within the generic industry seems likely due to the inability of smaller companies to offer cheaper prices or withstand the substantial product liability risk that U.S. jury verdicts pose.

FDA Preemption of State Law

Q 10.11 Does the FDCA preempt state law product liability claims against brand-name drug manufacturers and generic drug manufacturers?

The short answer is that while there is no express preemption provision in the FDCA, there have been some recent decisions by the courts providing pharmaceutical manufacturers with very strong arguments for application of the preemption defense in future cases, especially in cases brought against generic manufacturers.

The doctrine of federal preemption is based on the Supremacy Clause of the U.S. Constitution, which provides that federal law is "the supreme Law of the Land; . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding."[56] As such, any state law that conflicts with the exercise of federal power is preempted and has no effect.[57] State law is preempted under the Supremacy Clause where Congress has *expressly* preempted state law.[58]

There is no express preemption for prescription drugs under the FDCA. Prescription drugs are different from medical devices in this regard. In particular, section 360k (a) of the Medical Device Act of 1976 does include an express preemption provision, which provides that:

> No State or political subdivision of a State may establish and continue in effect with respect to a device intended for human use any requirement—
>
> (1) which is different from, or in addition to, any requirement applicable under [the MDA] to a device, and
>
> (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under [the Act].

CASE STUDY: In *Riegel v. Medtronic, Inc.*, the Supreme Court held that the MDA's preemption clause bars state tort claims challenging the safety or effectiveness of medical devices that received FDA premarket approval.[59] Plaintiffs sued Medtronic for damages under state law after an FDA-approved catheter

ruptured. Plaintiffs alleged that the catheter was defective under state law, but the Court held that plaintiffs' claims were expressly preempted by the MDA, because of state law requirements that were inconsistent with federal law.[60]

Prescription drugs, however, are governed by a different regulatory framework than medical devices. The Supreme Court has explained that "Congress could have applied the pre-emption clause to the entire FDCA. It did not do so, but instead wrote a pre-emption clause that applies only to medical devices."[61] "The case for federal preemption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there [is] between them."[62]

Q 10.12 What is "implied preemption" and how have the courts applied the doctrine to ban claims against drug manufacturers?

The absence of an express provision in the FDCA, however, has not kept courts from preempting state law claims against drug manufacturers. In certain instances, courts have applied the implied or conflict preemption doctrine to preempt state law claims.

Implied preemption has been divided into "field" preemption, where "pervasive" federal regulation "preclude[s] enforcement of state laws on the same subject" and "conflict preemption" that nullifies state law "to the extent that it actually conflicts with federal law."[63] "Implied" or "conflict" preemption exists where it is "impossible for a private party to comply with both state and federal requirements."[64] Courts have reasoned that the absence of express preemption does not preclude a finding of preemption.[65]

The claim against the drug manufacturer could be impliedly preempted in certain circumstances. The issue turns on whether it is possible for the brand-name drug manufacturer to comply with both state law warning requirements (that is, those imposed by the state's failure to warn claim determinations) and the federal law requirements (that is, the FDCA requirements for labeling changes). A brand-name drug manufacturer may be able to benefit from preemption if it shows that FDA specifically rejected the particular drug warning that plaintiff claims is missing, such that it would have been impossible for the drug company to have included that enhanced warning and also complied with its obligation to use an FDA-approved drug label.

A brand-name manufacturer's ability to invoke the implied preemption defense may be difficult (depending on the facts). For example, in *Wyeth v. Levine*, the U.S. Supreme Court held that a state tort action against a brand-name drug manufacturer for failure to provide an adequate warning label was not preempted because it was possible for the manufacturer to comply with both state and federal law under FDA's CBE regulation.[66]

But unlike brand-name manufacturers, the Supreme Court has recently provided strong support for an implied preemption defense to generic manufacturers. The Supreme Court's reasoning was principally based on the differences in the FDA enforcement regime

applicable to brand-name manufacturers, as opposed to generic manufacturers. The fact that generics are constricted to follow the brand-name manufacturer's labeling, as well as its designs for the drug, strongly weighed in favor of finding that there was a conflict between federal and state law.

In *Mensing*, the Supreme Court held conflict preemption existed insofar as it was impossible for the defendant generic drug manufacturers to simultaneously comply with both the federal regulations for updating drug labeling and duties imposed by state laws to include additional warnings about adverse risks. The Court explained that state law imposed a duty on the generic manufacturers to take certain action (that is, update its drug label), but the federal law barred the generic manufacturer from taking such action. This bar existed because the generic manufacturer could not unilaterally undertake the CBE process without FDA's instruction. The Court noted that from the perspective of the injured plaintiff, finding that failure to warn claims against generic companies are preempted but not preempting the same types of claims against brand-name manufacturers "makes little sense." The Supreme Court's response to such criticism was that "it is not this Court's task to decide whether the statutory scheme established by Congress is unusual or even bizarre."[67] This commentary leaves open the possibility for legislative, or perhaps regulatory, action. Indeed, in *Mensing*, the Supreme Court concluded that "Congress and the FDA retain the authority to change the law and regulations if they so desire." Until such action occurs, generic manufacturers are largely insulated from liability for failure to warn about post-marketing adverse events.

FDA has now released a Proposed Rule (that responds to the Court's invitation in *Mensing*). That Proposed Rule would radically change a generic company's obligations and capabilities with respect to safety monitoring and label updating. (See Q 10.10.)

While the "clear evidence" test in *Levine* may be difficult to establish, nevertheless a detailed record of active FDA consideration of an alleged association between a drug and an adverse event and of FDA's determination that any association was tenuous at best will likely support a preemption defense. As products liability cases are filed where a REMS was in place, we can likely anticipate an increased reliance on agency actions in the context of requiring and overseeing a risk minimization process as the basis for post-*Levine* preemption.

Brand-Name Manufacturer Liability

Q 10.13 Can the brand-name manufacturer be held liable when the plaintiff purchased the product from the generic manufacturer?

There have been several appellate decisions concluding that the brand-name manufacturer can face the risk of liability, even under circumstances where the injured party has taken only the generic form of the prescription drug.

In *Wyeth v. Weeks*, the Supreme Court of Alabama considered the issue in the context of inadequate warnings by the brand-name manufacturer placed on a prescription drug manufactured by a generic-drug manufacturer. The *Weeks* court believed that it is not

fundamentally unfair to hold the brand-name manufacturer liable for warnings on a product it did not produce. It reasoned that the manufacturing process is irrelevant to misrepresentation theories based, not on manufacturing defects in the product itself, but on information and warning deficiencies, when those alleged misrepresentations were drafted by the brand-name manufacturer and merely repeated by the generic manufacturer. The Alabama Supreme Court's opinion in *Weeks v. Wyeth* was reconsidered by that court in September 2013, but the holding was reaffirmed[68] despite being inconsistent with the weight of authority.

Similarly, in *Conte v. Wyeth*,[69] the California Court of Appeals held that a "brand name" manufacturer may be held liable for injuries suffered by a patient who purchased a generic form of the drug if the injuries were foreseeably caused by negligent or intentional misrepresentations of the pharmaceutical company that developed the drug. Likewise, in *Kellogg v. Wyeth*,[70] the Vermont federal court held that a brand-name manufacturer of a drug has a duty to use reasonable care to avoid causing injury to consumers who have been prescribed the generic bioequivalent of its drug.[71]

Notwithstanding these cases, the vast majority of appellate decisions have declined to impose liability on the part of the drug innovator when evidence establishes that only a generic version was administered. The *Sindell* DES case[72] applied a theory of market share liability that was widely criticized as imposing liability proportional to the manufacturer's share of the market, when proof of product identification was lacking. Most courts, however, adhere to the basic principle that liability would not attach where the manufacturer had no involvement with the drug a plaintiff had taken.

Design Defect Claims

Q 10.14 Do manufacturers of prescription drugs face the risk of design defect claims? Can a design defect claim against a drug manufacturer be preempted?

Plaintiffs continue to search for new theories of liability against drug manufacturers and the law on implied preemption is still being written by the courts. Notwithstanding clear authority in this area, prescription drug manufacturers—both innovator and generic—can anticipate claims that allege that the design of their drugs is defective, even if they received FDA approval.

In a recent U.S. Supreme Court decision, generic drug manufacturers received certain protection from design defect claims based on adequacy of warnings. In *Mutual Pharmaceutical Co. v. Bartlett*, the Supreme Court ruled that "state law design defect claims that turn on the adequacy of a drug's warnings are preempted."[73]

The *Bartlett* case involved "tragic circumstances" where respondent suffered horrible injuries and obtained a trial verdict of $21 million in state court. But the Supreme Court explained that the plaintiff's case against the generic company defendant fails as a matter of law. The Supreme Court reasoned that it was impossible for the generic company to

comply with the warning requirements under state law (that is, to warn of risks beyond those required by FDA), while at the same time complying with FDA requirements that the generic company's labels be the same as those of the original brand-name manufacturer. *Bartlett* clearly stated, with respect to allegations premised on the concept of liability arising from design defects, that "[o]nce a drug, whether generic or brand-name is approved, the manufacturer is prohibited from making any major changes to the 'qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved application.'"[74]

Fraud and Negligence Claims

Q 10.15 Are claims for fraud and negligence impliedly preempted?

No, some claims for fraud and negligence may not be impliedly preempted when the fraud is alleged to be perpetrated against public consumers and users (instead of FDA).

In *Buckman Co. v. Plaintiffs' Legal Committee*, the U.S. Supreme Court held that state-law "fraud on the FDA" claims are preempted because such claims "inevitably conflict with FDA's responsibility to police fraud consistently with the Administration's judgment and objectives."[75] The plaintiffs in *Buckman* brought a state-law negligence suit for damages alleging injuries resulting from a medical device. Defendant Buckman was not the manufacturer of the device, but was a consulting company that plaintiffs alleged had made fraudulent misrepresentations to FDA in the course of obtaining pre-market approval for its client, the manufacturer.[76] The Court characterized the plaintiffs' state-law claims against Buckman as "fraud-on-the-FDA" claims. It wrote that such claims

> conflict with, and are therefore impliedly preempted by, [the MDA]. The conflict stems from the fact that the federal statutory scheme amply empowers the FDA to punish and deter fraud against the Administration, and that this authority is used by the Administration to achieve a somewhat delicate balance of statutory objectives. The balance sought by the Administration can be skewed by allowing fraud-on-the-FDA claims under state tort law.[77]

The *Buckman* decision, however, does not necessarily preclude fraud claims by consumers of prescription drugs for harm done to them *directly*. Further, many courts have read *Buckman* to apply only to fraud claims that necessarily depend on violations of specific federal requirements. Thus, the *Buckman* decision does not insulate the manufacturer from all fraud claims. If plaintiffs can satisfy the elements of a fraud claim—such as that the manufacturer made direct misrepresentation to the consumer and the consumer justifiably relied on these misrepresentations and suffered damages—then the fraud claim against the manufacturer may be able to proceed in state courts.

CASE STUDY: In *Woods v. Gliatech*,[78] the court noted that *Buckman* was concerned with a situation in which the plaintiffs' claims focused specifically on the existence of a federal enactment. The *Woods* case was different because the plaintiffs' fraud claim was based upon material misrepresentations made to consumers and users. In *Woods*, plaintiff sued Gliatech for fraud, negligence and breach of warranty for hiding and manipulating information about certain clinical results. The court denied the summary judgment motion and held that plaintiff's claims were not preempted, because unlike *Buckman*, the *Woods* case involved allegations of a fraud committed against the public generally and not against FDA.

Court decisions support that negligence and fraud claims can proceed against drug manufacturers for breach of duties owed directly to consumers. The bounds of the manufacturers' duty to consumers, however, and the interrelationship of this duty with the manufacturers' obligations under FDA regulations, are still being defined by the courts. New cases present new issues and challenges. Clearly, the FDCA establishes a critical framework and has a major impact on drug manufacturers' liability under state law. Nevertheless, compliance with FDCA regulations will not insulate the company from all liability under state law in all circumstances.

Risk Management Developments

Q 10.16 How have the recent developments in risk management affected product liability for pharmaceutical manufacturers?

Although risk management processes have been utilized by regulatory agencies for an extended period of time (for example, the Accutane® pregnancy prevention program requiring monthly pregnancy testing, one-month supply limitation, and patient surveys instituted in 1988), more stringent risk management tools have been utilized more frequently since 1989. These tools have frequently served to communicate safety information to healthcare professionals and patients, as part of labeling.

The FDAAA is the most recent development in risk management. The FDAAA may be characterized as the most impactful change to the FDCA since the Kefauver Amendments of 1962 requiring proof of efficacy, in addition to safety, for drug approval. Although FDAAA is far-reaching in scope, the most profound change can be seen in the expansion of FDA authority to actively direct and manage risks observed in marketed drugs post-approval. FDAAA permits the agency to require post-approval studies and/or clinical trials for any pharmaceutical product as a condition of approval if deemed necessary to (1) assess a known risk, (2) assess signals of serious risk, or (3) identify a serious unexpected risk when available data indicates the potential for a serious risk. For products already approved and marketed, FDA would have the authority to require studies and/or clinical trials under circumstances where the agency becomes aware of "new safety information."

The authority afforded FDA by the new law profoundly affected the agency's ability to require a wide range of risk management tools, particularly the power to issue an order instructing the manufacturer to institute a labeling change. Previously, FDA's authority did not extend post-approval and any changes in labeling would, theoretically, be at the manufacturer's volition.

Q 10.17 What risk management tool does FDA use?

The overall risk minimization process utilized by FDA is referred to as "Risk Evaluation and Mitigation Strategy" (REMS) (see *supra* chapter 9, "Risk Evaluation and Mitigation Strategies (REMS) and Related Post-Market Safety Oversight"), which are risk management plans specifically tailored to each product's particular safety profile. REMS are developed and implemented if FDA has determined that a plan is necessary to ensure that the benefits of the drug being marketed continue to outweigh the risks. Depending on those risks, a REMS may include special communication requirements directed to healthcare practitioners, patients and caregivers; mandatory education and certification of prescribers and/or institutions; or restrictions on the distribution system for the drug in question.

The question remains whether the effect of the provisions of the FDAAA in general and

of REMS in particular, can impact a manufacturer's product liability exposure. Given the fact that there have been no appellate cases that specifically address this issue, we can extrapolate based on existing case law authority.

The first analysis involves the decision of the U.S. Supreme Court in *Wyeth v. Levine* and the issue of preemption for prescription pharmaceuticals. While the majority clearly declined to extend the preemption defense in the absence of direct legislative authority, as seen in the medical device field and articulated by the *Riegel* decision, a careful reading of *Wyeth* presents a possible pathway to a successful product liability defense, including preemption.

Although the *Wyeth* court failed to hold that the manufacturer was entitled to preemption for merely including FDA-approved safety information in its labeling, the court nevertheless indicated that "[I]t is also possible that state tort law will sometimes interfere with FDA's desire to create a drug label containing a specific set of cautions and instructions."[79] Nevertheless, the court determined it would need a more complete record to find the existence of a "direct and positive conflict" between an FDA labeling decision and the requirements imposing liability under state tort law. A careful examination of the provisions of the FDAAA and of the REMS process would presumably provide the factual basis to establish a "direct and positive conflict" should a sufficient record be established by the manufacturer in its negotiations with the agency.

The REMS process has also been raised in examining the distinction between innovators and generic manufacturers in the context of product liability. Generic manufacturers have claimed that innovator companies are withholding vital information and drug product in an effort to utilize proprietary REMS risk management programs to forestall generic competition while innovators face potential liability as well. (See second paragraph of response to Q 9.22 that addresses the recent FDA Draft Guidance for issuance of a letter from FDA to a generic drug company that states that giving the drug to a particular generic company recipient will not violate a drug company's REMS program.)

While the *Pliva* and *Wyeth* cases support the argument that innovator companies have control over the content of their label subject to FDA approval, generic companies assert that potential liability may yet be imposed. Uncertainty arises where both innovator and generic manufacturers distribute their respective products under a "shared REMS" process, a concept FDA believes would be appropriate. However, in the event the shared REMS contains a strict risk management process which includes Elements to Assure Safe Use (ETASU) in addition to a label change, would a person taking a generic formulation be denied recovery under *Pliva*, or would the court instead find the innovator responsible for the claimant's injuries by virtue of having agreed to allow the generic to utilize the ETASU requirements under the shared risk plan? These issues remain to be addressed.

FDA and OIG Oversight of Product Liability Exposures

Q 10.18 What role does FDA and OIG oversight play relative to product liability exposure?

As discussed throughout this volume, oversight of the pharmaceutical industry, relating both to innovators as well as generic manufacturers, is both pervasive and complex, most notably through the regulations in the FDCA and related statutes. Indeed, the quality of these regulations has formed the basis of the continuing arguments for judicial recognition of preemption as a defense to product liability claims premised on an alleged failure to warn. However, activities of the pharmaceutical manufacturer are also monitored by other governmental entities, including state attorneys general in the context of consumer protection laws and local false claims acts, as well as by the OIG of the HHS. The latter enforcement function has focused on examining the extent to which pharmaceutical manufacturers are promoting their products for indications not approved by FDA and outside of the labeling in violation of the FDCA, as well as determining whether such off-label promotion serves as a foundation for civil and criminal prosecution for violation of the False Claims Act (FCA) and other statutes.

The question of the impact of overlapping and conflicting oversight functions on product liability exposure can be seen in the circumstances that gave rise to the action filed by Allergan against FDA in *Allergan, Inc. v. United States.*[80] In a series of circumstances reminiscent of a Kafka or Joseph Heller novel, Allergan faced a dilemma in 2009 arising from its widely used drug, Botox®. While known widely for its cosmetic-related indications marketed under Botox Cosmetic, FDA-approved product labeling included such therapeutic indications as muscle disorders of the eye and cervical dystonia (marketed under Botox Therapeutic™). However, in addition to those indications approved by the agency, Botox has been prescribed for other non-labeled indications by healthcare practitioners, including post-stroke spasticity, migraine, and juvenile cerebral palsy, among others.

In April 2009, FDA, pursuant to its authority under the FDAAA, required Allergan to modify its Botox label to add a boxed warning as part of a REMS to share safety information with healthcare practitioners relating to both approved indications and several but not all known off-label uses. Allergan had previously determined that information on appropriate patient selection, injection sites, and dosage would benefit healthcare practitioners and patients, particularly where usage was outside the scope of approved labeling, as well as serve as a potential defense to product liability litigation. Failure to accede to FDA's REMS directive would potentially render the drug misbranded under the FDCA. Yet, including information relating to off-label uses in such communication vehicles as a "Dear Health Care Provider" letter could be perceived as evidence of active off-label promotion and support a prosecution for violation of the FCA. In response, Allergan filed suit against FDA in 2009 challenging its policies regarding dissemination of "truthful,

accurate and complete" risk and benefit information, even if not within approved labeling. In the interim, and following an investigation into Botox marketing practices, the DOJ filed suit against Allergan for engaging in illegal off-label promotion.

In 2010, Allergan reached settlement with the DOJ. Allergan entered into a five-year Corporate Integrity Agreement and agreed to pay $600 million. Moreover, and in an unprecedented action, DOJ required the company to withdraw its lawsuit against the FDA that had been based on First Amendment grounds. (A similar series of events subsequently played out when Par Pharmaceuticals filed suit against the FDA on similar First Amendment grounds (arising from its drug, Megace®).

Potential product liability exposure arising from Botox administration is not a theoretical matter. Lawsuits have been filed against Allergan with resulting trials as early as 2004 and such lawsuits continue to be filed with mixed results.[81] Nevertheless, the ability of pharmaceutical manufacturers to prepare effective defenses in failure to warn cases where off-label use is alleged may be compromised when compliance, regulatory and liability requirements conflict.

Q 10.19 Can allegations of off-label promotional activity serve as the basis of a *qui tam action under the False Claims Act?*

In several cases, litigants have attempted to rely on allegations of off-label promotion as a vehicle for bringing a qui tam action under the False Claims Act; one of the more recent cases is *United States ex rel. Colquitt v. Abbott Labs*,[82] which involved a vascular stenting procedure that was allegedly utilizing the product off-label. Although a medical device, rather than a pharmaceutical, was involved, the principles and holding of the court would be relevant in either circumstance where FDA approval for marketing would be required.

The plaintiffs argued that Medicare reimbursement required that the device be "reasonable and necessary" for diagnosis or treatment, further alleging that to be considered "reasonable and necessary," the FDA would have had to determine the product to be safe and effective. Given that FDA had not made such a finding, the product would not be eligible for reimbursement under Medicare, effectively banning all off-label use where federal reimbursement was available.

The *Colquitt* court rejected plaintiffs' argument, finding that FDA approval and a determination that Medicare reimbursement would be available are totally independent of each other, and lack of FDA approval of a specific use would not automatically serve to preclude coverage. The court reinforced an important principle, that utilization of a medical product following off-label promotion might represent appropriate and state-of-the-art medical practice.

Q 10.20 What is the potential impact of the FDA Draft Guidance Relating to "Emerging Signals" on Pharmaceutical Manufacturer Liability?

On December 14, 2016, FDA issued a proposed guidance in the context of medical devices that may be of interest to pharmaceutical manufacturers as well. The guidance,

entitled Public Notification of Emerging Postmarket Medical Device Signals ("Emerging Signals")[83] indicates that FDA would strongly consider public notification as to possible medical device risks if the "emerging signals" meet certain criteria. The criteria are:

- that the information supports a new causal association, or a new aspect of a known association (such as an increased rate or severity of adverse event reporting or reduced benefit) between a medical device and one or more AEs or clinical outcomes; and
- that the available information is of sufficient strength; and
- that the information could have important clinical implications for patient management decisions and/or known benefit-risk profile of the device.

This Guidance is applicable to medical device manufacturers, but also of potential interest to pharmaceutical manufacturers.

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1. The authors thank George Benaur, Esq., co-author of an earlier version of this chapter, rtions of that earlier version remain unchanged in this version.
2. Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 *et seq.*
3. While FDA has strong enforcement and oversight mechanisms, any federal agency has ed resources to fulfill their legislatively mandated duties. In the case of FDA, in addition to eeing the process of drug approval, FDA is also responsible for monitoring food safety and nly recently been given oversight over tobacco.
4. *See* Wyeth v. Levine, 555 U.S. 555, 574 (2009).
5. *See id.* at 575.
6. *Id.* at 578.
7. Perez v. Wyeth Labs Inc., 161 N.J. 1, 24 (1999).
8. *See also* N.J.S.A. 2A:58C-4; Niemiera by Niemiera v. Schneider, 114 N.J. 550, 559 9) ("In New Jersey, as elsewhere, we accept the proposition that a pharmaceutical ufacturer generally discharges its duty to warn the ultimate user of prescription drugs by lying physicians with information about the drug's dangerous propensities.").
9. Centocor Inc. v. Hamilton, 372 S.W.3d 140, 158 n.17 (Tex. 2012), citing *In re* lant Contraceptive Prods. Liab. Litig., 215 F. Supp. 2d 795, 806–09 (E.D. Tex. 2002) (for roposition that "the learned intermediary doctrine either applied or was recognized without unt exception in forty-eight states.") (Note 17 of *Centocor* identifies thirty-five states with ons from each state's highest court, and forty-eight states with opinions from "scores of intermediate courts and federal courts applying state law.").
10. Tyree v. Bos. Sci. Corp., 56 F. Supp. 3d 826, 828 n.3 (S.D. W. Va. 2014).
11. *See* Rimbert v. Eli Lilly & Co., 577 F. Supp. 1174, 1214 (D.N.M. 2008) (predicting he Supreme Court of New Mexico would not adopt the learned intermediary doctrine).
12. *See* Kellogg v. Wyeth, 762 F. Supp. 2d 694, 700 (D. Vt. 2010).
13. Note that the Product Liability Advisory Council has cited an unpublished case in New co (Silva v. SmithKlineBeecham Corp., 2013 WL 4516160, at *2–3 (N.M. App. Feb. 7,

)) and observed that "[o]n appeal, a skeptical Tenth Circuit invited reconsideration of the Mexico decision (*Rimbert*, 647 F.3d 1247, 1256–57 (10th Cir. 2011)), but *Rimbert* ed before reconsideration occurred. *See* PLAC Amicus Brief in Medicis Pharm. Corp. v. ıda Watts, No. CV-15-0065-PR filed in Arizona Supreme Court (Oct. 21, 2015) at 3 &

14. Watts v. Medicis Pharm. Corp., 239 Ariz. 19 (Jan. 21, 2016), citing RESTATEMENT RD) OF TORTS: PRODS. LIAB. (Am. Law Inst. 1998) § 6(d).

15. *In re* Norplant Contraceptive Prods. Liab. Litig., 215 F. Supp. 2d 795, 803 (E.D. Tex.) (additional citation omitted).

16. *See* State of W. Va. *ex rel.* Johnson & Johnson Corp. v. Hon. Mark A. Karl, 220 W. Va. 2007).

17. *Id.* at 477.

18. Tyree v. Bos. Sci. Corp., 56 F. Supp. 3d 826 (S.D. W. Va. Oct. 23, 2014).

19. W. Va. Code 55-7-30 (signed by the Governor on February 17, 2016, and effective y days thereafter, *i.e.,* May 17, 2016).

20. The learned intermediary doctrine has been found to apply in many jurisdictions, *but see* in v. Ortho Pharm. Corp., 661 N.E.2d 352, 356–57 (Ill. 1996); Shanks v. Upjohn Co., P.2d 1189, 1200 (Alaska 1992); West v. Searle & Co., 806 S.W.2d 608, 613–14 (Ark.); *In re* Norplant Contraceptive Prods. Litig., 165 F.3d 374, 379 (5th Cir. 1999).

21. *See id.* at 475 (citing cases for different jurisdictions); *see also Perez,* 161 N.J. at 20–21 iding a potential exception to the learned intermediary rule when a pharmaceutical ɔany markets a prescription drug directly to consumers).

22. *See* Torsiello v. Whitehall Labs., 165 N.J. Super 311, 322 (App. Div.), *cert. denied*, 81 50 (1979).

23. *See* Edwards v. Basel Pharm., 933 P.2d 298, 300 (Okla. 1997).

24. 21 U.S.C. § 321(k).

25. 21 U.S.C. § 321(m).

26. Pliva, Inc. v. Mensing, 131 S. Ct. 2567, 2576–77 (2011).

27. 21 U.S.C. § 355(b); 21 C.F.R. § 312.21.

28. *Id.*

29. 21 U.S.C. § 355(d)(5).

30. *See* Mutual Pharm. Co. v. Bartlett, 133 S. Ct. 2466, 2474 (2013).

31. *Id.*

32. Pliva, Inc. v. Mensing, 131 S. Ct. 2567, 2577 (2011).

33. *See* Wyeth v. Levine, 555 U.S. at 570–71.

34. 21 C.F.R. § 314.80.

35. 21 C.F.R. § 314.81.

36. T.H., a Minor v. Novartis Pharm. Corp., No. S233898, 407 P. 3d 18 (Cal. filed Dec. 017.

37. Rafferty v. Merck & Co., N.E.3d, 2018 WL 1354064 (Mass. Mar. 16, 2018).

38. *See Levine*, 555 U.S. at 568.

39. *Id.*, citing 21 C.F.R. § 314.70(c)(6)(iii)(A), (C).
40. *Id.*
41. *Id.* at 571.
42. 21 C.F.R. § 314.70(c)(7).
43. *See generally Levine*, 555 U.S. 555.
44. Pliva, Inc. v. Mensing, 131 S. Ct. 2567 (2011).
45. Proposed Rule, Supplemental Applications Proposing Labeling Changes for Approved s and Biological Products, 78 Fed. Reg. 67,985 (Nov. 13, 2013).
46. *Id.*
47. *See Mensing*, 131 S. Ct. at 2574.
48. 21 C.F.R. § 314.98.
49. Fulgenzi v. Pliva, Inc., 711 F.3d 578, 581 (6th Cir. 2013).
50. *Mensing*, 131 S. Ct. at 2575–76.
51. For example, a CBE-0 may be warranted to add or strengthen: (a) a contraindication, ing, precaution, or adverse reaction (but only if there is sufficient evidence of a causal iation); (b) a statement about drug abuse, dependence, psychological effect, or overdosage; an instruction about dosage and administration that is intended to increase the safe use of rug. *See* 21 C.F.R. § 314.70(c)(6)(iii).
52. Letter from Biotechnology Innovation Organization to U.S. Food and Drug inistration (Mar. 14, 2014) (Re: Docket No. FDA-2013-N-0500 Proposed Rule: lemental Applications Proposing Labeling Changes for Approved Drugs and Biological ucts), www.bio.org/advocacy/letters/drug-labeling-bio-comments-cbe-0-proposed-rule.
53. For comments from GPhA and others, search for "Docket No. FDA-2013-N- 0500" or "Regulatory Information Number (RIN) 0910-AG94" on REGULATIONS.GOV, .regulations.gov.
54. *Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling: Hearing e the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 111th Cong. 2 (Apr. 14) (statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and urch Food and Drug Administration, Department of Health and Human Services), .fda.gov/NewsEvents/Testimony/ucm389606.htm.
55. FDA Webview, "CBE Rule Delay Risking Generic Drug Patients: Public Citizen" (Dec. 15), addressing Public Citizen's concerns about the delays and demanding more litious action.
56. U.S. Const. art. VI, cl. 2.
57. *See* Maryland v. Louisiana, 451 U.S. 725, 746 (1981).
58. *See, e.g.*, Cipollone v. Liggett Grp., Inc., 505 U.S. 504, 516 (1992).
59. Riegel v. Medtronic, Inc., 552 U.S. 312 (2008).
60. *Id.* at 325.
61. Wyeth v. Levine, 555 U.S. at 574 (citing *Riegel*, 552 U.S. at 326).
62. *Id.* (citing Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 166–67))).

63. *See* Fulgenzi v. Pliva, Inc., 711 F.3d 578, 584 (6th Cir. 2013).

64. *See* Pliva, Inc. v. Mensing, 131 S. Ct. 2567, 2577 (2011) (quotation omitted).

65. *Id.*

66. *See Levine*, 555 U.S. at 572–73. *See also Mensing*, 131 S. Ct. at 2581 (articulating the ›e holding but distinguishing its applicability to generic manufacturers).

67. *Mensing*, 131 S. Ct. at 2582.

68. *See* Opinion on rehearing of certified question from the U.S. District Court for the lle District of Alabama, Southern Division (Aug. 15, 2014), in Wyeth v. Weeks, No. 1:10-)2, 2014 WL 4055813 (Ala. Aug. 15, 2014).

69. Conte v. Wyeth, 168 Cal. App. 4th 89 (2008).

70. Kellogg v. Wyeth, 762 F. Supp. 2d 694 (D. Vt. 2009).

71. *See* Strayhorn v. Wyeth Pharm., Inc., 737 F.3d 378, 405–06 (6th Cir. 2013) ıowledging that the outcomes in *Conte* and *Kellogg* are outliers).

72. Sindell v. Abbott Labs., 26 Cal. 3d 588 (Cal. 1980).

73. Mutual Pharm. Co. v. Bartlett, 133 S. Ct. 2466 (2013).

74. *Id.* at 2471.

75. Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001).

76. *Id.* at 343.

77. *Id.* at 348.

78. Woods v. Gliatech, 218 F. Supp. 2d 802 (W.D. Va. 2002).

79. Wyeth v. Levine, 555 U.S. at 582 (J. Breyer, concurring).

80. Allergan, Inc. v. United States, No. 09-1879 (D.D.C. Oct. 2, 2009).

81. In an article appearing in the *Journal of the American Society for Dermatologic Surgery*, ed *Analysis of Botulinum Toxin Products and Litigation in the United States*, by J.B. Koran, Jalian and M.M. Aram, the authors reviewed federal and state cases filed between 1985 and . Of twenty-four cases identified in LexisNexis Academic online database, most lawsuits dismissed or settled; in two cases, the juries returned multi-million dollar verdicts.

82. United States *ex rel.* Colquitt v. Abbott Labs, 2016 U.S. Dist. LEXIS 1556, 2016 WL 0 (N.D. Tex. Jan. 7, 2016).

83. FDA, Public Notification of Emerging Postmarket Medical Device Signals ("Emerging ıls"), Guidance for Industry and Food and Drug Administration Staff (Dec. 14, 2016), ://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocumen m479248.pdf.

11

Specific FDA Enforcement Tools

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The ability of the Food and Drug Administration (FDA) to regulate food, drugs, medical devices, and biologics depends upon its specific rights to enforce the Food, Drug, and Cosmetic Act (FDCA), its own regulations, and related provisions of law. A company may violate the FDCA or FDA regulations in various ways, including improperly conducting clinical trials, selling misbranded or adulterated products, failing to report adverse events, or failing to maintain production facilities that comply with current Good Manufacturing Practices (cGMP). FDA has a number of enforcement tools at its disposal that are intended to encourage regulated companies to correct such violations voluntarily and to punish those that do not. Some of FDA's enforcement tools are informal, such as issuing a Warning Letter advising a company of an alleged regulatory violation, requesting that a company conduct a voluntary recall, or detaining adulterated products before they are imported into the United States. Other enforcement tools are more formal and severe, such as product seizures, injunctions, and the imposition of civil money penalties that require either judicial or administrative approval to be imposed. FDA is also involved in the enforcement of criminal prohibitions. This chapter covers a number of FDA's most widely used enforcement tools, and describes how and when FDA utilizes them.

Warning Letters

Q 11.1 What is a Warning Letter?

A Warning Letter is a written notice advising that FDA believes a regulated entity has violated the FDCA or an FDA regulation.[2] Warning Letters inform a company of FDA's position and provide it with an opportunity to address alleged violations before FDA initiates formal enforcement proceedings.[3] Although FDA is not required to issue a Warning Letter prior to initiating an enforcement action, it has traditionally done so based on its "expectation that most individuals and firms will voluntarily comply with the law."[4]

Q 11.2 What is the source of FDA's authority to issue a Warning Letter?

No specific statute or regulation empowers FDA to issue a Warning Letter. Rather, FDA's authority inherently arises from its obligation to enforce the FDCA and its own regulations.[5] For example, a Warning Letter may precede an FDA-requested recall, or encourage a company-initiated recall, actions which themselves are governed by statutes and/or regulations.[6] As a prelude to formal enforcement, a Warning Letter is meant to give a company the chance to avoid the gravity and complexity of a formal enforcement action.

Q 11.3 What violations of the FDCA can prompt the issuance of a Warning Letter by FDA?

As a general rule, FDA issues a Warning Letter when it believes that a significant regulatory violation exists that a company can correct prior to an FDA enforcement action.[7] FDA assesses the following factors to determine if a violation is "significant" and a Warning Letter is warranted:

1. Whether the violation would also lead FDA to consider an enforcement action;
2. Whether there is reason to believe that the company "will take prompt corrective action" and whether it is aware of the violation but has failed to correct it;
3. Whether the company has committed serious violations or failed to prevent and remedy violations in the past;
4. The nature and significance of the violation and the risks involved;
5. Whether the company has already initiated corrective action addressing the specific violations effectively and on an adequate timetable;
6. Whether FDA has gathered sufficient documentation to make an informed evaluation of the suspected violation; and
7. Whether issuing a Warning Letter is consistent with FDA policy.[8]

The director of the FDA District or Center[9] handling a matter weighs these factors and has discretion to send a Warning Letter. For certain types of cases, the directors of some or all of the four main FDA Centers must agree on the appropriateness of a Warning Letter. For example, in order to issue a Warning Letter based on a violation of labeling or product advertising regulations, the directors of all four FDA Centers must concur that the violation warrants a Warning Letter.

If a violation is based on unapproved changes to drug formulations, on the other hand, then concurrence with the Center for Drug Evaluation and Research (CDER), and that Center only, is required.[10]

Q 11.4 Are there circumstances where a Warning Letter will not be issued prior to an FDA enforcement action?

Yes. Some violations may be so severe that FDA will not issue a Warning Letter prior to bringing an enforcement action. Pursuant to its own internal guidelines, FDA does not issue Warning Letters for violations which are "intentional or flagrant," create a risk of death or bodily injury, or are part of a course of improper conduct which continues in spite of some prior notice. Further, violations accompanied by criminal fraud[11] are not the proper subject of a Warning Letter.[12] In these instances, FDA will proceed directly with a formal enforcement action.

Q 11.5 How long does a company have to respond to a Warning Letter?

Warning Letters generally state that a company must respond within fifteen working days of receipt.[13] In some instances, FDA may require a response within as few as ten working days.[14] FDA expects that a company's response will explain in detail the steps that have been and will be taken to rectify the alleged violation and to prevent its future occurrence. Depending on the circumstances, FDA may grant a company's reasonable request for additional time to explain the violation and how the company plans to correct it.[15]

Q 11.6 Are Warning Letters available to the public?

Yes. Warning Letters are available to the public on a dedicated FDA website.[16] Letters are generally posted in redacted form within a week of their issuance.[17] A Warning Letter may also be obtained through a Freedom of Information Act (FOIA) request.

The Warning Letters posted on the FDA website span several years, and are searchable by company, subject, and issuing office, among other things.[18] Consequently, alleged violations of the FDCA receive immediate and significant public exposure. A company's response to a Warning Letter will generally be attached to the published Warning Letter upon the company's request, unless FDA considers the response misleading as to a product's safety or effectiveness.[19] When a matter is "closed out" (see Q 11.7 below), FDA will post the close-out letter with the published Warning Letter.

Q 11.7 What is a Warning Letter close-out letter?

A close-out letter is a correspondence from FDA that states that the violations cited in a Warning Letter have been addressed to FDA's satisfaction. FDA sends a close-out letter only after verifying that a company has completed the necessary corrective action. If any action remains to be taken, even under an FDA-endorsed plan, FDA will not issue a close-out letter.[20] FDA verification consists of:

1. A written reply from the company demonstrating that the listed violations have been corrected;
2. A follow-up inspection by FDA (or a reliable source of verified information submitted to FDA) showing that corrective measures were implemented to FDA's satisfaction; and
3. An absence of any new violations.

Receipt of a close-out letter "does not relieve the recipient from [its] responsibility for taking all necessary steps to assure sustained compliance with the Act."[21]

Product Recalls

Q 11.8 What is a product recall?

A recall occurs when a company removes a product from the market due to a violation that could subject the product to legal action by FDA.[22] "Correcting" a product (for example, adding or removing labels) under the same legal circumstances also constitutes a recall. Most recalls are executed voluntarily, whether on a company's initiative or at the request of FDA.

Q 11.9 Does FDA have statutory authority *to order a product recall?*

Yes, but only for six product categories, namely: medical devices,[23] biologics,[24] infant formula,[25] tobacco products,[26] food,[27] and certain human tissue intended for transplantation.[28] FDA has no explicit authority to order a recall of a pharmaceutical product.

Q 11.10 Under what circumstances can FDA *order the recall of medical devices and biologics?*

For medical devices and biologics, FDA's power to order a recall is triggered as follows:

Medical Devices. FDA has the authority to order a recall where there is a "reasonable probability" that a device "would cause serious, adverse health consequences or death."[29] Under such circumstances, the FDCA requires the agency to issue a "cease distribution and notification order," which requires all appropriate persons (manufacturers, distributors, and retailers) "to immediately cease distribution" of the device, "to immediately notify" users about the recall order, and to instruct users to cease using the device.[30]

Upon receipt of a "cease distribution and notification order," the company may seek a regulatory hearing (which must be held within ten days of the order's issuance), or it may submit a written request seeking modification or cancellation of the order.[31] If the company does not request a hearing or review, or if its request is denied, FDA *must* amend its cease and notify order to require a recall.[32] The resulting recall order may set a timetable for correction or removal of the product. It may also require that the recall be directed toward specific distribution points.[33]

FDA may not compel the recall of a device from individual users.[34] Nor may it require a recall from a device user facility (that is, a hospital) if: (1) doing so would create a health risk greater than the risk from not recalling the device; and (2) no equivalent replacement device is immediately available.[35]

In September 2013, FDA issued a Guidance describing the status of certain mobile smartphone applications and its intent to exercise its enforcement discretion in regulating

those apps.[36] In addition to requiring that the app meet the definition of a medical device, FDA stated that it would focus its efforts on those apps that are either intended to be used as an accessory to a regulated device or transform a mobile platform into a regulated device. FDA stated that it did not intend to enforce regulatory requirements against apps that helped patients self-regulate their diseases or conditions without providing specific treatment suggestions, provided coaching or information to help patients manage their health, or merely facilitated health-related communications. FDA also indicated that it did not intend to regulate as medical device manufacturers the operators of app stores or makers of smartphones.

Biologics. Biologics, including human tissue and blood products, must be recalled when FDA determines that "a batch, lot, or other quantity of a product licensed under [the Public Service Health Act's Regulation of Biological Products section, 42 U.S.C. § 262] presents an imminent or substantial hazard to the public health."[37] Violation of such a recall order can result in a $100,000 per day fine.[38]

Q 11.11 Can FDA request that a company conduct a voluntary recall?

Yes. In "urgent situations" FDA may "request" that a recall "be undertaken voluntarily." FDA may also engage in informal discussions with a company that include voluntary recall as an option. In 2017, for example, it requested that a pharmaceutical company "remove" an opioid pain medication from the market based on the agency's "concern that the benefits of the drug may no longer outweigh its risks."[39] FDA may resort to more aggressive remedies, such as a product seizure, if a company refuses to recall its product after the request is made.[40] FDA can pursue this course of action for products against which it cannot *order* a recall, such as pharmaceuticals. FDA may request a recall when:

1. A product that has been distributed presents a risk of illness or injury or gross consumer deception;
2. The company has not initiated a recall of the product; and
3. An agency action is necessary to protect the public health and welfare.[41]

If FDA requests a voluntary recall, it will notify a responsible official of the company in a letter which provides details of the alleged violation, the health hazard classification of the recall, FDA's recall strategy and other instructions necessary for the company to conduct the recall.[42]

Q 11.12 When a company voluntarily implements a recall, what are the responsibilities of the company and FDA?

The following chart summarizes the roles of the company and of FDA in a company-initiated recall.

CHART 11-1

Obligations in a Company-Initiated Recall

The Company	FDA
Notify FDA of recall	Determine whether company violated law
Submit information required by 21 C.F.R. 7.46(a)	Inspect company facilities if necessary
Submit to possible inspections by FDA	Determine whether that violation would trigger FDA enforcement, and assign it a recall classification
Prepare recall communication, send to FDA for review, and distribute to customers	Review and revise recall communication
Follow up on recall communications	Inform general public
Submit status reports to FDA	Review status reports and monitor recall progress until end

Notification of FDA. If a company voluntarily removes or corrects a product because it believes that the product violates the FDCA or an FDA regulation, the company is required to immediately notify the nearest FDA field office.[43] FDA will then verify that the product being recalled was, in fact, violative and subject to FDA enforcement. This notification is not necessary if FDA previously requested the recall, but is required if FDA merely informed the company of its violation.[44]

Information-gathering and classification. If FDA confirms that the company's action is a recall, then the company must provide FDA with the following information:

1. The identity of the product involved;
2. The reason for the recall and the date on which the problem was discovered;
3. An evaluation of the potential risk involved;
4. The total amount of product affected and the time span of the production;
5. The total amount of product estimated to be in distribution channels;
6. Distribution information, including the number and names of direct accounts;
7. A copy of the proposed or issued recall communication;
8. A proposed recall strategy; and
9. The name and telephone number of the company representative to be lead contact.[45]

The company may also be subjected to inspections conducted by the local FDA District Office.[46] After receiving the desired information, FDA will classify the recall (see Q 11.13 and Q 11.14 below) and review the recall strategy and proposed recall communication.[47]

Public Notification. The company must send a recall communication to individuals and/or entities to whom it sold affected product. FDA will review the company's proposed recall communication to ensure that it clearly conveys:

1. That the product in question is subject to a recall;
2. The model, size, lot number(s), code(s), serial number(s) and any other pertinent description of the affected product;
3. The reason for the recall and the nature of the potential hazard;
4. That further use and distribution of affected product should cease immediately;
5. That the recipient of the letter should notify its customers of the recall, where appropriate;
6. Instructions about what to do with affected product; and
7. Ready means for the recipient to report whether it has any affected product.[48]

After sending the recall communication, the company is required to conduct "effectiveness checks" to ensure that the communication was received and is being followed. A company should accomplish this with phone calls, follow-up letters, and/or personal visits.[49]

Meanwhile, FDA will inform the wider public of the recall. FDA utilizes its webpage to disseminate information about product recalls.[50]

Status reports and continued FDA supervision. As the recall proceeds, FDA assumes a monitoring and auditing role.[51] The company must submit status reports for FDA's review, usually every two to four weeks, until the recall is formally terminated.[52] Status reports should include:

1. The number of customers notified of the recall, and the date and method of notification;
2. The number of customers who responded to the recall communication and the quantity of affected product that each reported having;
3. The number of customers who did not respond;
4. The amount of affected product returned by each customer;
5. The number and results of the company's effectiveness checks; and
6. The estimated time frames for completion of the recall.[53]

Q 11.13 What is a health hazard evaluation?

FDA will conduct a health hazard evaluation to determine the necessity, nature, extent, and classification of any recall. In this evaluation, FDA scientists consider, among other factors:

1. Whether injury or disease has already been caused by the product;
2. Whether any existing conditions could contribute to a clinical situation that could expose individuals to a health hazard;
3. The effect of the hazards on specific, that is, vulnerable, population segments such as pediatric or elderly patients;
4. The degree of seriousness of the hazard;
5. The likelihood that patients will experience the hazards; and
6. The immediate versus long-range consequences of an individual suffering the hazard.[54]

FDA uses the results of the health hazard evaluation to classify the recall.

Q 11.14 What are the different recall classifications?

FDA regulations provide for three classifications of recalls: Class I, Class II, and Class III.[55] The classification is based on the results of the FDA's health hazard evaluation.[56] The recall's classification usually determines the level of publicity and monitoring FDA employs. For example, a Class I recall will generally warrant a press release.[57]

The most serious recall is a Class I recall. A Class I recall is "a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death." Class II recalls are reserved for situations where "use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences," but "the probability of serious adverse health consequences is remote." Finally, Class III recalls are for scenarios "in which use of, or exposure to, a violative product is not likely to cause adverse health consequences."[58]

Q 11.15 What are the differences among a recall, market withdrawal and stock recovery?

All three of these terms describe different situations in which a company removes a product from the market or takes some action to "correct" it.

A market withdrawal is defined as the removal or correction of a product due to a deficiency that either: (1) does not violate the FDCA or FDA regulations; or (2) is a violation but is not significant enough to trigger an FDA enforcement action.[59] Examples include taking a product off the market due to consumer complaints, a need for "routine equipment adjustments and repairs," or "normal stock rotation practices."[60] In contrast, a recall is defined as a product removal or correction triggered by a significant statutory or

regulatory violation which could warrant an FDA enforcement action.[61] Thus, the difference between a recall and a market withdrawal depends on the existence and severity of a violation. If a company initiates a market withdrawal but the product's deficiency is "not obvious or clearly understood," FDA regulations recommend that the company consult with its local District Office to determine the cause.[62]

Lastly, when a company removes or corrects its products but those products have never "been released for sale or use," its action is considered a stock recovery.[63] Simply put, a company cannot recall a product that it has not yet distributed.

Q 11.16 When is a recall considered complete?

FDA regulations state that a recall is complete, or "terminated," when FDA "determines that all reasonable efforts have been made to remove or correct the product in accordance with the recall strategy, and when it is reasonable to assume that the product subject to the recall has been removed and proper disposition or correction has been made commensurate with the degree of hazard of the recalled product."[64]

A company may request in writing that FDA "terminate" the recall. The request must explain the effectiveness of the recall and the company must attach its most recent recall status report to the request.[65] When the recall is, in fact, completed, the appropriate FDA District Office or Center will inform the company of this determination in writing. For Class I Recalls, however, concurrence among the relevant FDA Centers on the appropriateness of termination is generally required.[66]

Import Detentions and Alerts

Q 11.17 What is an import detention?

An import detention occurs when FDA refuses to allow a product to be imported into the United States, based on its determination that the product does not meet the standards applicable to domestic goods. Under the FDCA, FDA may detain products that "appear," based on "samples or otherwise," to violate the FDCA or FDA regulations.[67] FDA also may refuse entry into the United States of food, drugs, and devices made at facilities whose owners have refused to permit inspection. The most common violations by imports come from the adulteration or mislabeling of products.[68] Since 1974, FDA has broadly utilized its ability to detain products without physical examination.[69] Under current FDA procedure, "one violative sample . . . may support a recommendation for detention without physical examination of products from a specific manufacturer, shipper, grower, or from a specific growing area or country."[70] In other words, one violation can cause a country's entire output of a product to be detained. Detention may also "be based on the violative history of a product, manufacturer, shipper, grower, importer, geographic area, or country," or on information about polluted water, unsanitary conditions, or anything else which demonstrates that future shipments could violate FDA regulations.[71]

The practice of detaining entire batches or categories of imported products comports with FDA's view that it is "a regulatory agency, not a quality control laboratory," and that "[d]etention without physical examination properly places the responsibility for ensuring compliance with the law on the importer."[72]

The 2012 Food and Drug Administration Safety and Innovation Act authorized FDA to destroy detained drugs having a value of less than $2,500 without opportunity for export, upon notice and an opportunity for hearing.[73]

Q 11.18 What is an import alert?

An import alert is a document FDA issues to "identify and disseminate" information regarding shippers, importers, and/or imported products that have violated the FDCA or FDA regulations. Import alerts have a dual purpose: (1) they aid the FDA's enforcement mechanisms by informing the entire agency of recent and/or incipient import detentions; and (2) they make the public aware of FDA's enforcement efforts against imported products that violate the FDCA or FDA regulations. An alert will generally identify a product or batch of products that is subject to detention, sometimes defining the violative product by the specific shippers or importers that are dealing in them.[74]

Any unit of FDA, whether a Field Office or a Center, can propose or recommend an alert. All proposed import alerts are submitted to the Division of Import Operations (DIO), which reviews, clears, and issues all import alerts. An alert generally stays active for

two years, and is then reviewed semi-annually by DIO. DIO's review assesses whether the product is still being detained and whether the import problem remains significant to human health.[75]

Though import alerts primarily aid FDA's internal enforcement mechanisms, as noted above, they are also available to the public on an FDA Internet page. Like Warning Letters, they are searchable by subject and arranged in lists based on a product's country of origin, industry, and date of the alert's publication.[76] Each alert specifically identifies the detention and the alleged regulatory violation that triggered its issuance.[77]

Product Seizures

Q 11.19 What is a product seizure?

A product seizure is an act by which FDA confiscates and takes possession of a company's product due to alleged violations of the FDCA or FDA regulations. Product seizure is FDA's most powerful enforcement tool and, accordingly, FDA's exercise of that power must comport with the company's due process and property rights.[78]

Q 11.20 What is the source of FDA's authority to seize products?

Under 21 U.S.C. § 334, any misbranded or adulterated product which is introduced into interstate commerce "shall be liable to be proceeded against," that is, "seized," by FDA.[79]

Q 11.21 Are there different types of seizures that FDA can implement?

Yes. There are four categories of seizures that FDA can pursue.[80] The simplest type of seizure is a *lot-specific seizure*, where "a specific lot or batch of a product" known to contain violative products is seized.[81]

When FDA seizes all of the regulated products located in a particular facility, the action is called a *mass seizure*. A mass seizure is conducted when the facility where the products are produced or stored is contaminated or fails to comply with cGMPs.[82] Because FDA recognizes that mass seizures can have a drastic effect on the operations of a company, mass seizures occur infrequently compared to lot-specific seizures.[83]

In an *open-ended seizure*, FDA seizes the company's entire inventory of a particular product or category of products. The seizure is based on some ubiquitous or continuous condition affecting all units of a product, regardless of which facility or batch from which the products originated. A violation leading to this type of seizure extends to an entire product line, but not necessarily everything produced by a company. Mislabeling is a common violation that causes an open-ended seizure.[84]

Finally, FDA uses the term *multiple seizures* when the same product is seized through proceedings filed in more than one district court. This occurs when FDA wants to prevent the ongoing distribution of a product which has spread across multiple districts. The FDCA prohibits FDA from initiating multiple seizure actions against a misbranded product unless FDA has probable cause to believe the alleged misbranding is dangerous, fraudulent, or misleading to consumers.[85]

Q 11.22 Under what circumstances may FDA seize a product?

Although the FDCA grants FDA broad authority to seize any misbranded or adulterated

product,[86] FDA employs this enforcement mechanism sparingly.[87] In addition, despite having no obligation to notify a company of a forthcoming seizure, FDA generally issues a Warning Letter or other written communication to provide a company with "an opportunity to voluntarily take appropriate and prompt corrective action prior to the initiation of enforcement action."[88] Whether a company has received prior notice of the violation is the first factor that FDA considers in deciding whether to seize a product.[89]

In addition to notice, FDA requires that additional preconditions be met before it formally recommends a seizure. If the District Office pursuing a seizure ("seizing district") is not the same as the district where the violation actually occurred ("home district"),[90] then both the home and seizing district must agree that a seizure is warranted. There is also a monetary requirement: FDA will not seize quantities valued under $2,000 unless, among other things, "there is a documented hazard to health," or "the violative product will be incorporated into other products, thus receiving more extensive distribution."[91] FDA also considers, among other things, whether it can gain control over the product another way, whether it appears that the violations will continue, and whether a company has failed to correct a violation about which it has already been warned.[92]

Q 11.23 Can FDA take possession of a product before a seizure action is filed?

Yes. If an FDA official conducting an inspection of food, medical devices, or tobacco products "has reason to believe [the products are] adulterated or misbranded," 21 U.S.C. § 334 provides FDA with the authority to immediately "detain" the product for up to twenty days. If FDA determines that a longer period of time is required in order to initiate a seizure action, the product may be detained without court order for up to thirty days.[93] Any company entitled to claim the detained devices may appeal the detention and receive an informal hearing. If an appeal is filed, FDA must issue an order confirming or revoking the detention within five days of the appeal.[94] FDA is not empowered to detain drugs in this fashion.

Q 11.24 What is FDA's process for seizing products?

The FDCA requires FDA to proceed against a product(s) in a district court through the filing of a "libel of information," a form of complaint.[95] The seizure process begins when an FDA unit makes a seizure recommendation. FDA District Office in the seizing district approves the seizure recommendation, refers the matter to the United States Attorney's Office for prosecution, and submits a package containing a draft complaint and supporting documents to the U.S. Attorney.[96]

The U.S. Attorney will then file a complaint for forfeiture in district court, seeking a warrant for arrest and a directive for the U.S. Marshal to seize the violative product.[97] To obtain a seizure order, the government must simply prove that the goods to be seized were introduced into interstate commerce and, based on a preponderance of the evidence, were

misbranded or adulterated.[98] If a seizure order is obtained, the U.S. Marshal's Office seizes the product.[99] Once the product is seized, FDA follows specific directions on the proper disposition of the seized product, as set out in its *Regulatory Procedures Manual*.[100]

Q 11.25 What must a company do to contest a product seizure?

In order to contest a seizure action, a company must (1) file a proper, verified claim identifying its right to the product and (2) file an answer to the government's complaint within twenty days. The contest will then proceed in court as a civil matter.[101] "If the FDA chooses to proceed . . . it must prove in a court of law by a preponderance of the evidence that the product seized is adulterated or misbranded."[102]

Q 11.26 Are there any requirements attendant to an amicable resolution of a seizure action?

Yes. A company may enter into a consent decree with FDA that requires the company to recondition or convert the seized product. In any consent decree, the company must agree to: (1) a finding that the products were in violation of the FDCA; (2) a penal bond set at twice the retail value of the seized products; (3) provide for the removal and supervision costs incurred by the U.S. Marshals and FDA; and (4) bring the articles into satisfactory compliance.[103] If a company violates a consent decree, FDA is entitled to pursue sanctions for contempt.[104]

Injunctive Relief

Q 11.27 May FDA obtain injunctive relief against a company?

Yes. FDA may, through the U.S. Attorney, seek an injunction requiring a company to take certain steps to prevent regulatory violations from occurring, to cease engaging in certain conduct that violates the FDCA or FDA regulations, or even to cease operations.[105] The FDCA grants the district courts the authority to "restrain violations" of the FDCA (with a few exceptions).[106] In practice, FDA must take the following steps in order to obtain an injunction:

1. Determine that a request for injunctive relief is warranted under FDA's internal guidelines (see Q 11.28 below).
2. Ensure that the company is notified that injunctive relief may be sought (see Q 11.29 below).
3. Prepare a complaint accompanied by supporting documents (that is, affidavits) that show adequate grounds for an injunction (see Q 11.30 below).
4. Persuade the court that the company has violated a statute or regulation and will likely violate it again (see Q 11.30 below).

FDA's authority to obtain an injunction extends to individuals associated with a company as well. Responsible individuals, such as those who supervise shipping, inventory, and customer service, can be bound by an injunction.[107]

Q 11.28 Under what circumstances may FDA seek an injunction?

FDA may seek an injunction where there is a significant statutory or regulatory violation, particularly where a health hazard has been identified. In deciding whether to seek an injunction FDA will consider the seriousness of the alleged violation, the actual or potential impact on the public, whether other enforcement actions would be more effective, whether prompt judicial action is required, and the likelihood that the violation will continue without an injunction. FDA considers injunctions to be the best course of action where:

1. A seizure is impractical and immediate action is necessary to prevent "a current and definite health hazard" or "gross consumer deception";
2. A company that owns large quantities of a violative product is failing to conduct a recall and seizure is impractical or uneconomical; or
3. A company has committed long-standing or chronic violations which have not yet caused a health hazard or consumer fraud but have not been cured voluntarily or

through other regulatory approaches.[108]

Q 11.29 Can FDA obtain injunctive relief before it affords a company notice and a hearing?

Technically, FDA does not have to provide a company with notice before seeking an injunction. As a matter of internal policy, however, the agency typically provides a company with prior notice before it seeks injunctive relief.[109] The agency reasons that its legal position is strengthened when it "document[s] a conscious effort to get the objectionable products or practices corrected without court involvement."[110] Further, FDA may rely on the prior notice to "demonstrate a defendant's resistance to compliance and enhance the agency's request for court intervention."[111] The method FDA uses to provide notice can vary by situation, but it is usually directed to the company representative who is in the best position to correct the alleged violation.[112]

Q 11.30 What standard must FDA meet to obtain a preliminary injunction?

In order to obtain a preliminary injunction, FDA must show that:

1. the company violated the FDCA or an FDA regulation, and
2. there is a cognizable danger of recurrent violations.[113]

The typical "likelihood of success and irreparable injury" test for an injunction does not apply in cases brought by FDA because the FDCA specifically empowers FDA to enjoin statutory and regulatory violations and because there is a strong public interest in a government agency enforcing the laws Congress charged it to enforce.[114]

In assessing whether there is a chance of recurrent violations, a court will evaluate several factors including:

1. the company's degree of scienter;
2. the isolated or recurrent nature of the violation;
3. the company's recognition of the wrongful nature of its conduct;
4. the sincerity of the company's assurances against future violations; and
5. the nature of the company's business.

A court will also consider whether the company voluntarily ended the challenged practice, whether it made a genuine effort to improve its conduct and conform to the law, and whether it has complied with any of FDA's recommendations.[115] Courts have warned that injunctive relief in FDCA cases must be used "sparingly" and only "to prevent future harm, . . . not to punish past violations."[116]

Q 11.31 What types of injunctions may FDA seek?

In addition to seeking a preliminary injunction, as discussed above, FDA can seek and obtain a temporary restraining order if it demonstrates an emergent need to control a serious statutory or regulatory violation. Further, FDA may seek a permanent injunction at any time after a complaint and hearing, or it may enter into a consent decree.[117]

Civil Money Penalties

Q 11.32 What is a civil money penalty?

A civil money penalty (CMP) is a fine FDA can impose pursuant to specific legal authority, after an administrative hearing, against a company whose product(s) or practice(s) violates the law. [118]

Q 11.33 Under what circumstances may FDA impose a CMP, and under what legal authority?

FDA may only impose a CMP on a company when it is specifically authorized by statute. The FDCA and the Public Health Service Act identify specific statutory violations for which FDA may impose a CMP. For each FDA-regulated product, the violations that could trigger a CMP vary greatly. For example, FDA has very limited authority to impose a CMP for food safety violations.[119] FDA's authority to impose a CMP on a medical device manufacturer is much broader, as the FDCA states that "any person who violates *a requirement of this Act which relates to devices* shall be liable to the United States for a civil penalty."[120]

Notably, individuals and companies alleged to have violated provisions of the FDCA may also be targets of civil fraud and other claims brought by the United States seeking damages.[121]

The statutory provisions which authorize FDA to impose a CMP for a prescription drug, medical device, or biologics violation, and the maximum penalties allowed, are listed at 45 C.F.R. § 102.3 as follows:

Statute (21 U.S.C.)	Product/Violation	Maximum Fine ($)
333(b)(2)(A)	Prescription drug sample distribution (for the first two violations in any ten-year period)	98,935
333(b)(2)(B)	Prescription drug sample distribution (for each violation after a second conviction in any ten-year period)	1,978,690
333(b)(3)	Prescription drug samples, failure to make reports	197,869
333(f)(1)(A)	Medical devices	26,723 per violation; 1,781,560 per proceeding

333(f)(3)(A)-(B)	Clinical trial information	11,383; plus 11,383 for each day violation remains after 30 days
333(f)(4)(A)(i)	Drugs, post-market studies, clinical trials, and REMS	284,583 per violation; 1,138,330 per proceeding
333(f)(4)(A)(ii)	REMS	284,583; penalty doubles monthly, to max of 1,138,330 in any 30-day period, or 11,383,300 per proceeding in the aggregate
333(g)(1)	DTC drug and biologics advertisements	284,583 for the first violation; 569,165 for each subsequent violation within three years
335b(a)	New drug applications	419,320 (individual); 1,677,280 (company)
360pp(b)(1)	Electronic devices	2,750 per violation; 937,500 for series of related violations
42 U.S.C. 300aa-28(b)(1)	Vaccine manufacturer recordkeeping	120,000 per occurrence

Q 11.34 May FDA impose a CMP against individuals within a company that committed a violation?

Yes. FDA is empowered to impose CMPs against "any person" who violates the CMP device and drug advertising sections of the FDCA.[122] Meanwhile, the FDA is empowered to impose CMPs against a "manufacturer or distributor" that violates certain sections governing prescription drugs.[123] However, the same statute calls for *criminal* penalties against "any person" who violates certain of those provisions.[124] Case law suggests that if FDA has power to impose a CMP on a company while contemporaneously having the power to hold responsible individuals criminally liable, then the power to impose a CMP extends to include individuals who are shown to have a "responsible relationship" to the violative acts of the company.[125]

FDA reasons that the individuals comprising drug and device companies "occupy a virtual fiduciary relationship to the public."[126] FDA's position has been bolstered by cases such as *United States v. Park*, which stated that FDA sanctions should "reach and touch the individuals who execute the corporate mission" because of their duties to ensure compliance.[127] This view applies to other enforcement mechanisms, in addition to CMPs.[128]

Q 11.35 How does FDA impose a CMP?

FDA must meet certain procedural requirements in order to impose a CMP. FDA must file and serve an administrative complaint which states, among other things, the statutory

basis for the CMP.[129] If the company contests a CMP, it must answer the complaint within thirty days of service. The matter will then be set for a hearing and decided by an Administrative Law Judge who reports directly to the FDA Commissioner's Office.[130] The losing party is entitled to administratively appeal the Administrative Law Judge's decision to the FDA Commissioner and, beyond that, to the appropriate federal court of appeals.

Q 11.36 Are there exceptions to the FDCA's broad authority to impose CMPs on a medical device manufacturer?

Yes. 21 U.S.C. § 333(f)(1) precludes FDA from imposing a CMP on a medical device company for violations of the cGMP requirements[131] or the adverse event recordkeeping and reporting requirements unless the violations constitute a significant or knowing departure from the requirements, or are a risk to the public health.

If a violation of these provisions is "major" or part of a "series of incidents that collectively are consequential," then the departure is "significant" and not exempted.[132] A "[k]nowing departure, for the purposes of interpreting 21 U.S.C. § 333[(f)](1)(B)(i), means a departure from a requirement taken: (a) [w]ith actual knowledge that the action is such a departure[;] (b) in deliberate ignorance of a requirement[;] or (c) in reckless disregard of a requirement."[133]

Q 11.37 Are there limits on FDA's authority to impose a CMP on drug manufacturers?

Yes. FDA's authority to impose a CMP against a drug manufacturer is generally limited to the following types of violations:

1. When a sales representative is convicted of illegally selling, purchasing or trading or offering to sell, purchase or trade a prescription drug sample.[134]
2. Failing to report such a sales representative's conviction to FDA.
3. Failing to submit required clinical trial information or submitting false or misleading clinical trial information to FDA.
4. Disseminating false or misleading direct-to-consumer advertising.
5. Making false statements or misrepresentations of material fact to FDA in connection with an Abbreviated New Drug Application (ANDA).
6. Bribing or attempting to bribe an FDA employee in connection with an ANDA submission.
7. Destroying any material FDA documents or evidence in connection with an ANDA submission.
8. Obstructing an FDA investigation into a clinical trial subject.
9. Knowingly using a disqualified clinical trial investigator in connection with a New

Drug Application (NDA).[135]

Q 11.38 What factors does FDA consider in determining the amount of a CMP against a medical device company?

With respect to medical devices, the FDCA at 21 U.S.C. § 333(f) states that:

> In determining the amount of a civil penalty . . . the Secretary shall take into account the nature, circumstances, extent, and gravity of the violation or violations and, with respect to the violator, ability to pay, effect on ability to continue to do business, any history of prior such violations, the degree of culpability, and such other matters as justice may require.[136]

In addition to these statutory factors, FDA will consider: (1) whether a violation can and should be addressed with a more forceful regulatory option such as a seizure or injunction, and (2) whether the company has received prior warning (that is, a Warning Letter or other correspondence with the FDA) or whether the conduct was so egregious that no warning needed to be given.

In assessing the "nature of the violations," FDA considers the categorical seriousness of the violation. It also considers whether the provision violated goes to the "core purpose" and "mission" of FDA in ensuring basic "safety and effectiveness." In assessing the "circumstances of the violation," FDA considers whether a violation was preceded by a warning, and whether the company violated a clear and unambiguous law. In assessing the "gravity" of a violation, FDA considers the risks created by a violation and whether the violative actions were calculated to confer some economic advantage on the company.[137]

The "ability to pay" and "ability to continue to do business" factors require FDA to consider whether a company has assets sufficient to cover the fine. This relates to FDA's separate statutory directive to levy lesser fines on small businesses.[138] Upon passage of the Small Business Regulatory Enforcement Fairness Act of 1996, the FDA modified its section 333(f) assessment to take into account a company's small size.[139] Nevertheless, FDA is barred from reducing CMPs on this basis where the conduct was willful, created serious safety or environmental hazards, demonstrated a lack of good faith compliance, and/or occurred within five years of another enforcement action.

"Culpability" refers to the overall blameworthiness of the company. Here FDA considers any evidence of the company's *mens rea*, that is, whether it acted intentionally, recklessly, carelessly, or inadvertently. The input of high-level company officials, and their response upon learning of the violation, is considered here as well. Whether the company "took timely action to correct the violation, eliminate or reduce the risk that the instant violation would cause future harm, and [whether it] made restitution to any parties harmed by the violative conduct" is also relevant in determining blameworthiness.[140]

Lastly, the discretionary catch-all at the end of the statutory provision allows FDA to weigh any other aggravating and mitigating factors.[141]

Q 11.39 What factors does FDA consider in determining the amount of a CMP against a drug company for a violation of the laws governing drug advertising?

21 U.S.C. § 333(g) states that a company "shall be liable" for a CMP up to $250,000 (or up to $500,000 for subsequent offenses) when it "disseminate(s) a direct-to-consumer advertisement that is false or misleading." In setting the amount of the penalty, the FDCA directs FDA to consider "the nature, circumstances, extent, and gravity of the violation or violations."[142] In particular, FDA assesses whether the company (or any person therein) submitted the advertisement to FDA for advisory review, whether the company waited until the forty-five-day comment period was complete before disseminating the advertisement, whether the company ceased distribution of the advertisement upon notice, and the scope of any "voluntary, subsequent remedial action by the [company]," among other factors.[143]

Clinical Trial Penalties

Q 11.40 What is a clinical trial penalty?

A "clinical trial penalty" is a measure taken by FDA against a sponsor of a clinical trial (normally the company seeking approval of a new drug), or the trial's researchers, in response to a violation of the laws governing clinical trials of new drugs. The penalties FDA may impose range from disqualifying a clinical trial investigator to suspending or altogether terminating a clinical trial.

Q 11.41 What is the source of FDA's authority to impose clinical trial penalties?

FDA's authority to impose clinical trial penalties comes from the FDCA sections covering new drug applications (21 U.S.C. § 355). The statute sets forth the requirements governing clinical trials, and FDA regulations provide for the imposition of penalties when those requirements are violated.[144]

Q 11.42 What types of violations will prompt FDA to impose a clinical trial penalty?

FDA usually imposes a clinical trial penalty when, in the course of a clinical trial, a violation occurs that jeopardizes the welfare of human subjects or the integrity of the trial's results. For example, FDA will disqualify a clinical trial investigator who endangers test subjects, fails to keep records, or actively misrepresents test results (see Q 11.43 below). FDA also has the power to suspend or terminate a clinical trial if unsafe conditions exist, inaccurate results are reported, or misrepresentations are made to the agency or to test subjects (see Q 11.45 through Q 11.49 below).

Q 11.43 Does FDA have the authority to disqualify a clinical trial investigator?

Yes. FDA may bar a clinical trial investigator from receiving investigational drugs, biologics, and devices if FDA learns that the investigator "repeatedly or deliberately failed to comply with" the agency's regulations (which are intended to protect the integrity of trial data and the rights of trial subjects), or "repeatedly or deliberately submitted false information to the sponsor of the investigation or in any required report."[145] FDA internal guidelines recommend that the disqualification of a clinical trial investigator be limited to violations that: (1) present "an unreasonable and significant risk" of injury or illness for the subjects under the care of the investigator; (2) seriously compromise subjects' rights; or (3) seriously compromise the integrity or reliability of the data.[146]

Some violations may warrant criminal proceedings against the clinical trial investigator.

Courts have allowed FDA to pursue, through the U.S. Attorney, criminal charges against investigators who violated 21 U.S.C. § 355 and its implementing regulations, reasoning that the FDCA provides for criminal liability and allows FDA to define specific violations in its regulations.[147]

Q 11.44 What procedures does FDA follow to disqualify a clinical trial investigator?

Once FDA determines that the disqualification of a clinical trial investigator is warranted, it will prepare a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE), which describes the alleged violation(s). FDA will then deliver the NIDPOE to the clinical trial investigator, and offer him or her an opportunity to explain the alleged violations either in writing or at a conference.[148] The NIDPOE will also include a proposed consent agreement which the investigator can sign, effectively settling the matter by agreeing to cease investigating the product and/or participating in future clinical trials.[149]

If the clinical trial investigator contests the allegations or FDA receives no response to the NIDPOE, FDA will schedule an informal hearing, under 21 C.F.R. § 16, to "determine whether the investigator should remain eligible to receive certain investigational products."[150] If the Commissioner finds that the clinical trial investigator committed a violation sufficient to trigger disqualification, then FDA formally disqualifies the investigator, notifies the company conducting the clinical trial and the sponsor(s) of all approved applications to which the investigator contributed data, and any unreliable data contributed by the disqualified investigator is "eliminated from consideration."[151]

Q 11.45 What is a clinical hold letter?

A clinical hold letter informs the company conducting or proposing the clinical investigation that FDA is suspending or "holding" a clinical trial. Upon receipt of a clinical hold letter, the investigators must stop administering the investigational drug to all subjects, and the company must stop recruiting new subjects.[152] A clinical hold letter is not required for FDA to impose a clinical hold, as FDA is free to use other informal methods to inform the company.[153]

Q 11.46 Under what circumstances can FDA issue a clinical hold letter?

A clinical hold is warranted when an Investigatory New Drug (IND) "represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved."[154] The types of violations that may support a clinical hold are found at 21 C.F.R. § 312.42(b), and vary depending on the phase of the clinical trial (Phase 1, 2, or 3).[155] FDA may institute a

clinical hold due to, among other things, an unreasonably high risk of subjects becoming ill, a "misleading, erroneous, or materially incomplete" brochure produced by the investigator, or an unqualified team of investigators.[156] FDA can suspend a Phase 2 or 3 study if it finds that "the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives."[157] FDA may suspend any study that "is not designed to be adequate and well controlled."[158]

Q 11.47 How much time does the company have to respond to a clinical hold letter?

FDA regulations do not specify a time frame in which a company must respond to a clinical hold letter. However, 21 C.F.R. § 312.42 states that if a clinical trial is under clinical hold for more than one year, FDA may make the IND "inactive" under 21 C.F.R. § 312.45 and notify the company and clinical trial investigators of this designation.[159]

Q 11.48 How much time does FDA have to take further action after receiving the company's response to a clinical hold letter?

If the company corrects or explains the alleged violations, it may request that FDA lift the clinical hold. FDA must issue a written decision within thirty days either maintaining or lifting the clinical hold and providing the reasons for its decision.[160] If FDA informs the company that the hold has been lifted, the company may resume the clinical trial.[161]

Q 11.49 Under what circumstances may FDA terminate a clinical investigation?

The FDA has the power to terminate a new drug investigation. Termination can be based on many of the same grounds that allow FDA to suspend a clinical trial, or on one of several additional grounds, including an investigator's failure to conduct the investigation in accordance with the application's protocols, or failure to adequately "maintain appropriate standards of identity, strength, quality, and purity" in the drug in order to keep test subjects safe.[162] As with clinical holds, the grounds for termination vary based on the phase of the clinical trial.

Criminal Penalties

Q 11.50 Under what authority are criminal prosecutions for violations of the FDCA authorized?

Criminal violations of the FDCA generally result from the interaction of two statutory provisions. Most often, criminal activity is prosecuted under 21 U.S.C. § 333 for violations of section 331 (Prohibited Acts), a provision broadly proscribing acts including the delivery into commerce of adulterated or misbranded food, drugs, devices, cosmetics, and tobacco products. But section 333 also covers a patchwork of special cases and violations of underlying statutes and regulations, including those relating to prescription drug marketing,[163] the distribution of Human Growth Hormone,[164] devices (including tobacco products),[165] and direct-to-consumer advertising.[166] FDA occasionally utilizes criminal enforcement to raise the profile of certain compliance obligations, such as with REMS programs.[167] Penalties range from misdemeanors calling for prison sentences of one year or less and fines of $1,000 or less,[168] to prison sentences of up to twenty years and fines of up to $1 million for knowing and intentional adulteration of a drug creating a reasonable probability of serious adverse health consequences or death to humans or animals.[169] Additionally, companies and individuals convicted of violating the FDCA face mandatory or permissive debarment.[170]

FDA does not have the authority to institute criminal prosecutions itself. Rather, potential violations are investigated in the first instance by FDA's Office of Criminal Investigations, which in an appropriate case will refer a matter to the Department of Justice, typically through local U.S. Attorneys.

Q 11.51 Under what circumstances does the FDCA impose criminal liability on corporate executives?

The U.S. Supreme Court has held that individuals who are "responsible corporate officers" may be subject to misdemeanor criminal penalties under the FDCA without the requirement of criminal intent.[171] Under the so-called "*Park* doctrine," corporate officials who are in a position of authority to prevent violations may be held criminally liable for failing to do so, even if they were unaware of the violation. A 2016 appellate decision, however, suggests that *Park* should be read to require at least negligence on the part of the defendant in *Park* doctrine prosecutions, and the dissent in that case argued that *Park* has been limited by subsequent Supreme Court opinions requiring that a criminal defendant possess *mens rea*, at least where imprisonment is ordered.[172]

Withdrawal of Approval

Q 11.52 Can FDA withdraw its approval of a new drug or medical device application?

Yes. After a drug or medical device is approved or cleared for marketing, FDA continues to monitor the product and has the right to withdraw its approval or clearance of the product upon the receipt of new information.

Q 11.53 What is the source of FDA's authority to withdraw approval of a product?

21 U.S.C. § 355(e) grants FDA the authority to withdraw its approval of drug applications in certain situations. Similarly, 21 U.S.C. § 360e(e) provides FDA with the same authority over approved medical device applications.

Q 11.54 Under what circumstances will FDA withdraw its approval of a new drug application?

FDA is obligated to withdraw its approval of a new drug application as a means of protecting the public health when new tests, clinical experience or other scientific data, evaluated together with information contained in the original application, show that the product is unsafe or ineffective for its intended use.[173] FDA may even seek voluntary action on threat of the withdrawal of approval. In 2017, for example, it requested that a pharmaceutical company "remove" an opioid pain medication from the market based on the agency's "concern that the benefits of the drug may no longer outweigh its risks."[174]

The FDCA requires FDA to withdraw its approval when it learns that a new drug application contained false statements of material fact.[175] FDA may also withdraw approval of a new drug application as an enforcement method when a company fails to correct certain statutory and regulatory violations within a reasonable time. For example, FDA may withdraw its approval of a product where the labeling is shown to be false and misleading, where the company's production methods are shown to be inadequate to ensure the drug's "identity, strength, quality and purity," and where the company failed to establish and maintain required recordkeeping systems.[176]

Q 11.55 Under what circumstances will FDA withdraw its approval of a medical device application?

FDA is also obligated to withdraw its approval or clearance of a medical device application if it receives new information that, when evaluated in light of the evidence contained in the original application, shows that:

1. The medical device is unsafe or ineffective for its intended use;
2. The original application contained false statements of material fact;
3. The labeling for the device is false or misleading;
4. The product deviates from a performance standard established by FDA;
5. The product is not manufactured or produced in compliance with cGMPs; or
6. The company failed to establish required recordkeeping systems of submit required reports to FDA.[177]

Q 11.56 What is the process FDA must follow to withdraw approval?

To withdraw its approval of a drug or medical device application, FDA must provide due notice and an opportunity for the company to be heard.[178]

An order withdrawing a drug approval must be personally served on the company by a designated FDA officer or employee, or served by mail sent to the last known address of the company.[179] A withdrawal of a drug approval may be appealed by "filing in the United States court of appeals for the circuit wherein [the company] resides or has [its] principal place of business, or in [ ] the District of Columbia Circuit, within sixty days after the entry of such order."[180]

An order withdrawing a device approval must be served in the same manner.[181] An appeal of a withdrawal of a device approval must, however, be conducted administratively. FDA provides a hearing, the nature of which is described in the FDCA. For withdrawals based on certain grounds, however, FDA instead empanels an advisory committee to review the withdrawal.[182]

Q 11.57 Can FDA withdraw approval of a product indication?

Yes. Implicit in the statutes authorizing FDA to withdraw approval is its ability to withdraw its approval of a particular indication for a drug or medical device. When FDA approves a drug or device for any use (that is, treatment of a certain condition), that use becomes a "labeled indication." Under 21 U.S.C. § 355(e)(3) and § 360e(e)(1)(B), FDA may withdraw its approval if new evidence shows that the drug or device is not safe or effective for each of its labeled uses. A withdrawal can be avoided if a company removes the indication in controversy from the product label.

Some Special Enforcement Issues

Q 11.58 What is FDA's authority to combat the importation of counterfeit and unapproved drugs?

FDA has civil administrative and criminal enforcement tools at its disposal to combat the importation into the United States of counterfeit or otherwise unapproved drugs, and to protect the U.S. supply chain. Drugs manufactured abroad outside of the FDA regulatory system may not lawfully be imported into the United States, and are subject to detention.[183] Drugs that are counterfeit—that is, that violate laws protecting intellectual property rights—are subject to separate FDA prohibitions.[184] Through its Office of Criminal Investigations (OCI), and in coordination with U.S. Customs and Border Protection, U.S. Attorneys, and the Drug Enforcement Agency, FDA may pursue criminal violations against the manufacturers and importers of counterfeit and other illegal drugs.[185]

Q 11.59 What enforcement actions has FDA taken against manufacturers and sellers of counterfeit and unapproved drugs?

FDA has taken action against individuals and entities at all points on the distribution chain for illegal drugs, including foreign manufacturers,[186] websites promoting the products to U.S. consumers,[187] U.S. wholesalers,[188] U.S. pharmacies,[189] individual intermediaries,[190] practitioners,[191] and smugglers.[192] The problem of illegal "rogue" websites is especially vexing because of the ease with which such websites can be launched and the difficulty in stopping shipments to individual consumers effected by means of express courier services. Still, in 2017 FDA joined other bodies worldwide in seeking to address the problem by participating in Operation Pangea X, coordinated by INTERPOL. This effort led FDA to send thirteen Warning Letters to the operators of 401 websites, to seize nearly 100 website domain names, and to detain nearly 500 parcels shipped to the United States with illegal medicines.[193]

Q 11.60 What enforcement actions may FDA take against compounding pharmacies?

Prompted by an outbreak of fungal meningitis that was traced to a compounding pharmacy, Congress increased regulation of such businesses through the Drug Quality and Security Act (DQSA),[194] enacted in November 2013. The DQSA created a new class of regulated entities—"outsourcing facilities"—that compounding pharmacies could elect to become through registration with FDA. A compounding pharmacy that becomes an outsourcing facility must provide FDA with certain general and product information, and becomes subject to the cGMP regulations and FDA inspection. Such entities thus become subject to all of the enforcement tools described in this chapter applicable to regulated

facilities. In 2015, FDA issued five draft guidances and a draft MOU to further implement the DQSA.[195]

Q 11.61 What enforcement actions may FDA take against manufacturers of tobacco products?

In 2009, Congress enacted the Family Smoking Prevention and Tobacco Control Act (TCA),[196] ending years of uncertainty over the authority of FDA to regulate cigarettes and similar products. The TCA confirmed that authority, and extended it to the manufacture, marketing, distribution, and sale of regulated tobacco products. The TCA exempted covered items from the "safe and effective" standard applicable to drugs in favor of a public health balancing test. It applied immediately to a number of specified products containing tobacco, and permitted FDA by administrative action to "deem" others to be covered. FDA recently finalized a rule to exercise this power to extend its authority to e-cigarettes, cigars, and hookah and pipe tobacco.[197] Section 103 of the TCA made FDA enforcement provisions, including recall authority, generally applicable to tobacco products. Retailers are made subject to new statutory penalties, which increase with the frequency of violations to a maximum of $15,000 per violation and $1,000,000 for all violations adjudicated in a single proceeding. FDA took its first regulatory action under the TCA in 2015, issuing Warning Letters to manufacturers in connection with their marketing of cigarettes as "additive-free" or "natural,"[198] and prohibiting the further sale of other cigarettes found not to be "substantially equivalent" to a product already marketed.[199] In 2017, FDA issued 702 Warning Letters to tobacco retailers in New York State alone to enforce TCA provisions prohibiting the sale of certain newly regulated tobacco products to minors.[200]

Q 11.62 What are FDA's enforcement powers for genetically modified foods?

Commercial interest in genetically modified (GM) foods, and public interest in the sale of such products, has presented regulatory and enforcement challenges to FDA. The agency's general position is that GM foods are like any others, and are subject to overall requirements of safety. In connection with GM plant products, FDA since the early 1990s has maintained a voluntary Plant Biotechnology Consultation Program to evaluate new plant technologies before they are marketed. To date, more than 150 plant varieties have been evaluated under the program, with details relating to the reviews available on a public Biotechnology Consultations database.[201] GM foods are not subject to special labeling requirements, but FDA has issued a draft guidance and a final guidance on the voluntary labeling of GM foods, principally directed to manufactures that wish to note that their products are GM-free.[202] And it has opened a docket to receive comments on the use of the term "natural" in food labels, including GM foods.[203] In 2015, FDA approved its first GM animal for human consumption—a farm-raised salmon—regulating the recombinant DNA construct introduced into the animal as a drug.[204]

Q 11.63 What are FDA's enforcement powers to enforce preventative food safety requirements?

The 2011 Food Safety Modernization Act (FSMA)[205] was watershed legislation authorizing FDA to promulgate regulations and take enforcement actions to prevent food safety problems, not merely respond to them. The legislation created a new suite of enforcement authority, some unique to food safety. FDA's powers under FSMA include mandatory recall, expanded administrative detention, suspension of registration of food facilities, and the denial of entry for imported foods.[206]

Q 11.64 What are FDA's enforcement powers with respect to stem cell therapies and regenerative medicine?

In August 2017, FDA announced new policy and enforcement efforts with regard to stem cell therapies and regenerative medicine to address two issues. First, acknowledging "close calls" regarding the scope of its authority, FDA stated its desire to provide clear guidance to scientists as to the distinction between new products that are subject to FDA regulation and require prior approval and those, not regulated by the agency, that reflect "individualized treatments by a doctor within the scope of his medical practice."[207] Second, FDA announced heightened enforcement efforts against "unscrupulous actors" promoting "unproven and, in some cases, dangerously dubious" stem cell products.[208] Details regarding new or clarified FDA policies have yet to be announced.

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1. This chapter was originally prepared by Beth S. Rose, Vincent R. Lodato, and Brian N. ı from Sills Cummis & Gross P.C. Mr. Reznick and Ms. O'Connor have been responsible ·visions and updates since 2015.

2. U.S. FOOD AND DRUG ADMINISTRATION, REGULATORY PROCEDURES ıUAL (RPM), §§ 4-1-1, 4-1-10. All references to the RPM are current as of January 1, .

3. *Id.* Warning Letters are directed to the "highest known official" responsible for cting a company's product or procedure." RPM § 4-1-10.

4. RPM § 4-1-1. According to statistics posted on FDA's website, 17,232 Warning Letters issued in Fiscal Year 2015, representing a 98% increase over fiscal year 2014. *See* FDA rcement Statistics Summary Fiscal Year 2015, .fda.gov/downloads/ICECI/EnforcementActions/UCM484400.pdf.

5. The general remedial powers of FDA are set out in the FDCA, 21 U.S.C. § 360h tification and other remedies"). Note that in the FDA's Regulatory Procedures Manual, ıing Letters are described in the RPM chapter entitled "Advisory Actions."

6. *See* Recall Policy, 21 C.F.R. § 7.40.

7. RPM § 4-1-1. If the "significant regulatory infraction" is so severe that a Warning Letter d not alleviate the dangerous situation, then FDA does not use a Warning Letter. *See infra* .4.

8. *See* RPM § 4-1-3 ¶¶ 1–2. Compliance Policy Guides state FDA policy for particular ıct areas, and may provide "additional instructions for Warning Letters in specific product ." RPM § 4-1-1.

9. FDA maintains four Centers that assert authority over human drugs, medical devices and :co products: the Center for Biologics, Evaluation and Research; the Center for Devices and ɔlogical Health; the Center for Drug Evaluation and Research; and the Center for Tobacco ıcts. Meanwhile, the FDA's Office of Regulatory Affairs, which conducts the vast majority ɛ FDA's field activities, maintains five regional offices and twenty District Offices spread s the United States.

10. RPM §§ 4-1-3, 4-1-4.

11. 18 U.S.C. § 1001.

12. RPM § 4-1-1.

13. RPM § 4-1-10.

14. Richard M. Cooper & John R. Fleder, *Responding to a Form 483 or Warning Letter: A ical Guide*, 60 FOOD & DRUG L.J. 479, 490 (2005).

15. Some practitioners suggest seeking extra time to generate a thorough response, when a ɔany has a strong rebuttal to offer. On the other hand, a timely response may enhance 's view of the company and its faith in the company to correct the violations on its own. "It better to be right than to be quick," wrote Richard M. Cooper and John R. Fleder, both bers of the defense bar in Washington, D.C. That said, a timely response "helps persuade that the company has taken seriously the observed violations." *Id.*

16. *See* U.S. FOOD AND DRUG ADMINISTRATION, INSPECTIONS, ΛPLIANCE, ENFORCEMENT, AND CRIMINAL INVESTIGATIONS: WARNING ΓERS, www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.

17. RPM § 4-1-13.

18. *See supra* note 15.

19. *See id.*; RPM § 4-1-8 ¶ 3.

20. RPM § 4-1-8 ¶ 2.

21. *Id.*

22. 21 C.F.R. § 7.3(g).

23. 21 U.S.C. § 360h(e); 21 C.F.R. §§ 810.1–810.18.

24. Public Service Health Act, 42 U.S.C. § 262(d).

25. 21 U.S.C. § 350a(e)(1)(B); 21 C.F.R. § 107.200.

26. 21 U.S.C. § 387h(c).

27. 21 U.S.C. § 3501.

28. 42 U.S.C. § 264; 21 C.F.R. § 1271.440.

29. 21 U.S.C. § 360h(e).

30. 21 U.S.C. § 360h(e)(1)(A)–(B); 21 C.F.R. § 810.10.

31. 21 U.S.C. § 360h(e)(1)(B); 21 C.F.R. § 810.12.

32. It must do the same if, after a hearing, FDA nonetheless determines that "the order ıd be amended to require a recall of the device." 21 U.S.C. § 360h(e)(2)(A); 21 C.F.R.

).13.

33. 21 C.F.R. § 810.13(b).

34. 21 C.F.R. § 810.13(c)(1).

35. 21 C.F.R. § 810.13(c)(2); § 810.2(f) ("Device user facility means a hospital, ambulatory cal facility, nursing home, or outpatient treatment or diagnostic facility that is not a cian's office.").

36. Mobile Medical Applications, Guidance for Industry and Food and Drug inistration Staff (Sept. 25, 2013), .fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ 263366.pdf.

37. 42 U.S.C. § 262(d)(1).

38. 42 U.S.C. § 262(d)(2).

39. News Release, FDA, FDA requests removal of Opana ER for risks related to abuse (June 17), www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm.

40. 21 C.F.R. § 7.40(b)–(c).

41. 21 C.F.R. § 7.45.

42. 21 C.F.R. § 7.45(b); *see also* 21 C.F.R. § 7.42(a) on factors shaping FDA's recall gy.

43. 21 C.F.R. § 7.46(a).

44. 21 C.F.R. § 7.46(c).

45. 21 C.F.R. § 7.46(a)(1)–(9).

46. RPM § 7-5-1 ¶ 3.

47. 21 C.F.R. § 7.46(b); *see generally* RPM § 7-3.

48. 21 C.F.R. § 7.49. FDA will recommend changes to the submitted recall communication eded to comply with these requirements. 21 C.F.R. § 7.46(b).

49. *See* 21 C.F.R. § 7.49(c)(2); *see generally* RPM § 7-8-1. In circumstances where the pany is unable to check the effectiveness of its recall (because, for example, the recall extends e consumer-user level, confidential business records of customers are not accessible, and ulty cooperating with wholesalers, distributors, or retailers), FDA will directly assist with ffectiveness check. RPM § 7-8-1.

50. 21 C.F.R. § 7.50; *see* U.S. FOOD AND DRUG ADMINISTRATION, RECALLS, KET WITHDRAWALS, & SAFETY ALERTS, www.fda.gov/Safety/Recalls. The FDA ict Office will also inform other government offices about the recall. RPM § 7-7-2. FDA delay informing the public if the recall involves "certain drugs and devices . . . [and] the y determines that public notification may cause unnecessary and harmful anxiety in nts and that initial consultation between patients and their physicians is essential." 21 R. § 7.50. Detailed information about FDA's approach to informing the public of a recall e found in the agency's Regulatory Procedures Manual. RPM § 7-7-3.

51. 21 C.F.R. § 7.53.

52. 21 C.F.R. § 7.53(a)–(c); *see also infra* Q 11.16.

53. 21 C.F.R. § 7.53(b). The FDA's Regulatory Procedures Manual contains details on the

:y's auditing program for ongoing recalls. RPM § 7-8-2.

54. 21 C.F.R. § 7.41(a).

55. 21 C.F.R. § 7.3(m).

56. The evaluations are conducted by an informal committee of scientists. 21 C.F.R. 1(b).

57. *See* RPM § 7-7-3.

58. 21 C.F.R. § 7.3(m)(1)–(3).

59. 21 C.F.R. § 7.3(j).

60. *See id.*

61. 21 C.F.R. § 7.3(g).

62. 21 C.F.R. § 7.46(d).

63. 21 C.F.R. § 7.3(k).

64. 21 C.F.R. § 7.55(a).

65. 21 C.F.R. § 7.55(b).

66. RPM § 7-9.

67. *See* FDCA, 21 U.S.C. § 381(a) ("Imports and Exports").

68. *Id.*; RPM § 9-6.

69. RPM § 9-6.

70. *Id.*

71. *Id.*

72. *Id.*

73. 21 U.S.C. § 381(a)

74. RPM § 9-13.

75. *Id.*

76. *See* U.S. FOOD AND DRUG ADMINISTRATION, IMPORT ALERTS, .fda.gov/forindustry/importprogram/actionsenforcement/importalerts/default.htm. Each states: "[t]his import alert represents the Agency's current guidance to FDA field personnel ding the manufacturer(s) and/or product(s) at issue. It does not create or confer any rights r on any person, and does not operate to bind FDA or the public." *E.g.,* Detention Without ical Examination and Surveillance of Enriched Pasta Products for Standard of Identity, rt Alert # 04-06 (Dec. 29, 2016), www.accessdata.fda.gov/cms_ia/importalert_5.html.

77. *See, e.g., id.*

78. On this point, courts are generally deferential to the agency. *See* Ewing v. Mytinger & lberry, Inc., 339 U.S. 594, 600 (1950).

79. 21 U.S.C. § 334(a)–(b); United States v. Food, 2,998 Cases, 64 F.3d 984, 988 (5th Cir.) ("[T]o initiate an action for seizure and condemnation, FDA must prove only that the s have been introduced into interstate commerce, notwithstanding the fact that the goods be removed at some later time from interstate commerce."); *see also* RPM § 6-1.

80. *See* RPM § 6-1-3.

81. *Id.* ¶ 1.

82. *Id.* An open-ended seizure is prepared in the same manner as a standard lot-specific re.

83. *See* David F. Weeda, *FDA Seizure and Injunction Actions: Judicial Means of Protecting the c Health*, 35 FOOD DRUG COSMETIC L.J. 112, 118 (Feb. 1980). For the same reasons, treats such seizure recommends with special care. For example, it generally requires that nce of the conditions of the facility be no more than thirty days old when FDA refers the o the U.S. Attorney. RPM § 6-1-3 ¶ 3.

84. RPM § 6-1-3 ¶ 1.

85. *See* 21 U.S.C. § 334(a)(1)(A)–(B).

86. 21 U.S.C. § 334(a)(1).

87. Internal guidelines on when and how FDA implements a seizure action are located in the 's Regulatory Procedures Manual. RPM § 6-1-2.

88. RPM §§ 10-2-2, 10-2-3.

89. RPM § 6-1-2.

90. The designation of the home district depends on when the alleged violation occurred. If iolation occurred before the products were shipped, the home district is the location from n the products were shipped. If the violation occurred after the product was shipped, the e district is the location to which the products were shipped. *Id.*

91. *Id.*

92. *Id.*

93. 21 U.S.C. § 334(g)(1), (h)(2).

94. *Id.* The same power to detain and accompanying process applies to food products, as *Id.* § 334(h).

95. 21 U.S.C. § 334(a)–(b). A "libel of information" is borrowed from admiralty court and d to implement various seizure actions in the district courts. FDA proceeds under the lemental Rules for Certain Admiralty and Maritime Claims. RPM § 6-1-1.

96. Details on what the FDA District Office must include in this packet to the U.S. ney are found at RPM § 6-1-5 ¶ 1. Before being transferred to the U.S. Attorney by the ict Office in the seizing district, the recommendation is also reviewed by any/all appropriate ers within FDA, the Division of Compliance Management and Operations, and the Office ief Counsel. *See* RPM § 6-1-6 ¶¶ 2–4.

97. *See* RPM § 6-1-1.

98. United States v. Food, 2,998 Cases, 64 F.3d 984, 989 (5th Cir. 1995). If FDA seeks iple seizures (seizure actions in more than one district court at once) against a certain randed product, it must also show that it had probable cause to believe that the product is ful to consumers due to its misbranding, or otherwise harmful to health. *See* 21 U.S.C. (a)(1); United States v. Alcon Labs., 636 F.2d 876, 886 (1st Cir. 1981); *see also* Ewing v. nger & Casselberry, Inc., 339 U.S. 594, 595–96 (1950).

99. RPM § 6-1-8 ¶ 2.

100. RPM § 6-1-9.

101. RPM § 6-1-9 ¶ 6.

102. *See Food, 2,998 Cases*, 64 F.3d at 989.

103. RPM § 6-1-9 ¶ 3.

104. *Criminal Contempt for Allegedly Storing Dietary Supplements Under Insanitary Conditions*, LAW BLOG (June 7, 2011), .fdalawblog.net/fda_law_blog_hyman_phelps/2011/06/criminal-contempt-for-allegedly-ıg-dietary-supplements-under-insanitary-conditions.html.

105. *See, e.g.*, News Release, FDA, California dietary supplement maker, Cusompax ıbited from manufacturing (Oct. 13, 2015), .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm580369.htm.

106. *See* 21 U.S.C. § 332(a).

107. United States v. Universal Mgmt. Servs., 191 F.3d 750, 759–60 (6th Cir. Ohio 1999) g United States v. Park, 421 U.S. 658, 672 (1975)) (finding that an employee's "various s of independent authority" and "shared responsibility for the business process resulting in vful distribution" are sufficient to hold him criminally or civilly liable, and subject to an ction).

108. RPM § 6-2-4 ¶ 1.

109. RPM § 6-2-5.

110. *Id.*

111. *Id.*

112. RPM § 6-2-5 ¶ 1.

113. *E.g.*, United States v. N.Y. Fish, Inc., 10 F. Supp. 3d 355, 370 (E.D.N.Y. 2014); United s v. Organic Pastures Dairy Co., 708 F. Supp. 2d 1005, 1011 (E.D. Cal. 2010).

114. United States v. Barr Labs., Inc., 812 F. Supp. 458, 485 (D.N.J. 1993); *see also* United s v. Lane Labs-USA, Inc., 324 F. Supp. 2d 547, 571 (D.N.J. 2004).

115. United States v. Lane Labs-USA, Inc., 324 F. Supp. 2d 547, 571 (D.N.J. 2004) (citing ed States v. Barr Labs., Inc., 812 F. Supp. 458, 486 (D.N.J. 1993)). The court must be aded that, on the whole, injunctive relief is the proper remedy. *Id.* at 571 ("Because the ıage of [21 U.S.C.] section 332(a) is not mandatory, the Court retains discretion to grant or equitable relief.").

116. United States v. Organic Pastures Dairy Co., 708 F. Supp. 2d 1005, 1013 (E.D. Cal.).

117. *See generally* RPM § 6-2-3.

118. *See* 21 U.S.C. § 333(f).

119. It may only impose CMPs for a violation of the ban on food containing pesticide ıes (and the grower of the food is always exempted). *See* 21 U.S.C. § 333(f)(2).

120. 21 U.S.C. § 333(f)(1)(A) (italics added).

121. *See, e.g.*, News Release, FDA, Federal judge approves consent decree with Florida dietary lement distributor, Viruxo (Feb. 26, 2016), .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm488063.htm.

122. 21 U.S.C. § 333(f)–(g).

123. 21 U.S.C. § 333(b)(2).

124. 21 U.S.C. § 333(b)(1).

125. TMJ Implants, Inc. v. United States HHS, 584 F.3d 1290, 1302–03 (10th Cir. 2009) g United States v. Hodges X-Ray, Inc., 759 F.2d 557, 561 (6th Cir. 1985)).

126. Eric M. Blumberg, *Abbott Laboratories Consent Decree and Individual Responsibility r the Federal Food, Drug, and Cosmetic Act,* 55 FOOD DRUG L.J. 145 (2000) [hereinafter ıberg].

127. *See Park*, 421 U.S. at 672. *See also* Q 11.51.

128. *See* Blumberg, *supra* note 125.

129. 21 C.F.R. §§ 17.5, 17.7.

130. *Id.* §§ 17.9, 17.13; *see also* 21 U.S.C. § 333(f)(5)(A). The same regulations also provide :dures for fact-finding and motion practice before an Administrative Law Judge. *See* 21 R. §§ 17.23–17.32.

131. 21 U.S.C. § 360j(f).

132. 21 C.F.R. § 17.3(a)(1). If the violation of these laws rises to a "significant departure," ver, then the provision in § 333(f)(1)(B)(i)(I) exempting such violations from CMPs does pply.

133. *Id.* § 17.3(a)(2). In addition, the exemption for device maker violations from the device ing and correction reporting laws, 21 U.S.C. § 360i(e), (g), only applies if the violation is or," per 21 U.S.C. § 333(f)(1)(B)(ii). A minor violation "means departures . . . that do not ɔ a level of a single major incident or a series of incidents that are collectively :quential." 21 C.F.R. § 17.3(a)(3).

134. Even if a sales representative is convicted, a CMP may not be imposed against the ɔany if; (1) the company or any of its representatives provided information in aid of the :cution of the sales representative; (2) the company properly investigated the "events or ıctions" before the criminal proceeding began; or (3) the company had in place "an ɔendent audit and security system designed to detect such a violation (except where the sentative convicted was a supervisory employee). 21 U.S.C. § 333(b)(4)(B).

135. *See* 21 U.S.C. § 333(b), (g).

136. 21 U.S.C. § 333(f)(5)(B).

137. *Id.* at 11–12.

138. *Id.* at 11.

139. U.S. FOOD AND DRUG ADMINISTRATION, DIVISION OF COMPLIANCE ICY, REDUCTION OF CIVIL MONEY PENALTIES FOR SMALL ENTITIES, at 5, .fda.gov/OHRMS/DOCKETS/98fr/010049gd.pdf.

140. *Id.*

141. *Id.* at 8.

142. 21 U.S.C. § 333(g).

143. 21 U.S.C. § 333(g)(1), (3).

144. *E.g.*, 21 C.F.R. §§ 312.42(b), 312.70, 812.119.

145. 21 C.F.R. §§ 312.70, 812.119.

146. U.S. FOOD AND DRUG ADMINISTRATION, OFFICE OF THE

MISSIONER, OFFICE OF GOOD CLINICAL PRACTICE, INFORMATION ET GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS, CLINICAL ESTIGATORS, AND SPONSORS: CLINICAL INVESTIGATOR ADMINISTRATIVE IONS—DISQUALIFICATION (May 2010) [hereinafter DISQUALIFICATION DANCE], at 3–4.

147. United States v. Palazzo, M.D., 558 F.3d 400, 407–08 (5th Cir. 2009), *cert. denied*, zo v. United States, 130 S. Ct. 196 (2009)); *see also* United States v. Garfinkel, 29 F.3d 457 (8th Cir. 1994). *But see* United States v. Smith, 740 F.2d 734, 738 (9th Cir. 1984).

148. DISQUALIFICATION GUIDANCE, *supra* note 145, at 3–4.

149. *Id.* at 5.

150. *Id.* This "Part 16" hearing is preceded by a Notice of Opportunity for Hearing (NOOH) e investigator, which specifies a mandatory response time, and will be granted if there is any uine and substantial issue of fact that warrants a hearing." *Id.* at 5–6.

151. *Id.* at 7–8.

152. 21 C.F.R. § 312.42(a); *see also* 21 U.S.C. § 355(i)(3).

153. 21 C.F.R. § 312.42(d).

154. 21 U.S.C. § 355(i)(3)(B)(i)–(ii). The statute in subsection (ii) provides for additional nds for a clinical hold to be announced via duly enacted regulations.

155. *See* 21 C.F.R. § 312.42(b). The phase of a study is determined by the definitions found C.F.R. § 312.21, which are based on the goals and context of the study.

156. *Id.* § 312.42(b)(1).

157. *Id.* § 312.42(b)(2).

158. *Id.* § 312.42(b)(4). There are additional complexities in this list of potential grounds for ical hold, which are best understood by reading § 312.42 in its entirety.

159. *Id.* § 312.45 (" . . . all investigators shall be so notified and all stocks of the drug shall be ned or otherwise disposed.").

160. 21 U.S.C. § 355(i)(3)(C); 21 C.F.R. § 312.42(e).

161. 21 C.F.R. § 312.42(e). The company has no right to resume the trial upon the passing DA's thirty-day decision requirement.

162. *See* 21 C.F.R. § 312.44.

163. *See* 21 U.S.C. § 333(b).

164. *See id.* § 333(e).

165. *See id.* § 333(f).

166. *See id.* § 333(g).

167. News Release, FDA, Criminal and civil actions filed against Aegerion Pharmaceuticals . 22, 2017), www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577101.htm.

168. *See, e.g., id.* § 333(a).

169. *Id.* § 333(b)(7).

170. *See* Friedman v. Sibelius, 686 F.3d 813, 824 (D.C. Cir. 2012). *Cf.* Parrino v. Price, 869 392, 400 (6th Cir. 2017) (distinguishing *Friedman's* application of permissive debarment sion because the D.C. Circuit had not found offense to have involved a "program-related

:").

171. *See* United States v. Park, 421 U.S. 658, 670 (1975); United States v. Dotterweich, 320 277 (1943).

172. *See* United States v. DeCoster, 828 F.3d 626 (8th Cir. 2016). A senior U.S. Justice ırtment official indicated in a 2015 speech that civil as well as criminal actions against iduals remained a priority of the Department in investigations involving compliance with food and drug laws. *See also* Justice News, Principal Deputy Assistant Attorney General ımin C. Mizer Delivers Remarks at the 16th Pharmaceutical Compliance Congress and Practices Forum (Oct. 22, 2015), www.justice.gov/opa/speech/principal-deputy-assistant-ney-general-benjamin-c-mizer-delivers-remarks-16th ("[The Department of Justice] will from the outset of an investigation–on both the criminal and civil sides–on individuals.").

173. 21 U.S.C. § 355(e).

174. News Release, FDA, FDA requests removal of Opana ER for risks related to abuse (June 17), www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm.

175. *Id.*

176. *Id.*

177. 21 U.S.C. § 360e(e).

178. 21 U.S.C. § 355(e) (regarding drug applications); § 360e(e)(3) (regarding devices cations, the withdrawal of which only require an informal hearing); § 360(c) (providing for : on scientific matters from an ad hoc panel, a requirement of device application ırawals).

179. 21 U.S.C. § 355(g).

180. 21 U.S.C. § 355(h). This section sets out the requirements of the court filing, and states ɔnly objections that "have [already] been urged before the Secretary" can be heard on ıl, "unless there were reasonable grounds for failure to do so." *Id.*

181. *See* 21 U.S.C. § 360e(h).

182. 21 U.S.C. § 360e(g).

183. *In re* Canadian Imp. Antitrust Litig., 470 F.3d 785 (8th Cir. 2006); 21 U.S.C. § 355(a); .S.C. § 545.

184. *See, e.g.*, 21 U.S.C. §§ 331(i)(3), 333(b)(8).

185. The sale of adulterated and misbranded drugs may be prosecuted as misdemeanors or ies, depending on the circumstances. *See* 21 U.S.C. §§ 331(i), 333(a)(1) and (2). Illegal of controlled substances carry separate penalties and, notably for many online "rogue" nacies, the sale of such drugs without a valid prescription is a separate offense. 21 U.S.C. ɜ(b). OCI also has jurisdiction over violations of the U.S. Code implicated by illegal drug rts, including 18 U.S.C. §§ 542 (entry of goods by means of false statements), 543 (entry ods for less than legal duty), 545 (smuggling), 2320 (trafficking in counterfeit goods).

186. Press Release, U.S. Dep't of Justice, Chinese National Sentenced to Federal Prison for ïcking Counterfeit Pharmaceutical Weight Loss Drug (June 3, 2011), //www.fda.gov/ICECI/CriminalInvestigations/ucm257912.htm (manufacturer and rter); Press Release, U.S. Dep't of Justice, Distributor of Counterfeit Pharmaceutical Drugs

:nced (Jan. 15, 2009), www.fda.gov/ICECI/CriminalInvestigations/ucm261012.htm
:).

187. Press Release, U.S. Dep't of Justice, Nine Sentenced for Illegally Distributing Controlled :ances Over the Internet (Mar. 27, 2013), .justice.gov/usao/can/news/2013/2013_03_27_nine.sentenced.press.html.

188. Press Release, U.S. Dep't of Justice, Paul Daniel Bottomley Sentenced in U.S. District :t (July 12, 2013), www.fda.gov/ICECI/CriminalInvestigations/ucm360948.htm.

189. Press Release, U.S. Dep't of Justice, Alvarado Pharmacy and Owner Plead Guilty to :rting Unapproved Oncology Drugs and Fraudulently Billing Medicare (Dec. 4, 2013), .fda.gov/ICECI/CriminalInvestigations/ucm378038.htm.

190. Press Release, U.S. Dep't of Justice, Pakistani Man Sentenced in Counterfeit Viagra® and s® Case (May 2, 2014), www.fda.gov/ICECI/CriminalInvestigations/ucm397115.htm.

191. Press Release, U.S. Dep't of Justice, Local Oncology Practice Sentenced to Pay Millions Medicare Fraud (June 28, 2013), .fda.gov/ICECI/CriminalInvestigations/ucm359636.htm.

192. News Release, FDA, Second Turkish man sentenced for smuggling counterfeit drugs 23, 2015), www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm431343.htm.

193. News Release, FDA, FDA conducts major global operation to protect consumers from :tially dangerous prescription drugs sold online, .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577178.htm.

194. Drug Quality and Security Act, Pub. L. No. 113-54 (2013).

195. News Release, FDA, FDA issues new draft documents related to compounding of :n drugs (Feb. 13, 2015), .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm434270.htm.

196. Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31 (2009).

197. 81 Fed. Reg. 28,973 (May 10, 2016).

198. News Release, FDA, FDA takes action against three tobacco manufacturers for making :tive-free" or "natural" claims on cigarette labeling (Aug. 27, 2015), .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm459840.htm.

199. News Release, FDA, FDA issues order that will stop further U.S. sale and distribution of R.J. Reynolds Tobacco Company cigarette products (Sept. 15, 2015), .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm462407.htm.

200. A search engine allowing an examination of warning letters sent by FDA to tobacco :ct retailers following compliance checks may be found at: ://www.accessdata.fda.gov/scripts/oce/inspections/oce_insp_searching.cfm.

201. FDA, Biotechnology Consultations on Food from GE Plant Varieties, .accessdata.fda.gov/scripts/fdcc/?set=Biocon.

202. Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Been Derived from Genetically Engineered Plants (Nov. 2015), .fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm0590 :m; Draft Guidance for Industry: Voluntary Labeling Indicating Whether Food Has or Has

Been Derived from Genetically Engineered Atlantic Salmon (Nov. 2015), .fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm4698 :m.

203. 21 C.F.R. pt. 101.

204. AquAdvantage Salmon Approval Letter and Appendix (Nov. 19, 2015), NADA 141- .fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/Genetically neeredAnimals/ucm466214.htm.

205. Pub. L. No. 111-353, 124 Stat. 3885 (2011).

206. Information about FSMA and FDA's enforcement authority under it may be found at 's webpage devoted to the statute, .fda.gov/Food/GuidanceRegulation/FSMA/ucm359436.htm.

207. News Release, FDA, Statement from FDA Commissioner Scott Gottlieb, M.D. on the 's new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies egenerative medicine, .fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573443.htm.

208. *Id.*

12

Criminal Prosecution As a U.S. Food and Drug Administration Enforcement Tool

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The U.S. Food and Drug Administration (FDA) has pledged to "use any and all available enforcement tools" to safeguard public heal (DOJ) for prosecution th and welfare.[1] One of the most consequential of those tools is FDA's authority to conduct criminal investigations and refer cases to the U.S. Department of Justice (DOJ) for prosecution.

FDA-regulated products account for nearly a quarter of "all consumer spending in the United States annually."[2] Those products, though often capable of providing substantial benefits, have the potential to inflict significant harm on the nation's public health if not appropriately regulated.[3] The threat of criminal enforcement buttresses FDA's efforts to ensure voluntary compliance with federal laws regulating the safety of food, drugs, medical devices, tobacco products, and cosmetics.[4] Accordingly, as FDA explained in a July 2010 summary of the agency's enforcement strategy, "[a]ll FDA components are committed to swift, aggressive enforcement actions to protect the public health."[5] Given FDA's commitment to "aggressive enforcement," the complexities of the criminal law entrusted to FDA enforcement, and the scope of FDA's regulatory ambit, a keen understanding of FDA's criminal enforcement powers is critical for regulated industries. This chapter discusses FDA's role in criminal enforcement of the Federal Food, Drug, and Cosmetic Act (FDCA)[6] and other federal statutes under Title 18 of the U.S. Code.

This chapter first focuses on FDA's criminal investigations arm, the Office of Criminal Investigations (OCI), and the federal prosecutors and investigators with whom the OCI collaborates. Second, the chapter discusses the OCI's and its partners' techniques for investigating apparent criminal violations of the statutes within FDA's purview. Third, this chapter addresses the criteria that the OCI considers in determining whether to refer a case to DOJ for criminal prosecution and the factors that DOJ entities, including DOJ Civil Division's Consumer Protection Branch and local U.S. Attorneys' Offices, weigh in deciding whether to pursue criminal charges. Fourth, this chapter describes the criminal statutes that FDA enforces, addressing the elements of misdemeanor and felony violations of the FDCA and related statutes and the potential penalties that accompany conviction for those offenses. In that discussion, this chapter explains the *Park* doctrine, which exposes executives and employees of FDA-regulated organizations to criminal prosecution even absent proof of any criminal intent. Finally, this chapter highlights some of the severe

collateral consequences that may result from conviction of an FDA-related offense.

Criminal Enforcement: FDA's Office of Criminal Investigations and Other Governmental Agencies

Q 12.1 What roles do FDA's Office of Criminal Investigations and other governmental agencies play in FDA criminal enforcement?

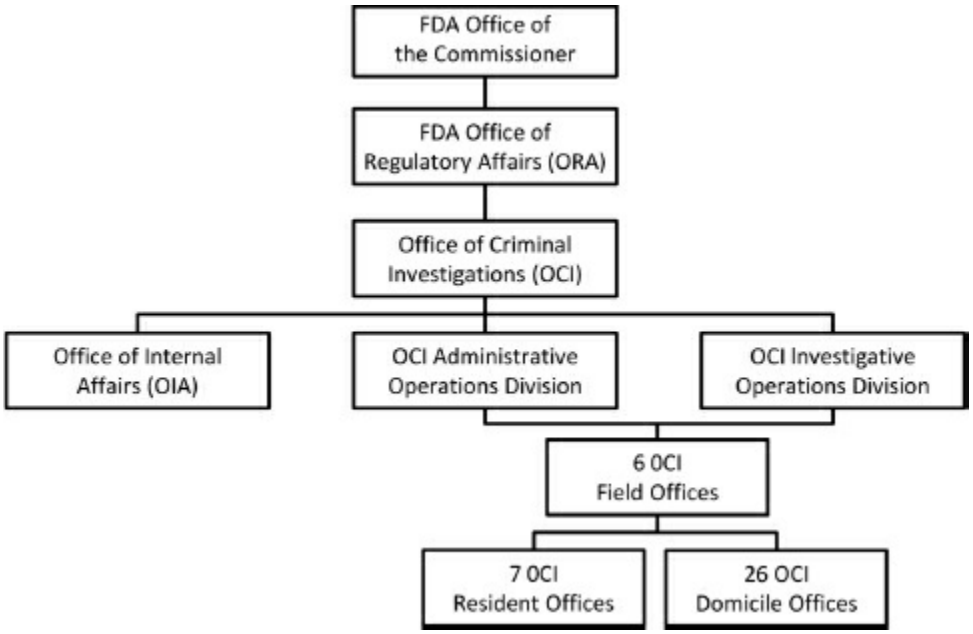
The Secretary of the U.S. Department of Health and Human Services (HHS) has empowered FDA to conduct criminal investigations relating to violations of the FDCA, the Federal Anti-Tampering Act (FATA),[7] "and other statutes including provisions of Title 18 of the U.S. Code."[8] Within FDA, the OCI handles any such investigations.[9]

Q 12.2 What is the structure and role of FDA's Office of Criminal Investigations?

The OCI was established in 1991 to "conduct and coordinate criminal investigations of violations" of FDA-related laws.[10] The OCI "review[s] all matters in FDA for which a criminal investigation is recommended, and is the focal point for all criminal matters."[11] "FDA personnel must refer all criminal matters, regardless of their complexity or breadth, to OCI."[12] The OCI, in turn, collaborates with various federal entities in conducting its criminal investigations and, ultimately, in pursuing convictions of those who violate the federal statutes within FDA's purview.[13] In fulfilling its role, the OCI prioritizes conduct that may endanger public health and welfare, including "[b]reaches in the legitimate medical supply chain . . . [involving] unapproved, counterfeit, and substandard medical products[,]" activities that "the normal regulatory process has been unable to remedy[,]" conduct "where the risk of harm to the public health is particularly significant and the only remedy appears to be through the criminal process," and misconduct "that prevents . . . FDA from being able to properly regulate" (such as false statements to FDA).[14] Through the OCI, FDA ensures that federal prosecutors bring to bear FDA's science-based regulatory expertise in criminal prosecutions under laws within the ambit of FDA's regulatory authority.

FIGURE 12-1

FDA's Organizational Structure for Conducting Investigations



Structurally, the OCI reports to FDA's Office of Regulatory Affairs (ORA).[15] The OCI comprises three subdivisions: (1) the OCI Administrative Operations Division; (2) the OCI Investigative Operations Division; and (3) the OIA, which investigates allegations involving FDA employees.[16] The Investigative Operations Division and the Administrative Operations Division together form a headquarters office; the OCI also maintains six field offices throughout the United States.[17] The OCI field offices generally conduct investigations, and each investigation culminates in a decision as to whether to refer the case to the local U.S. Attorney's Office or DOJ's Consumer Protection Branch for prosecution.[18] Notably, FDA itself cannot file charges, but must refer cases to attorneys within DOJ for prosecution.[19] However, attorneys from FDA's Office of the Chief Counsel not only liaise with DOJ during criminal litigation, but also may be appointed as Special Assistant U.S. Attorneys to "assum[e] primary responsibility for prosecuting violations of the FDCA or related statutes."[20]

Q 12.3 What efforts has FDA undertaken to improve the Office of Criminal Investigations?

Since 2009, FDA has made concerted efforts to improve the performance of the OCI. A January 2010 Government Accountability Office (GAO) review of OCI spurred several improvement initiatives. Among other measures, FDA continues to threaten an increased use of misdemeanor prosecutions to target responsible corporate officers and has developed quantitative performance metrics that will allow FDA to monitor the OCI's success in investigating criminal misconduct.[21]

During the course of its review, GAO examined "FDA's (1) oversight of OCI investigations[;] (2) oversight of the OIA investigations[;] and (3) the funding, staffing, and workload of OCI."[22] Among other observations, GAO found that "FDA's oversight of OCI's criminal investigations [was] limited" and that "FDA lack[ed] performance measures

that could enhance its oversight of OCI by allowing it to assess OCI's overall success."[23] The GAO thus recommended that FDA "regularly monitor OCI, and establish performance measures for OCI to assess whether OCI is achieving its desired results."[24] The GAO report acknowledges that it may prove difficult to link precisely the OCI's efforts to statistics such as convictions, but noted that other federal investigative agencies have developed such performance measures.[25]

In response to the GAO audit, FDA formed an internal committee to address the GAO's findings and ultimately agreed with the majority of the GAO's recommendations.[26] In a letter to Senator Charles E. Grassley, FDA listed responsive recommendations from an internal FDA committee, including increasing "the appropriate use of misdemeanor prosecutions . . . to hold responsible corporate officials accountable."[27] Further, in light of the GAO's findings, FDA agreed to develop meaningful performance metrics, to compile that data quarterly through an FDA-wide initiative called "FDA-TRACK," and to review that data quarterly.[28] FDA apparently has struggled to identify quantitative measures of OCI's performance. To date, FDA-TRACK's data on the OCI's performance includes quarterly information regarding the "[c]umulative number of convictions" for violations of the FDCA and the "[c]umulative amount of money recovered through OCI actions," as well as monthly data on the "[n]umber of U.S. Attorney press releases issued relative to OCI investigative activities."[29]

Q 12.4 What role does the U.S. Department of Justice play in prosecuting criminal violations of statutes within FDA's purview?

Because FDA lacks the authority to initiate criminal charges, DOJ is an indispensable partner in FDA's criminal enforcement efforts.[30] By regulation, "[a]ll civil and criminal litigation and grand jury proceedings arising under the [FDCA]" are entrusted to DOJ's Civil Division.[31] Part of that point deserves emphasis: Attorneys within DOJ's *Civil Division* prosecute *criminal* violations of the FDCA. FDCA enforcement is a specialized area, and FDCA violations are both civil and criminal in nature.[32]

The OCI refers cases for prosecution to the Consumer Protection Branch (formerly the Office of Consumer Protection Litigation) of DOJ's Civil Division.[33] The Consumer Protection Branch is responsible for litigating civil and criminal cases under the FDCA and is empowered to decide whether to file criminal charges at the OCI's behest.[34] After receiving an FDA referral, the Consumer Protection Branch coordinates with a local U.S. Attorney's Office where the criminal case is likely to be filed.[35] Whereas the U.S. Attorney's Office files cases in its own districts, the Consumer Protection Branch may litigate in federal courts nationwide.[36] After FDA makes a criminal referral, DOJ attorneys control the investigation, and FDA investigators "become in effect agents of the DOJ or [a] grand jury."[37]

Q 12.5 How do FDA's criminal enforcement efforts relate to those of the

Department of Health and Human Services' Office of the Inspector General?

Although HHS has "granted FDA the authority to conduct investigations of alleged criminal activity related to FDA-regulated products[,]" the OIG retains the authority to "conduct investigations of FDA-regulated entities and to investigate cases involving FDA employees."[38] The OIG's authority supersedes FDA's authority, and the OIG therefore may "investigate a case independently, jointly with FDA, or decline to investigate a case, which allows FDA to investigate the case independently."[39] The OIG also "focuses on investigating FDA-regulated entities when HHS programs—such as Medicare and Medicaid— . . . are involved."[40]

The OIG's significant leverage in handling FDCA enforcement arises from its statutory "exclusion" authority and the use of the federal False Claims Act in conjunction with DOJ.[41] By statute, in certain circumstances, the OIG must ban companies and individuals from participating in the federal health care programs ("mandatory exclusion"); in certain other circumstances, the OIG may exercise its discretion through an administrative process to prohibit such participation ("permissive exclusion") and to ban companies who employ the convicted individuals from participating in Medicare and Medicaid programs.[42] (See Q 12.31 below for additional information about exclusion.) If a company seeks, as part of a resolution of an enforcement matter, to include a waiver of the OIG's permissive exclusion administrative remedy, the company generally must agree to a Corporate Integrity Agreement of several years.[43]

In addition to coordinating with FDA and independently investigating FDCA offenses, the OIG also partners with DOJ through the Health Care Fraud Prevention & Enforcement Action Team (HEAT).[44] The initiative is a collaborative effort among "top level law enforcement agents, prosecutors, attorneys, auditors, evaluators, and other staff from DOJ and HHS" to: (1) "marshal significant resources across government to prevent waste, fraud, and abuse in the Medicare and Medicaid programs[;]" (2) "reduce health care costs and improve the quality of care by ridding the system of perpetrators who are preying on Medicare and Medicaid beneficiaries[;]" (3) "highlight best practices by providers and public sector employees who are dedicated to ending waste, fraud, and abuse in Medicare[;]" and (4) "build upon existing partnerships between DOJ and HHS . . . to reduce fraud and recover taxpayer dollars."[45] As part of the HEAT initiative, the government constituted Medicare Fraud Strike Force teams, including investigators and prosecutors, in nine areas (eight states) across the country.[46] These teams utilize investigative resources from the OIG and the Federal Bureau of Investigation (FBI) and prosecutorial support from DOJ's Criminal Fraud Section and U.S. Attorneys' Offices.[47]

Under the HEAT initiative, federal regulators have successfully executed significant enforcement actions in recent years. In June 2016, for example, DOJ announced that HEAT's Medicare Fraud Strike Force conducted "an unprecedented nationwide sweep" across thirty-six federal districts that resulted in criminal and civil charges against more than

300 individuals.[48] According to DOJ, these individuals allegedly participated in schemes involving almost $900 million in false billings, violations of anti-kickback statutes, money laundering, and aggravated identity theft.[49]

The HEAT initiative and Medicare Fraud Strike Force operations have continued under the Trump administration. In September 2017, for instance, DOJ announced an enforcement action against the owner of two New York medical clinics for paying kickbacks to induce patients to attend her clinics.[50] After pleading guilty, the owner received a sentence of eighty-four months in prison and was ordered to forfeit almost $30 million.[51] Twenty other individuals also pled guilty to related charges in connection with the case.[52]

Since its creation in March 2007, the Medicare Fraud Strike Force has charged nearly 2,100 defendants for more than $6.5 billion in allegedly fraudulent health care billings.[53]

Q 12.6 How does FDA collaborate with other agencies on criminal investigations?

Robust FDA criminal enforcement depends on successful partnerships among FDA, DOJ, and various other federal entities. As explained above, the OCI collaborates closely with DOJ attorneys to prepare criminal cases. When the OCI is keen on "pursuing an investigation toward prosecution, the agency typically works with the U.S. Attorney's Office to develop potential investigative strategies which will tend to increase the likelihood of developing admissible evidence necessary to facilitate prosecution."[54]

In practice, the OCI may partner with a wider range of federal agencies. For instance, in the course of an investigation from 2008 through June 2009 the OCI and FDA district offices "participated in two ambitious investigative operations (codenamed: 'Guardian' and 'Apothecary') in conjunction with ICE [U.S. Immigration and Customs Enforcement], CBP [U.S. Customs and Border Protection], . . . and other agencies."[55] The investigations led to the filing of more than sixty criminal cases charging importers of products such as toothpaste, unapproved and counterfeit drugs, and contaminated food products.[56] Similarly, in 2017, OCI partnered with the U.S. Attorney's Office for the District of Utah, the Drug Enforcement Administration, the Internal Revenue Service, the U.S. Postal Inspection Service, and special agents from the Department of Homeland Security in an investigation of an alleged international drug trafficking ring.[57] The probe resulted in six indictments of individuals who allegedly participated in manufacturing fake prescription drugs from Fentanyl.[58]

Notably, FDA collaborates with the U.S. Department of Agriculture (USDA) and the FBI under a specific statutory mandate. Under the FATA, "[i]n addition to any other agency which has authority to investigate violations of this section, the Food and Drug Administration and the Department of Agriculture, respectively, have authority to investigate violations . . . involving a consumer product that is regulated by a provision of law such Administration or Department, as the case may be, administers," although the

scope of these investigative powers is circumscribed.[59] FDA's *Investigations Operations Manual* (IOM) provides guidance to FDA personnel regarding this collaboration, and the roles and responsibilities of the agencies with a stake in FATA enforcement. As stated in the IOM, "FDA understands the FBI's primary interest in the FATA matters will be to investigate; particularly, those cases which involve a serious threat to human life or a death."[60] As to cooperation with the USDA, the IOM explains that "[i]f a counterfeiting/tampering complaint or report is made to an FDA District office and involves a USDA regulated product, the District office should report it directly to the USDA . . . ."[61]

Further, FDA and the Federal Trade Commission jointly regulate advertisements regarding over-the-counter drugs, devices, cosmetics, and food.[62] The range of agencies that assist each other in FDCA investigations may also include the Department of Defense, the U.S. Postal Service, and, particularly with respect to cases involving food or the Medicaid program, state inspectors, agents, and attorneys general.

Many of FDA's federal, state, and local inter-agency partnerships are rooted in formal and informal agreements that further collaboration. FDA's agreements and memoranda of understanding with other agencies "provide for more efficient use of FDA and other agency manpower and resources and . . . prevent duplication of effort . . . ."[63] Although a review of these agreements between FDA and other agencies may give companies insight into the FDCA enforcement authority of various government agencies,[64] OCI agreements and understandings are exempt from public disclosure requirements because they may contain confidential investigative techniques.[65] Nonetheless, the OCI inter-agency agreements may be disclosed upon request if such information is excised.[66]

FDA Criminal Investigations

Q 12.7 How does the Office of Criminal Investigations conduct its investigations?

Upon receiving an allegation or lead that warrants investigation, OCI investigators complete a Case Initiation Report and send the report to OCI headquarters for review.[67] OCI headquarters then decides whether a case should be opened based on the information in the report.[68] If OCI headquarters decides to open a case, a case number is assigned, and OCI investigators commonly begin their inquiry by reviewing consumer complaints and conducting detailed interviews with victims or witnesses.[69] Further, the OCI has been designated to administer FDA's consensual electronic surveillance program, but to comply with FDA Policy and DOJ mandates, OCI personnel must contact the appropriate field office to request approval before using electronic surveillance.[70]

In practice, the OCI sometimes employs aggressive investigative techniques. For example, OCI investigators and other federal agents have conducted operations at national sales meetings for pharmaceutical companies. During some of those operations, OCI cooperators have worn wires, and the OCI has established command and control centers in the hotels in which the meetings were held, allowing the OCI to pull meeting attendees aside to attempt to conduct interviews.

The OCI and its partner investigative agencies often use corporate whistleblowers, who have financial incentives under the federal False Claims Act's *qui tam* provisions, to gain access to a corporation's communications. For example, in coordination with the OCI and other agencies, a former sales representative of a pharmaceutical company (who had brought suit as a *qui tam* relator alleging that her company promoted a drug off-label) "wore a wire to surreptitiously record over two hundred (200) hours of conversations" with her colleagues and managers and provided the government a "bounty of documentary evidence."[71]

In addition, OCI investigators sometimes attend industry conferences and approach pharmaceutical booths to talk to company representatives and request product information. Investigators also might visit the homes of company employees after hours to attempt to obtain interviews. In the past, agents from the OCI and other agencies on occasion have coordinated visits to the homes of company employees and former employees, enabling the government to contact hundreds of potential witnesses almost simultaneously.

Although the OCI has the capacity to handle many aspects of a criminal investigation, the OCI must enlist DOJ to use grand jury subpoenas, search warrants, immunized testimony, and other investigative techniques that are entrusted exclusively to DOJ or are subject to court approval.[72]

To resolve a case, the OCI "requires that its criminal investigators document the outcome of each investigation in a closing [Report of Investigation], including any legal

action taken against subjects that are charged with criminal offenses."[73]

Q 12.8 What subpoena powers may the government invoke when investigating offenses within FDA's purview?

Federal enforcers may invoke several statutory grants of authority to subpoena documents and testimony during the course of investigations of FDA-related offenses. Four specific subpoena powers merit discussion.

The government may, of course, invoke the powers of a grand jury to "compel the production of evidence or the testimony of witnesses as [the grand jury] considers appropriate."[74] Information gathered by means of a grand jury subpoena is, however, subject to the confidentiality provisions of Federal Rule of Criminal Procedure 6(e).[75] Such information cannot be disclosed in a civil investigation without a court order.[76] Because FDA-related investigations (especially with regard to federal False Claims Act violations) often involve both civil and criminal components, the government tends to favor a compulsory process that is not subject to such restrictions.

For example, the government may use administrative subpoenas under the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA authorizes the government to issue administrative subpoenas in the investigation of a federal health care offense.[77] The Patient Protection and Affordable Care Act of 2010 modified the definition of "health care offense" to include the acts prohibited under section 301 of the FDCA.[78] Information obtained pursuant to a HIPAA subpoena may be used in both civil and criminal proceedings. HIPAA subpoenas may require: (1) the production of any records or other things relevant to the investigation; and (2) testimony by the custodian of the subpoenaed documents or items concerning the production and authenticity of the documents or items.[79]

Similarly, as amended by the Safe Medical Devices Act of 1990, the FDCA authorizes FDA to issue administrative subpoenas that require medical device manufacturers to produce documents or provide testimony regarding a "matter under investigation."[80] Despite the expanded reach of HIPAA subpoenas for investigation of FDCA offenses, FDA's own administrative subpoena power is unique to medical devices.[81]

U.S. Attorneys also may issue Civil Investigative Demands (CIDs), which are similar to HIPAA subpoenas. The federal False Claims Act authorizes CIDs, and such demands may require recipients to: (1) produce documentary material for inspection and copying; (2) answer in writing written interrogatories with respect to such documentary material or information; (3) give oral testimony concerning such documentary material or information; or (4) furnish any combination of such material, answers, or testimony.[82] Before 2010, only the U.S. Attorney General could authorize the issuance of CIDs; that year, however, then-Attorney General Eric Holder delegated his authority to issue CIDs to the U.S. Attorneys.[83] Since that time, the use of CIDs has become more common.

Finally, there are numerous situations in which companies produce information to the government, and individual witnesses appear for interviews, pursuant to a government

request that they do so voluntarily. In such situations, counsel must assess the rules governing the protection of confidential documents produced voluntarily rather than in response to compulsory process. Counsel also must consider issues relating to the representation of individual witnesses and the need to request a grant of immunity.

Q 12.9 How do routine FDA inspections intersect with FDA's criminal enforcement goals?

FDA may conduct warrantless administrative inspections pursuant to section 704 of the FDCA.[84] Such inspections may be routine periodic inspections for compliance or directed "for cause" inspections relating to a specific issue, such as a product safety issue raised to FDA's attention by a consumer or patient complaint.[85] By statute, FDA must conduct section 704 inspections "at reasonable times and within reasonable limits and in a reasonable manner . . . ."[86] FDA's findings from such inspections generally may form the basis of criminal charges despite the restrictive language of section 703 of the FDCA.[87] Indeed, FDA's IOM states that "[i]nspections conducted in accord with this responsibility to protect the public and limited in scope to the authorizing statute are lawful even when criminal action is being considered or pursued."[88] Although criminal defendants may argue that an inspection was a pretext for an otherwise impermissible warrantless search, if an inspection was conducted within the bounds of section 704 and "normal establishment inspection procedures," then it is unlikely that a court would suppress the evidence.[89] The courts generally have upheld such inspections against Fourth Amendment challenges on the ground that entities within FDA's regulatory realm are "heavily regulated."[90]

Federal Criminal Charges

Prerequisites for Filing Charges

Q 12.10 When does an FDA investigation result in criminal charges?

As explained above, the decision to pursue federal criminal charges against an individual or entity depends on two prerequisites: (1) FDA's determination that criminal prosecution is warranted; and (2) DOJ's willingness to file charges.

The questions and answers below address the factors that inform those two key decisions. Further, this discussion raises some of the issues that attend the decision to prosecute particular individuals and corporate entities.

FDA's Determination to Pursue Criminal Prosecution

Q 12.11 How does FDA determine whether to recommend criminal charges?

As explained below, various statutes, regulations, and internal policies guide the OCI in its exercise of discretion.

Q 12.11.1 What is a section 305 notice under the FDCA?

Section 305 of the FDCA provides that before FDA reports "any violation of th[e] [FDCA] . . . to any United States attorney for institution of a criminal proceeding," FDA must give to the individual or entity suspected of the violation "appropriate notice and an opportunity" to respond.[91] The suspect may opt not to respond, to respond in writing, or to meet with OCI personnel with or without counsel present to give "information and views to show cause why criminal prosecution should not be recommended to a United States Attorney."[92]

In certain circumstances, however, FDA is not required to provide notice pursuant to section 305. For instance, if the OCI's investigation relates to potential violations of Title 18 of the U.S. Code, as opposed to the FDCA, FDA need not provide a section 305 notice.[93] Nor must FDA give notice if the agency believes that notice might trigger the destruction of evidence or a suspect's flight to avoid charges.[94] Lastly, when the OCI is merely recommending that the Consumer Protection Branch or local U.S. Attorney's Office conduct additional investigation, FDA typically does not provide a section 305 notice.[95] Despite section 305's mandatory language, the courts have determined that such hearings are not a prerequisite to prosecution.[96] In practice, section 305 hearings rarely, if ever, occur.

Q 12.11.2 *What factors does the Office of Criminal Investigations consider in*

determining whether to recommend criminal charges?

On January 26, 2011, FDA issued revised guidelines relating to the process for referring matters to DOJ prosecutors. The prior version of FDA's *Regulatory Procedures Manual* stated, "With the exception of prosecution recommendations involving gross, flagrant, or intentional violations, fraud, or danger to health, each recommendation should ordinarily contain proposed criminal charges that show a continuous or repeated course of violative conduct."[97] FDA excised that language from the new guidelines, thereby expanding the discretion of the OCI to refer criminal matters. Nonetheless, factors such as the severity of the offense, the danger to public health, and the defendant's repeated course of misconduct will likely continue to influence the decision to refer matters to the local U.S. Attorney's Office or the Consumer Protection Branch.[98]

The *Regulatory Procedures Manual* also includes a new set of special procedures and considerations intended to guide the OCI as it considers potential FDCA prosecutions under the *Park* doctrine, which holds a responsible corporate officer liable for misdemeanor FDCA violations even if the prosecution cannot show that the official acted with criminal intent.[99] The *Park* doctrine and the special considerations relating to referrals for prosecutions under the doctrine are discussed below in Q 12.23, Q 12.24, and Q 12.25.

DOJ's Willingness to Bring Charges

Q 12.12 What factors do the Consumer Protection Branch and the U.S. Attorneys' Offices consider in determining whether to bring criminal charges for FDA-related offenses?

In deciding whether to prosecute an individual or corporate entity on the OCI's recommendation, the Consumer Protection Branch and U.S. Attorneys' Offices consider many factors ranging from over-arching DOJ policy priorities, to the impact of the alleged crime, to the strength of the OCI's case file.

First, "national prosecution priorities set by the [DOJ] based on a national assessment of crime problems" may impact the decision to pursue charges.[100] Among other recent initiatives, DOJ has prioritized anti-fraud enforcement actions, efforts to confront the opioid crisis, and enforcement actions against compounding pharmacies.

Although federal resources are spread thin, criminal enforcement of anti-fraud laws—in particular those relating to health care fraud and abuse—remains a DOJ priority.[101] In this spirit, the Consumer Protection Branch "attempts wherever possible to bring felony charges to deal with fraudulent behavior" relating to FDA-regulated products.[102]

- DOJ recently has prioritized initiatives to quell the opioid crisis. Both Attorney General Jeff Sessions and FDA Commissioner Dr. Scott Gottlieb have noted that combatting the growing opioid epidemic is now a top DOJ and FDA priority.[103] In August 2017, DOJ created the Opioid Fraud and Abuse Detection Unit to leverage data analytic techniques to "identify and prosecute individuals that are contributing to this prescription opioid epidemic," including those who operate "pill mill schemes and pharmacies that unlawfully divert or dispense prescription opioids for illegitimate purposes."[104] On February 28, 2018, DOJ announced that it would devote additional resources to its efforts to address the opioid epidemic, announcing that it had formed a DOJ "Prescription Interdiction & Litigation (PIL) Task Force, to fight the prescription opioid crisis."[105] According to DOJ, the PIL Task Force "will aggressively deploy and coordinate all available criminal and civil law enforcement tools to reverse the tide of opioid overdoses in the United States," with a particular focus on opioid manufacturers and distributors.[106]

- DOJ's focus on the opioid crisis has generated results. In July 2017, for instance, DOJ announced the largest health care enforcement action in DOJ history; the enforcement action involved 412 individuals responsible for $1.3 billion in false health care billings.[107] Roughly 120 defendants in that action were charged for unlawful prescription and distribution of opioids and other narcotics, which had

resulted in hundreds of millions of dollars of false health care billings.[108]

- In addition to escalating its fight against opioid abuse, DOJ has targeted compounding pharmacies.[109] In June 2017, for example, DOJ indicted two compounding pharmacy executives for conspiring to defraud the United States and for violations of the FDCA, including distributing an adulterated drug in interstate commerce.[110] According to the government, the pharmacy, Pharmakon, received numerous notices indicating that its drugs, including morphine sulfate and fentanyl, were either under- or over-potent.[111] Despite receiving these notices, Pharmakon allegedly decided not to contact recipients of its drugs or issue any product recalls.[112] According to the government, several infants subsequently received injections of overly potent drugs compounded by Pharmakon; the government alleged that some of the drugs had nearly twenty-five times the indicated strength on the product's label.[113] In November 2017, Pharmakon's compliance director, one of the two executives indicted in the case, pled guilty to introducing adulterated drugs into interstate commerce and conspiracy to defraud the United States.[114]

Second, local U.S. Attorneys' Offices "may establish their own investigative and prosecutorial priorities based on local crime problems and the needs of the local community."[115] Although the U.S. Attorneys' Offices presumably align their priorities with nationwide DOJ initiatives, this factor may also influence a prosecutor's charging decision.

Third, the nature of the alleged crime and the strength of the case are pivotal factors. Ultimately, a U.S. Attorney is empowered to "decline prosecution in any case referred directly to him/her by an agency unless a statute provides otherwise."[116]

Q 12.13 What individuals will federal prosecutors target for violations of the FDCA?

U.S. prosecutors "normally name[]" as defendants both the individuals responsible for the criminal activity and the "corporate entit[y] through which crimes are committed."[117] More specifically, the Consumer Protection Branch targets "the highest ranking officials in a firm who made decisions that violated the law, along with others who actively participated in fraudulent activity."[118] Accordingly, FDCA criminal cases often include both senior executives and operational personnel.[119] Generally, a corporate entity's decision to plead guilty is "not a basis for dismissal of charges against an individual."[120]

A September 9, 2015, memorandum issued by former Deputy Attorney General Sally Quillian Yates underscores that DOJ is focused on targeting individuals for corporate crimes and civil violations.[121] The so-called Yates Memorandum sets forth "six key steps to strengthen [DOJ's] pursuit of individual corporate wrongdoing."[122] Four of the six steps are particularly relevant to potential criminal liability for individuals.

First, the Yates Memorandum conditions "any cooperation credit" on whether

corporations "provide to the [DOJ] all relevant facts about the individuals involved in corporate misconduct."[123] Second, the Memorandum instructs that criminal and civil investigations should focus on potentially liable individuals from the start of the investigation, to ensure that DOJ can determine "the full extent of corporate misconduct," leverage cooperation from those with relevant information, and increase the likelihood of criminal or civil charges against the corporation and any responsible individuals.[124] Third, the Memorandum provides that corporate resolution documents may not contain "an agreement to dismiss charges against, or provide immunity for, individual officers or employees" unless there are "extraordinary circumstances."[125] Finally, the Yates Memorandum states that "[c]orporate cases should not be resolved without a clear plan to resolve related individual cases before the statute of limitations expires and declinations as to individuals in such cases must be memorialized."[126]

The Yates Memorandum does not alter the factors that federal prosecutors weigh in deciding whether to prosecute individuals for violations of the FDCA (and other criminal statutes within FDA's ambit). But the Memorandum nevertheless signals DOJ's eagerness to target individuals associated with corporate wrongdoing.

The Trump administration has signaled, however, that the Yates Memorandum and similar guidance may soon be revised. In an October 2017 speech, for instance, Deputy Attorney General Rod Rosenstein noted that the Yates Memorandum was one prior DOJ policy currently "under review" by the Trump administration.[127] Although he provided little insight on potential revisions, he emphasized that "[a]ny changes will reflect [DOJ's] resolve to hold individuals accountable for corporate wrongdoing," but added that "the government should not use criminal authority unfairly to extract civil payments."[128] Deputy Attorney General Rosenstein also focused on ensuring that DOJ policies are clear, a theme he returned to in a November 2017 speech: "[I]n most instances, the substance of a policy should be in the United States Attorneys' Manual, and it should be readily understood and easily applied by busy prosecutors."[129]

Q 12.14 How do federal prosecutors decide whether to bring criminal charges against a corporate entity?

On January 20, 2003, DOJ issued the *Principles of Federal Prosecution of Business Organizations*, which sets forth the factors that DOJ considers when determining whether to prosecute a U.S. company. In each subsequent iteration of the *Principles*, important factors to be considered by DOJ are whether the corporation made a "timely and voluntary" disclosure, and the corporation's willingness to provide relevant information and evidence and identify relevant actors within and outside the corporation, including senior executives.[130] Other factors include the pervasiveness of misconduct within the company, the company's history, the quality of the company's corporate compliance program, the company's commitment to pay restitution or remediation, and the collateral consequences to the company of an indictment.[131]

In response to concerns about federal prosecutors' pressure on companies to waive

privilege to demonstrate their "willingness to cooperate," then-Deputy Attorney General Mark Filip published revisions to the *Principles* on August 28, 2008.[132] The so-called Filip Memorandum significantly revised DOJ's definition of cooperation, stating that "[e]ligibility for cooperation credit is not predicated upon the waiver of attorney-client privilege or work product protection."[133] Accordingly, prosecutors "should not ask for such waivers and are directed not to do so."[134] The Filip Memorandum also instructs that prosecutors "should not take into account whether a corporation is advancing or reimbursing attorneys' fees or providing counsel to employees[.]"[135]

The Filip Memorandum nonetheless underscores that to secure cooperation credit a corporate entity may need to provide factual information, even if the entity obtained that information during the course of an internal investigation conducted by counsel.[136] In certain circumstances, disclosing such information may result in a subject-matter waiver of the entity's attorney-client privilege or work product protection, so such decisions must be made advisedly. In addition, as discussed above in Q 12.13, the September 9, 2015 Yates Memorandum raises the bar for corporations seeking cooperation credit: "To be eligible for any cooperation credit, corporations must provide to the [DOJ] all relevant facts about the individuals involved in corporate misconduct."[137]

Notably, the Trump administration has signaled a new approach to guidance documents like the Filip and Yates memoranda that may have significant implications for DOJ as it evaluates potential enforcement actions and pursues such actions in court. In a November 2017 memorandum detailing new procedures for DOJ guidance documents, Attorney General Sessions directed that guidance "may not be used to impose new requirements on entities outside the Executive Branch" or to "create binding standards by which [DOJ] will determine compliance with existing regulatory or statutory requirements."[138]

Then-Associate Attorney General Rachel Brand elaborated on these directives in a January 25, 2018 memorandum (the "Brand Memorandum") regarding the use of other government agencies' guidance documents in DOJ's civil lawsuits (e.g., actions under the False Claims Act).[139] FDA and HHS (like other agencies) regularly issue guidance interpreting statutes they administer, and DOJ has historically used failures to comply with these guidance documents to prove violations of the FDCA and health care fraud and abuse laws. The Brand Memorandum bars DOJ attorneys from doing so in civil suits, stating that DOJ litigators:

- "may not use [DOJ's] enforcement authority to effectively convert agency guidance documents into binding rules"; and
- "should not treat a party's noncompliance with an agency guidance document as presumptively or conclusively establishing that the party violated the applicable statute or regulation."[140]

In light of Attorney General Sessions' directive and the Brand Memorandum, corporate (and individual) defendants confronting DOJ investigations and enforcement actions can challenge executive efforts to redraw the legal bounds set by Congress.

Q 12.15 What tools can federal prosecutors use to settle criminal charges against corporations?

In lieu of pursuing criminal convictions against companies accused of violations of the FDCA or related health care offenses, U.S. prosecutors frequently negotiate deferred prosecution agreements (DPAs) or non-prosecution agreements (NPAs) to achieve institutional changes without criminal litigation and the severe consequences of convictions. As noted in Q 12.14, DOJ may consider the collateral consequences of a prosecution in deciding whether to pursue criminal charges against a corporation. For example, federal prosecutors may take into account "the possibly substantial consequences to a corporation's employees, investors, pensioners, and customers, many of whom may . . . have played no role in the criminal conduct, have been unaware of it, or have been unable to prevent it."[141] Where the potential collateral consequences of a corporate conviction "for innocent third parties would be significant," federal prosecutors may deem it appropriate to consider an NPA or DPA with provisions designed to "promote compliance with applicable law and to prevent recidivism."[142]

Both DPAs and NPAs are contract-based arrangements. In a DPA, prosecutors agree to defer prosecution of an entity or individual for a period of time in exchange for, depending on the agreement, an admission of misconduct, cooperation, a penalty, and compliance undertakings. Prosecutors file DPAs with a formal charging document, and the agreements are subject to judicial scrutiny.[143] Formal charges do not, on the other hand, accompany an NPA, which is an "agreement . . . maintained by the parties rather than . . . filed with a court."[144]

In recent years, DOJ has regularly turned to DPAs or NPAs to resolve FDCA cases.[145] For example, in January 2017, DOJ and Baxter Healthcare Corporation (Baxter) entered into a DPA in connection with allegations that Baxter failed to follow current Good Manufacturing Practices (cGMP) when manufacturing its sterile intravenous (IV) solutions and thus violated the FDCA by introducing adulterated drugs into interstate commerce.[146] The DPA required Baxter to pay $16 million in monetary penalties and forfeiture and to implement "enhanced compliance provisions, including periodic certifications to the government concerning its implementation" of certain provisions of the FDCA.[147]

Similarly, in December 2016, GNC Holdings, Inc. entered into an NPA in connection with its sale of dietary supplements produced by a supplier under indictment and awaiting trial for FDCA violations.[148] In the statement of facts accompanying the NPA, GNC acknowledged that it engaged in acts and omissions that allowed a misbranded supplement to be sold at its stores.[149] The NPA required GNC to pay $2.25 million to the United States, take certain actions to prevent unlawful dietary supplements from reaching its shelves in the future, and cooperate in dietary supplement investigations.[150]

In February 2014, Endo Pharmaceuticals Inc. also entered into a DPA in connection with allegations that the company promoted a drug off-label (and thereby misbranded the drug in violation of the FDCA).[151] The DPA required Endo Pharmaceuticals to pay a total

of $20.8 million in monetary penalties and forfeiture, implement enhanced compliance controls, and submit an annual certification from the CEO of the corporate parent regarding the company's compliance efforts.[152] And in February 2013, Honey Holding I, Ltd. entered into a DPA with the U.S. Attorney's Office for the Northern District of Illinois in connection with allegations that the company introduced adulterated honey into interstate commerce in violation of the FDCA. Under the DPA, Honey Holding agreed to: (1) cooperate with the DOJ's ongoing investigation (including allowing an undercover federal agent to pose as Honey Holding's Director of Procurement); (2) implement a company compliance program; (3) educate customers and other industry participants regarding illegally transshipped, misdeclared, and unsafe products; and (4) pay fines and restitution totaling more than $1.8 million.[153]

While senior DOJ officials have yet to make significant public remarks regarding DPA and NPA policy under the Trump administration, Attorney General Sessions did note in a memorandum that "deferred prosecution agreements, non-prosecution agreements, and plea agreements" are "useful tool[s] for Department attorneys to achieve the ends of justice at a reasonable cost to the tax payer."[154] Moreover, in an April 2017 speech, then-Acting Principal Deputy Assistant Attorney General Trevor McFadden stated he intended to dispel the "myth" that DOJ "was no longer interested in prosecuting white collar crime."[155] He noted that DOJ's Criminal Division "continues to focus on a wide array of white collar matters," including health care matters.[156] With white collar crime remaining a priority for DOJ, companies should continue to monitor how DOJ executes and enforces these agreements.

Notably, federal district courts may be trending toward asserting a greater role in evaluating and supervising DPAs.[157] In recent years, several federal judges have invoked their "inherent supervisory authority" to approve or deny DPAs and to maintain a role in monitoring the execution and implementation of an approved agreement. For example, in a November 20, 2017 order, Judge William Young of the U.S. District Court for the District of Massachusetts rejected a proposed settlement between Aegerion Pharmaceuticals Inc. and DOJ.[158]

On the other hand, two appellate courts recently reversed lower court decisions concerning DPAs and the courts' supervisory authority. The D.C. Circuit overturned a lower court's rejection of a DPA, holding that courts do not have the authority to reject a DPA based on findings that the "charging decisions" and other negotiated "conditions agreed to in the DPA" were somehow inadequate.[159] The Second Circuit reversed a lower court's order unsealing an independent corporate monitor's report regarding a company's DPA compliance.[160] According to the Second Circuit, the monitor report was not a "judicial document" subject to the presumption of public access.[161] The court also opined on the district court's authority in overseeing the DPA, stating that "absent unusual circumstances," the district court's role vis-à-vis a DPA is "limited to arraigning the defendant, granting a speedy trial waiver . . . and adjudicating motions or disputes as they arise."[162]

Federal Criminal Statutes Jointly Enforced by FDA and the DOJ

Generally

Q 12.16 What federal criminal statutes does FDA enforce with DOJ's assistance?

The OCI conducts and coordinates investigations not only of FDCA violations, but also violations of the FATA and various other sections of Title 18 of the U.S. Code. These statutes encompass a broad range of conduct. Indeed, since its formation in 1993, the OCI has "investigated thousands of criminal schemes involving the distribution of potentially dangerous FDA-regulated products."[163] The conduct the OCI has investigated in recent years includes "street level distribution of counterfeit, unapproved, and designer drugs, major organized illicit diversion of prescription drugs, fraudulent schemes involving ineffective . . . cures, large scale product substitution conspiracies, application and clinical investigator fraud, and health frauds involving harmful FDA-regulated drugs and medical devices."[164] In fiscal year 2013, U.S. prosecutors enforcing the FDCA obtained 314 criminal convictions and recovered more than $2.3 billion in fines and restitution.[165] The next fiscal year saw similar results; U.S. prosecutors secured 305 criminal convictions and recovered more than $2.1 billion in fines and restitution.[166] Fiscal year 2017, however, marked a slowdown of sorts as prosecutors secured only 222 convictions and $450.6 million in fines and restitution.[167]

The questions and answers below summarize the FDCA's provisions giving rise to criminal liability and differentiate between misdemeanor and felony violations of the Act. After explaining the *Park* doctrine, this section addresses potential defenses to FDCA charges, criminal penalties for FDCA violations, and collateral consequences that may accompany a FDCA conviction. This section then turns to the FATA and various other offenses under Title 18 of the U.S. Code that FDA may enforce through DOJ.

FDCA Provisions Giving Rise to Criminal Liability

Q 12.17 What conduct does the FDCA proscribe and what are the consequences for engaging in such conduct?

Section 301 of the FDCA sets forth myriad prohibited acts that may give rise to criminal liability for any "person,"[168] a term of art that includes individuals and corporate entities.[169] The FDCA proscribes not only the prohibited acts themselves, but also the "causing thereof."[170] Most broadly, section 301 proscribes the "introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or

cosmetic that is adulterated or misbranded," the "adulteration or misbranding" of any such product, the "receipt in interstate commerce of" any adulterated or misbranded food, drug, device, tobacco product, or cosmetic "and the delivery or proffered delivery thereof for pay or otherwise," and the "manufacture" of any adulterated or misbranded food, drug, device, tobacco product, or cosmetic.[171] Prosecutors may premise charges under multiple subsections of section 301 on the same conduct.[172]

Q 12.18 What constitutes "adulteration" under the FDCA?

The FDCA deems a regulated article "adulterated" if it is contaminated or defective, unapproved, banned, or manufactured under conditions that do not comply with cGMP.[173] For instance, despite some differences among the regulated product categories, food, drugs, medical devices, tobacco products, and cosmetics are deemed adulterated if they bear or contain any added "poisonous or deleterious substance," if they consist in whole or in part of "any filthy, putrid, or decomposed substance," or were "prepared, packed, or held under insanitary conditions."[174] Further, a drug or device is adulterated if the person who was granted an investigational exemption from the FDCA's pre-market approval process "fails to comply with a requirement prescribed by" the Act.[175]

Q 12.19 What constitutes "misbranding" under the FDCA?

Under the FDCA, a regulated article is misbranded if its labeling is false or misleading in any way.[176] Further, the FDCA deems a product misbranded unless its labeling includes adequate directions for use and warnings about possibly hazardous uses, doses, or methods of administration.[177] The statutory definition of misbranding also mandates that required information on a product's label be "conspicuous[] . . . and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use."[178] Under the statute, an article is deemed misbranded if its labeling "fails to reveal facts material in light of [the label's] representations."[179] Moreover, the FDCA sets forth various other packaging and labeling requirements and restrictions on advertising and promotion that, if not complied with, result in the product being deemed misbranded.[180]

Probably the most significant FDA enforcement issue, at least in terms of the size and frequency of the cases, is off-label promotion—the promotion of a product for a use not contained in its FDA-approved labeling—of drugs and, so far to a lesser extent, medical devices. The FDCA does not expressly prohibit off-label promotion, but FDA brings enforcement actions through the FDCA provisions that prohibit the introduction into interstate commerce of an unapproved new drug,[181] misbranding by false or misleading labeling,[182] or the failure to provide in labeling adequate directions for a new intended use.[183]

Q 12.19.1 What guidance has FDA provided regarding misbranding and

social media?

FDA's authority includes oversight of the labeling and advertising of prescription drugs and medical devices.[184] A product is "misbranded" under the FDCA if a company makes representations about the use of a product without disclosing required information, including facts that are:

> (1) [m]aterial in light of other representations made or suggested by statement, word, design, device or any combination thereof, or (2) [m]aterial with respect to consequences which may result from use of the article under: (i) [t]he conditions prescribed in such labeling or (ii) such conditions of use as are customary or usual.[185]

With the advent of websites such as Twitter, companies must balance the benefits of a social media presence with the disclosure requirements of the FDCA. Twitter, for example, now limits individual posts ("tweets") regarding a topic to 280 characters. Given this limit, companies struggle to determine how they should comply with the FDCA and FDA regulations that deem a product misbranded if a representation about the product does not "disclos[e] certain information about the product's risk."[186] To address this issue, FDA released draft guidance in June 2014 regarding micro-blog sites like Twitter and the similarly abbreviated "sponsored links" present on search engines like Google and Yahoo.[187]

The draft guidance notes generally that (1) if a company chooses to make a product benefit claim, the company should also incorporate risk information within the same character-space-limited communication and (2) the company should also provide a mechanism to allow direct access to a more complete discussion of the risks associated with its product (for example, a hyperlink to more detailed information).[188] The draft guidance also recommends that before promoting products through limited-character websites, companies should "first carefully consider the complexity of the indication and risk profiles for each of their products to determine whether a character-space-limited platform is a viable promotional tool for a particular product," and then consider certain "factors," "recommendations," and "hypothetical examples" outlined in FDA's draft guidance document to develop benefit and risk presentations.[189] Notably, FDA solicited comments in early 2017 on research entitled, "Character-Space-Limited Online Prescription Drug Communications[,]" which suggests that updated guidance may be forthcoming.[190]

While finalizing its guidance on social media, FDA continues to pursue companies for alleged failures to disclose adequate information on risks in social media posts. For example, FDA issued a Warning Letter in August 2015 to Duchesnay, Inc. regarding an Instagram post by Kim Kardashian West.[191] The post showed Ms. West posing with a bottle of Duchesnay, Inc.'s morning sickness drug, Diclegis, and included the following statement:

> OMG. Have you heard about this? As you guys know my #morningsickness

> has been pretty bad. I tried changing things about my lifestyle, like my diet, but nothing helped, so I talked to my doctor. He prescribed me #Diclegis, and I felt a lot better and most importantly, it's been studied and there was no increased risk to the baby. . . . If you have morning sickness, be safe and sure to ask your doctor about the pill with the pregnant woman on it and find out more www.diclegis.com; www.DiclegisImportantSafetyInfo.com.[192]

In the Warning Letter, FDA asserted that the post misbranded Diclegis by failing "to communicate any risk information associated with its use" and "omit[ing] material facts" such as Diclegis' full approved indication and limitations of the drug's use.[193] While the post contained a link to a Diclegis website with risk information, FDA stated that the link did not "mitigate the misleading omission of risk information."[194]

Although an isolated post may not prompt a criminal investigation, companies must remain attuned to whether their social media presences adhere to FDA's evolving guidance in this space.

Q 12.20 What other conduct does the FDCA proscribe?

Section 301 delineates nearly sixty separate criminal offenses.[195] Although a comprehensive analysis of all of those offenses is beyond the scope of this chapter, representative section 301 offenses include:

- Refusing to "permit entry or inspection" of a regulated entity's facility as authorized under section 374 of the FDCA[196];
- Falsely guaranteeing to a middleman or distributor that a product regulated by the FDCA is not adulterated or misbranded[197];
- Performing "any act which causes a drug to be a counterfeit drug," or selling, dispensing, or holding for sale a counterfeit drug[198];
- Altering, mutilating, destroying, or removing the label or any part of the label of a regulated article such that the article is adulterated or misbranded[199];
- Selling, purchasing, or trading a drug or drug sample that is not intended for sale but rather is intended for promotional purposes, or offering to sell, purchase, or trade such a drug or drug sample[200];
- Introducing or delivering for introduction into interstate commerce a "dietary supplement that is unsafe"[201]; and
- "Making any express or implied statement or representation directed to consumers with respect to a tobacco product" that conveys that FDA approved the product, deems the product safe, or endorses the product.[202]

Q 12.21 Are violations of the FDCA misdemeanors or felonies?

A violation of the FDCA is a felony if the defendant acted "with the intent to defraud or mislead" or if the defendant has a prior conviction for violating the act.[203] Although the statute does not expressly define *who* a defendant must intend to defraud or mislead, the courts have concluded that misleading or defrauding consumers or government agencies is punishable as a felony.[204] For instance, the FDCA's felony provisions could apply in situations in which a manufacturer or supplier does not provide a consumer with the product that it purports to provide.[205] Further, the courts have upheld felony FDCA convictions where the defendant conceals illegal activity from FDA[206] (or another government agency), or submits fraudulent data to FDA.[207]

All violations of the FDCA committed without the intent to defraud or mislead are misdemeanors (unless, of course, the violator has a past FDCA conviction).[208] As explained in greater detail in Q 12.22 below, prosecutors need not prove fraudulent intent, let alone knowing or willful conduct, to convict a defendant of a misdemeanor violation of section 301 of the FDCA.

Park *Doctrine*

Q 12.22 Is criminal intent an element of FDCA charges?

Because of FDA's pivotal role in ensuring the safety of much of the nation's food supply and the safety and effectiveness of its drugs, biological products, medical devices, and animal drugs and feed,[209] Congress and the Supreme Court have minimized the burden on FDA and its partner U.S. prosecutors to prove criminal violations of the FDCA. Under the so-called *Park* doctrine, a responsible corporate officer or employee may be convicted for statutory violations where, by virtue of his or her managerial position, the officer or employee had the power to prevent the act complained of and "could be deemed responsible for its commission."[210] As expressed by the Supreme Court, the doctrine establishes that sections 301 and 303 of the FDCA create strict liability offenses. And FDA and DOJ have expressed interest in increasing *Park* prosecutions: Former FDA Commissioner Dr. Margaret Hamburg stated, in a March 2010 letter to Senator Charles Grassley, that FDA intended to increase its "use of misdemeanor prosecutions, a valuable enforcement tool, to hold responsible corporate officials accountable" under the *Park* doctrine.[211] Likewise, Tony West, then-Assistant Attorney General for DOJ's Civil Division, stated in a February 2011 speech: "[D]emanding accountability means we will consider prosecutions against individuals, including misdemeanor prosecutions under the *Park* doctrine."[212]

Q 12.23 How did the Park doctrine originate?

In *United States v. Dotterweich*, the Supreme Court held that a corporate officer could be culpable for criminal violations of the FDCA without actively participating in or having knowledge of the wrongdoing.[213] Because Congress enacted the FDCA in the interest of

safeguarding public health, the FDCA "puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."[214] The *Dotterweich* Court refused to define "the class of employees which stands in such a responsible relation."[215] Instead, the Court instructed that responsibility for commission of misdemeanor violations of the FDCA falls on those who have a "responsible share in the furtherance of the transaction which the statute outlaws."[216] The Court opined that "in such matters the good sense of prosecutors, the wise guidance of trial judges, and the ultimate judgment of juries must be trusted."[217] In the wake of *Dotterweich*, government prosecutors have had the discretion to define and charge the responsible group of corporate officers.

In *United States v. Park*, the Supreme Court further defined the standard of liability for a corporate officer who fails to prevent a violation of the FDCA by third parties under his or her authority.[218] In *Park*, Acme Markets, Inc., a national grocer, exposed commercial food shipments to rodent contamination.[219] FDA initially informed John Park, the President and Chief Executive Officer of Acme, of the unsanitary conditions in Acme's Philadelphia warehouse.[220] In a subsequent visit to Acme's Baltimore warehouse, an inspector found similar conditions; after returning to the warehouse, the inspector noted evidence of "rodent activity" in the building, despite some overall improvement in the warehouse's sanitary conditions.[221] Park was charged with FDCA violations relating to the adulteration of food. At trial, Park acknowledged that he was responsible for "big, broad, principles of the operation of the company," but he premised his defense on the argument that he had delegated sanitation of the contaminated warehouse to the vice president of Acme's Baltimore division.[222] Park adduced evidence that the vice president had assured Park that he "was investigating the situation immediately."[223] Park testified that he did not "believe there was anything [Park] could have done more constructively than what [Park] found was being done."[224] The trial court instructed the jury that it need not find that Park personally participated in the conduct; rather, it could convict on the ground that Park had a "responsible relationship to the issue."[225] The jury convicted Park, who then challenged the jury instruction on appeal.

The *Park* Court rejected the defendant's argument. It noted that Park had received notice from FDA regarding the unsanitary conditions at the warehouse and admitted that the system for handling sanitation "wasn't working perfectly."[226] In concluding that Park's role sufficed to justify a conviction under the FDCA, the Court explained that "liability of managerial officers [does] not depend on their knowledge of, or personal participation in," the criminal violation.[227] Both "those corporate agents who themselves committed the criminal act," and "those who by virtue of their managerial positions" had the power to prevent the act complained of "could be deemed responsible for its commission."[228]

Q 12.24 What guidelines has FDA established with regard to the *Park doctrine?*

FDA's *Regulatory Procedures Manual* provides nonbinding guidelines with regard to *Park* prosecutions.[229] In determining whether to recommend a misdemeanor prosecution against a corporate official, the guidelines direct OCI investigators to consider "the individual's position in the company and relationship to the violation, and whether the official had the authority to correct or prevent the violation."[230] Other factors to consider include, but are not limited to:

- "Whether the violation involves actual or potential harm to the public;
- Whether the violation is obvious;
- Whether the violation reflects a pattern of illegal behavior and/or failure to heed prior warnings;
- Whether the violation is widespread;
- Whether the violation is serious;
- The quality of the legal and factual support for the proposed prosecution; and
- Whether the proposed prosecution is a prudent use of agency resources."[231]

Q 12.25 Who can be convicted under the *Park doctrine?*

Under *Park*, both "those corporate agents who themselves committed the criminal act," and "those who by virtue of their managerial positions" had the power to prevent the act complained of "could be deemed responsible for its commission."[232] Therefore, the primary factor in determining potential liability for a corporate officer under the *Park* doctrine is not the officer's "position in the corporate hierarchy, but rather his accountability, because of the responsibility and authority of his position, for the conditions which gave rise to the [FDCA] charges against him."[233]

For example, in 2013, Eric and Ryan Jensen pled guilty to introducing adulterated cantaloupe into interstate commerce under the FDCA.[234] The Jensen brothers were the principals in a Granada, Colorado, farming operation called Jensen Farms and, according to the plea agreement, "were both in a position to, and had authority to, order regular and seasonal employees and workers to set up and maintain a conveyor system for the purposes of packing cantaloupes from the farm."[235] According to the plea agreement, the defendants failed to use a "chlorine spray" in the conveyor system that would have "reduced the risk of microbial contamination of the fruit."[236] The cantaloupes were subsequently delivered in interstate commerce and "caus[ed] or contribut[ed]" to the deaths of thirty-three people,[237] even though Jensen Farms received a 96% "superior" rating from a third-party food inspector just four days before delivery of the cantaloupes.[238] The plea agreement cites both *Park* and *Dotterweich* in noting that the offense for which the Jensen brothers were prosecuted did not require criminal intent and that the FDCA imposes "misdemeanor criminal liability on individuals who have a 'responsible share' in furthering prohibited conduct, without regard to state of mind."[239]

In recent years, various executives have pled guilty in *Park* prosecutions, including, the vice president, director of regulatory and clinical affairs, and division presidents of a medical device company in 2011,[240] the chief executive officer of a pharmaceutical company in 2011,[241] and the president of a pharmaceutical compounding company in 2012.[242] These executives' convictions under *Park* theories have resulted in prison time,[243] as well as millions of dollars in fines, asset forfeiture, and restitution,[244] and exclusion from participation in federal health care programs.[245] (See Q 12.31 below for additional information about exclusion and other criminal penalties under the FDCA.)

The *Park* "responsible person" doctrine, however, does not apply where the corporate officer personally violates the FDCA.[246] In *United States v. Ballistrea*, the defendant argued that *Park* required the jury to find that the defendant was a legally responsible party in order to convict him of the FDCA-related offenses.[247] The Second Circuit rejected this argument, concluding that this element applies only if parties are charged with failing to prevent violations of the FDCA; *Park* "did not impose a similar requirement of responsible party status when the defendant is charged with personally violating the FDCA by his own conduct."[248]

In a notable 2016 decision regarding the constitutionality of prison sentences under the *Park* doctrine, the Eighth Circuit affirmed a lower court's imposition of three-month prison terms and $100,000 fines for two executives who pled guilty to FDCA violations.[249] Jack DeCoster and his son, Peter, were the owner and chief operating officer, respectively, of Quality Egg, LLC.[250] In 2010, federal and state officials determined that a salmonella outbreak that affected approximately 56,000 Americans had originated at Quality Egg's Iowa facilities.[251] The DeCosters each pled guilty to misdemeanor violations of the FDCA as responsible corporate officers, stipulating that, while they did not know their company's eggs were contaminated at the time of shipment, they were in positions to prevent the sale of contaminated eggs had they known about the contamination.[252] Among other arguments raised on appeal, the DeCosters challenged the constitutionality of sentences imposed by the lower court, arguing the sentences: (1) violated the Due Process Clause by imposing vicarious liability and (2) violated the Due Process Clause by requiring imprisonment for an offense lacking a *mens rea* requirement.[253]

A divided Eighth Circuit panel rejected the DeCosters' constitutional challenge. Writing for the majority, Judge Murphy noted that under the FDCA "a corporate officer is held accountable not for the acts or omissions of others, but rather for his own failure to prevent or remedy the conditions which gave rise to the charges against him."[254] The court detailed the lower court record and noted that the DeCosters were not found vicariously liable for the acts of others but rather "liable for negligently failing to prevent the salmonella outbreak."[255] The court also rejected the DeCosters' *mens rea* argument, noting that "[t]he elimination of a *mens rea* requirement does not violate the Due Process Clause for a public welfare offense where the penalty is relatively small, the conviction does not gravely damage the defendant's reputation, and congressional intent supports the imposition of the

penalty."[256]

The DeCosters subsequently filed a petition for writ of certiorari to the U.S. Supreme Court on January 10, 2017.[257] Raising these same due process concerns with the *Park* doctrine, the DeCosters went one step further in their petition and asked the Court to overturn its decisions in *Dotterwich* and *Park*.[258] The Court denied the DeCosters' petition on May 22, 2017.[259]

Q 12.26 What conduct might give rise to corporate criminal liability?

As with other criminal offenses, companies can be held liable for FDCA violations committed by employees acting within the scope of their authority and with at least partial intent to benefit the company.[260] Companies could be deemed criminally liable regardless of: (1) the position of the employee in the company; (2) whether the conduct was authorized or ratified by the company, or even was contrary to its express policies; (3) whether the conduct resulted in actual benefit to the company; or (4) whether the conduct resulted in actual injury to anyone or the public at large.[261]

Notably, in the administrative setting, FDA also has relied on *Park* in holding companies —and their officers—responsible for the activities of third parties. In a May 2014 Warning Letter regarding allegedly adulterated dietary supplements, the government noted that the company, "as a distributor that contracts with other manufacturers to manufacture, package, or label dietary supplements" under the company's name, had an obligation to "know what and how these activities [were] performed" so the company could decide whether the dietary supplements "conform[ed] to established specifications" and whether the company should "approve and release the products for distribution."[262] Citing *Park*, the government stated that although a company may "contract out certain dietary supplement manufacturing operations, it cannot, by the same token, contract out its ultimate responsibility to ensure that the [product] it places into commerce (or causes to be placed into commerce) is not adulterated . . . ."[263] This interpretation of *Park* suggests that the government may seek to hold executives liable for the conduct not only of company employees but also *third parties* who may be unknown to senior managers. While FDA Warning Letters are administrative in nature and not criminal charges, the reference to *Park* in the context of third-party activities is indicative of the government's view of the doctrine's scope. It is unclear whether this even more expansive *Park* theory will appear in criminal cases.

Given the *Park* doctrine's reach, U.S. companies should also be mindful of their operations overseas. FDA often issues Warning Letters to U.S. companies regarding alleged FDCA violations at foreign factories.[264] For example, in an August 2015 Warning Letter, FDA wrote to the president of a U.S. company that an investigation of three of the company's foreign manufacturing facilities revealed "significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals."[265] Similarly, in a March 2015 Warning Letter, FDA requested that a U.S. company "[p]rovide evidence of the effectiveness of [its] implemented global corrective actions and preventive actions" in

response to issues with two foreign manufacturing facilities.[266] Although FDA did not cite *Park* in these letters to U.S. companies, issues at foreign facilities are clearly on FDA's enforcement radar.

Defenses to FDCA Charges

Q 12.27 What defenses are available to charges under the FDCA?

Many FDCA-related criminal defense efforts focus on issues of intent, the legal and factual details of product manufacturing or labeling, the history of regulatory interactions, product safety, promotional practices, and the significant First Amendment concerns that arise when the government prosecutes companies for activities that involve speech. In addition, there are a few statutory defenses and a *Park*-specific defense that may be available to a defendant confronting charges related to certain prohibited acts.

Q 12.28 What must a defendant show to invoke the FDCA's statutory defenses?

Section 303 of the FDCA provides that "[n]o person shall be subject to" its criminal penalties in the limited circumstances set forth in the statute.[267] Three of those exceptions merit mention.

First, the FDCA exempts a defendant who "received in interstate commerce any article and delivered it or proffered delivery of it, if such delivery or proffer was made in good faith" and "furnish[es] on request" of FDA regulators identifying information regarding the person from whom he received the article and copies of all documents relating to the article.[268] Relying on the FDCA's legislative history, most courts have construed this exception narrowly.[269] On the other hand, at least one federal court has held that the exception "was designed to protect innocent dealers . . .who receive goods shipped in interstate commerce" and furnish information about the "guilty shipper."[270]

Second, the statute exempts a defendant who received in good faith a guaranty that the article was not adulterated or misbranded if the guaranty is signed by a person residing in the United States from whom the defendant received the article.[271]

Third, a defendant is exempt from criminal penalty for misbranding by failure to provide adequate directions for use and related violations if the "delivery or proffered delivery was made in good faith and the labeling at the time thereof contained the same directions for use and warning statements as were contained in the labeling at the time of . . . receipt."[272]

Q 12.29 What must a defendant show to invoke defenses to a *Park doctrine* FDCA prosecution?

In *Park*, the Supreme Court observed that the FDCA "does not require that which is objectively impossible."[273] The theory "upon which responsible corporate agents are held criminally accountable for 'causing' violations of the [FDCA] permits a claim that

defendant was 'powerless' to prevent or correct the violation to 'be raised defensively at a trial on the merits.'"[274] To avail himself of this defense, a defendant has the burden of coming forward with evidence that (1) he exercised extraordinary care and (2) he nevertheless could not prevent the criminal violations.[275] The government has the ultimate burden of proving beyond a reasonable doubt that the defendant had the power to prevent the violation.[276]

This "extraordinary care" defense is, in several ways, a double-edged sword. Evidence of the defendant's vigilance could imply that the defendant knew or should have known about the violative conduct. Moreover, the prosecution may be able to introduce evidence of the corporate entity's past compliance with the FDCA to dispel the notion that compliance was impossible.[277]

Criminal Penalties for FDCA Violations

Q 12.30 What criminal penalties could be imposed under the FDCA?

An individual convicted of violating the FDCA may be subject to a term of imprisonment and a fine; corporate entities often face significant fines. The severity of the criminal penalty under the FDCA depends on whether the defendant committed a felony or misdemeanor violation of the FDCA.

Although the FDCA provides that "[a]ny person who" commits a misdemeanor violation of the act "shall be imprisoned for not more than one year or fined not more than $1,000, or both,"[278] federal sentencing laws have increased the maximum fine to $250,000 for an individual or $500,000 for a corporate entity (if the misdemeanor results in a death) or, in cases where the infraction does not lead to a death, $100,000 for an individual or $200,000 for a corporate entity.[279]

If the defendant violated the FDCA with an "intent to defraud or mislead" or has a prior "final" conviction under the act, then the defendant is subject to the FDCA's felony penalties.[280] Under the FDCA, such violations carry possible prison sentences of as many as three years and a fine of $10,000.[281] However, federal sentencing laws have superseded the FDCA's penalty provision and cap fines at $250,000 for individuals and $500,000 for corporate entities.[282]

Regardless of the statutory thresholds for FDCA misdemeanors or felonies, the Alternative Fines Act provides that "[i]f any person derives pecuniary gain from the offense, or if the offense results in pecuniary loss to a person other than the defendant, the defendant may be fined not more than the greater of twice the gross gain or twice the gross loss. . . ."[283]

Section 2N2.1 of the U.S. Sentencing Guidelines governs sentencing for FDCA violations. It sets a base offense level for FDCA violations, but states that "[i]f the offense involved fraud," U.S.S.G. § 2B1.1 governs the offense level.[284] Section 2B1.1 has a similar base offense level, but delineates a series of specific offense characteristics (such as amount of loss, number of victims, or relation of the offense to a federal health care program) that

may result in a higher cumulative offense level (and therefore a higher advisory sentencing range).[285] Absent any increases in the offense level, the advisory guidelines range for FDCA violations is zero to twenty-one months in prison, depending on the defendant's criminal history. Regardless, "in all prosecutions of fraudulent activity, [the Consumer Protection Branch] seeks a prison sentence that reflects the serious injury to the public caused by the defendants," regardless of whether consumers or a government agency was the defrauded or misled party.[286]

Collateral Consequences That May Accompany an FDCA Conviction

Q 12.31 What collateral consequences are possible under the FDCA and related laws?

FDA may avail itself of the full range of remedies under the FDCA in response to conduct violative of the act. Indeed, FDA's pursuit of criminal sanctions does not preclude civil remedies such as injunctions, seizures, and disgorgement of profits.

In addition, conviction for certain FDCA offenses may result in debarment from participating in applications to FDA or exclusion from federal health care programs. By statute, an excluded individual or entity cannot participate in federal health care programs.[287] Depending on the basis of exclusion (such as a conviction or other conduct), exclusion may be mandatory or permissive.[288] If a conviction triggers mandatory exclusion, the OIG must exclude the individual or entity for a minimum of five years, except in limited circumstances.[289] Where exclusion is permissive, the OIG may, at its discretion, opt to depart from the default exclusion period of three years.[290] Notably, "[t]he threat of exclusion from Medicare, Medicaid, and all other healthcare programs . . . has been characterized as a corporate 'death sentence' for pharmaceutical companies."[291] In fiscal year 2016, the OIG excluded 3,635 individuals and entities.[292] These OIG sanctions included 1,362 exclusions based on criminal convictions for crimes related to Medicare, Medicaid, or other health care programs; 1,448 exclusions resulting from licensure revocations; and 299 exclusions for patient abuse or neglect.[293]

Statutory debarment prohibits a corporate entity from submitting or assisting in the submission of any drug application, and prohibits an individual from providing services in any capacity to a person who has a pending or approved drug product application.[294] Like exclusion, the debarment penalty can be mandatory or permissive depending on the basis for debarment.[295] Mandatory debarment generally punishes the violator for a minimum of one year and a maximum of ten years, although "permanent" debarment is possible in certain circumstances.[296] Permissive debarment punishes the offender for no more than five years.[297]

Recently, the OIG issued a rule that expands its authority to impose exclusions under the Affordable Care Act and the Medicare Prescription Drug, Improvement and Modernization Act of 2003.[298] The rule gives the OIG permissive exclusion authority as to

convictions for obstructing an audit relating to a federal health care program. This rule supplements the OIG's prior power to exclude health care participants convicted of obstructing a targeted "investigation."[299] As the OIG has explained, one reason for this expanded power is that audits, like investigations, are "formal in nature" and are similarly considered to be "integral to fraud prevention and detection by payors and by law enforcement."[300] Under the rule, the OIG also will have discretion to exclude participants who "knowingly made or caused to be made any false statement, omission, or misrepresentation of a material fact in any application, agreement, bid, or contract to participate or enroll as a provider of services or supplier under a Federal health care program . . . ."[301]

Criminal and Civil Liability

Q 12.32 How does criminal liability under the FDCA intersect with civil liability under the False Claims Act?

FDA criminal investigations may be triggered by *qui tam* relators filing suit under the federal False Claims Act.[302] In recent cases, such investigations have led to simultaneous criminal and civil settlements in which the civil damages component is often larger than the criminal fine. In November 2013, for example, the DOJ settled criminal and civil charges against Johnson & Johnson stemming from alleged off-label promotion and payment of kickbacks to doctors in violation of the FDCA and the False Claims Act.[303] The settlement included more than $485 million in criminal fines and forfeitures and an agreement to pay $1.72 billion to resolve civil claims.[304]

Such resolutions are complex; among other issues, a company must consider what offense and what level of offense it should plead guilty to and whether a subsidiary should enter into the guilty plea given the potential consequences to the company of exclusion from the federal health care programs.

Anti-Tampering Act and Other Offenses Under Title 18 of the U.S. Code

Q 12.33 What other federal statutes does FDA's OCI investigate?

In addition to enforcing the FDCA's criminal provision, FDA also investigates violations of the FATA and various other violations of Title 18 of the U.S. Code that relate to FDA-regulated activity.

Q 12.34 What conduct does the Federal Anti-Tampering Act prohibit?

As noted above, the OCI is empowered to "conduct and coordinate criminal investigations of violations of" the FATA.[305] Enacted in the wake of the 1982 Tylenol poisonings,[306] the FATA generally criminalizes tampering with consumer products and related conduct.[307] The Act contains six specific offenses:

(1) attempting to tamper or "tamper[ing] with any consumer product . . . or the labeling of, or container for, any such product" "with reckless disregard for the risk that another person will be placed in danger of death or bodily injury"[308]

(2) "taint[ing] any consumer product or render[ing] materially false or misleading the labeling of, or container for, a consumer product" "with intent to cause serious injury to the business of any person"[309]

(3) "knowingly communicat[ing] false information that a consumer product has been tainted, . . . and if such tainting, had it occurred, would create a risk of death or bodily injury to another person"[310]

(4) "knowingly threaten[ing], under circumstances in which the threat may reasonably be expected to be believed," to tamper with any consumer product[311]

(5) conspiring to tamper with any consumer product[312];and

(6) "intentionally tamper[ing] with a consumer product . . . by knowingly placing or inserting any writing in the consumer product, or in the container" before the sale of the product "without the consent of the manufacturer, retailer, or distributor."[313]

For each of the substantive offenses, the consumer product or conduct at issue must affect interstate or foreign commerce,[314] but the courts have interpreted this jurisdictional requirement expansively.[315] Notably, the statute defines "consumer product" as, among other articles, products, or commodities, "any 'food', 'drug', 'device', or 'cosmetic', as those terms are . . . defined in Section 201 of the [FDCA]."[316] Similarly, the FATA defines "labeling" by reference to section 201(m) of the FDCA.[317] As detailed below, each specific offense set forth in the FATA carries its own sentencing provision.

United States v. Walton demonstrates the role of FDA in pursuing convictions under the FATA.[318] In *Walton*, the prosecutorial team was composed of members of the U.S. Attorney's Office for the Northern District of Illinois, a member of the U.S. Attorney's Office for the Northern District of Indiana, a DOJ lawyer, and an FDA lawyer.[319] The defendant altered the "use-before" dates on "slips that accompanied . . . pacemakers" and then "sold the pacemakers to hospitals for implant."[320] He was indicted for tampering with the documents in violation of 18 U.S.C. § 1365(a), mail fraud in violation of 18 U.S.C. § 1341, and possession of a document-making implement in violation of 18 U.S.C. § 1028(a)(5).[321] The Seventh Circuit rejected Walton's argument that the FATA is unconstitutionally vague and impermissibly regulates commercial speech.[322]

Although *Walton* highlights collaboration among federal agencies, state and local regulators historically have had a "significant role in the investigation and prosecution of alleged tampering."[323] The FATA does not preempt applicable state and local laws.[324] Accordingly, DOJ's prosecution policy under the FATA states that "referral to [state and local] authorities is appropriate when no significant Federal interest requires vindication

(*e.g.*, in an isolated instance, when there is no serious impact upon commerce . . . etc.)."[325]

Q 12.35 What criminal penalties may be imposed for a conviction for violating the Federal Anti-Tampering Act?

A tampering violation resulting in the death of any person carries a sentence of as much as life imprisonment and a fine;[326] if the violation instead results in "serious bodily injury," the statute provides for a maximum sentence of twenty years' imprisonment and a fine.[327] Attempting to tamper, conspiring to tamper, and any other tampering offense carry possible sentences of as many as ten years in prison and a fine.[328] If convicted of tainting a consumer product (or rendering the product's labeling materially false), a defendant faces as many as three years' imprisonment and a fine.[329] Communicating false information and threatening to tamper with any consumer product may result in a prison sentence of as many as five years as well as a fine.[330]

Q 12.36 What other statutory offenses may be within FDA's purview?

If committed in connection with activity that FDA regulates, FDA also has the authority to investigate and enforce other statutes under Title 18 of the U.S. Code. Among other offenses, this category includes:

Statute	Proscribed Conduct
18 U.S.C. § 287	False, Fictitious or Fraudulent Claims
18 U.S.C. § 371	Conspiracy to Commit Offense or to Defraud the United States
18 U.S.C. § 1001	False Statements to the Government
18 U.S.C. § 1035	False Statements Relating to Health Care Matters
18 U.S.C. § 1341	Mail Fraud
18 U.S.C. § 1343	Wire Fraud
18 U.S.C. § 1347	Health Care Fraud
18 U.S.C. § 1505	Obstruction of Proceedings before Departments/Agencies
18 U.S.C. § 1518	Obstruction of Criminal Investigation of Health Care Offenses
18 U.S.C. § 2314	Interstate Transportation of Stolen Property, or Articles Used in Counterfeiting

18 U.S.C. § 2315	Sale or Receipt of Stolen Goods Moved Interstate
18 U.S.C. § 2320	Trafficking in Counterfeit Goods[331]

Federal prosecutors frequently bring FDCA or FATA charges alongside charges premised on the statutes listed above.[332]

Whereas section 301 of the FDCA—as interpreted by the Supreme Court in *Park*—sets forth a strict liability offense, criminal intent is an element of each of the crimes listed in the table above.[333] For instance, the "Obstruction of Proceedings" statute requires the prosecution to prove that the defendant acted "corruptly."[334] Similarly, the statutes proscribing fraud require that the prosecutor establish that the defendant acted with the intent to defraud a victim.[335]

Each of these offenses is a felony, but punishments vary widely under the statutes. For instance, a conviction for presenting false claims under 18 U.S.C. § 287 carries a potential prison sentence of "not more than five years" and a fine, whereas mail fraud and wire fraud convictions may result in as many as thirty years of imprisonment and a fine.[336]

Notably, DOJ under the Obama administration signaled a shift in policy regarding prosecuting false statements made to the government under 18 U.S.C. § 1001 and false statements involving a health care benefit program under 18 U.S.C. § 1035. Both statutes require that false statements be made "knowingly and willfully" to trigger criminal liability. The government has long held the position that a "knowing" and "willful" false statement is made with knowledge that *the statement is false*, as opposed to knowledge that *making a false statement is illegal*. In a March 2014 opposition to a petition for certiorari to the U.S. Supreme Court, however, the government stated that "it is now the view of the United States that the 'willfully' element of Sections 1001 and 1035 requires proof that the defendant made a false statement with knowledge that his conduct was unlawful."[337]

While the case in which the government revised its position involved section 1035, it is notable that the government stated its new position would also apply to section 1001 actions. Prosecutions for false statements to the government under 18 U.S.C. § 1001 are common in white collar criminal cases, as are charges stemming from witness and target conversations with prosecutors or government agents. The conversations subject to the false statements charge may be regarding FDCA issues or unrelated statutes. DOJ's shift in position may make securing convictions under 18 U.S.C. §§ 1001 and 1035 more difficult by requiring proof that the defendant knew that making the allegedly false statement was against the law. With the recent change in administrations, future prosecutions may clarify whether DOJ will maintain this position under the leadership of Attorney General Sessions.

FDA enforcement undoubtedly raises challenging legal issues and complex strategic decisions. When FDA's criminal investigators come calling, individuals and companies should consider their exposure and, as appropriate, contact counsel.

1. FDA, ENFORCEMENT STRATEGY 1 (July 15, 2010) [hereinafter FDA ORCEMENT STRATEGY 2010], .fda.gov/downloads/ICECI/EnforcementActions/UCM225183.pdf.
2. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-10-221, FOOD AND DRUG MINISTRATION: IMPROVED MONITORING AND DEVELOPMENT OF FORMANCE MEASURES NEEDED TO STRENGTHEN OVERSIGHT OF MINAL AND MISCONDUCT INVESTIGATIONS 1 (2010) [hereinafter GAO OCI ORT], www.gao.gov/assets/310/300503.pdf.
3. FDA ENFORCEMENT STRATEGY 2010, *supra* note 1, at 1.
4. *Cf.* FDA, REGULATORY PROCEDURES MANUAL § 653 (2011) [hereinafter FDA ULATORY PROCEDURES MANUAL] ://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ (noting that cutions "can have a strong deterrent effect on the defendants and other regulated entities").
5. FDA ENFORCEMENT STRATEGY 2010, *supra* note 1, at 2.
6. Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301–99.
7. Federal Anti-Tampering Act (FATA), 18 U.S.C. § 1365.
8. GAO OCI REPORT, *supra* note 2, at 6.
9. FDA REGULATORY PROCEDURES MANUAL, *supra* note 4, § 652.
10. *Inspections, Compliance, Enforcement, and Criminal Investigations*, FDA, ://www.fda.gov/ICECI/CriminalInvestigations/ucm550316.htm [hereinafter FDA, PECTIONS, COMPLIANCE, ENFORCEMENT, AND CRIMINAL ESTIGATIONS].
11. FDA REGULATORY PROCEDURES MANUAL, *supra* note 4, § 652.
12. *Id.*
13. *Id.*
14. FDA, INVESTIGATIVE PRIORITIES, ://www.fda.gov/ICECI/CriminalInvestigations/ucm546093.htm; *see also* FDA ORCEMENT STRATEGY 2010, *supra* note 1, at 1.
15. FDA, OFFICE OF REGULATORY AFFAIRS QUALITY MANUAL 35 (Mar. 2012), .fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandP /ORA/UCM136320.pdf; *see also* GAO OCI REPORT, *supra* note 2, at 8.
16. GAO OCI REPORT, *supra* note 2, at 8–9.
17. *Id.* at 7.
18. *Id.* at 7–8.
19. II ARTHUR N. LEVINE, FDA Enforcement Manual ¶ 1301 (2007) [hereinafter II [NE].
20. FDA, OFFICE OF THE CHIEF COUNSEL, //www.fda.gov/AboutFDA/CentersOffices/OC/OfficeoftheChiefCounsel/default.htm.
21. *See, e.g.*, FDA, CUMULATIVE NUMBER OF CONVICTIONS AT THE END OF QUARTER (2013), https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm? am=ora&status=public&id=ORA-OCI-Criminal-Convictions-and-Monies-

vered&fy=2013 (showing that OCI completed 76 criminal convictions during FY 2013 ɔringing the fiscal year total to 216 and recovered over $1.9 billion in fines and restitution).

22. GAO OCI REPORT, *supra* note 2, at *Highlights*.

23. *Id.* at 10.

24. *Id.* at *Highlights*.

25. *Id.* at 15–16.

26. *See* Letter from Dr. Margaret Hamburg, Commissioner of Food and Drugs, to Sen. les E. Grassley, Ranking Member, Senate Comm. on Fin. 1 (Mar. 4, 2010), [hereinafter burg Letter] (on file with author).

27. *Id.* at 2.

28. *Id.*

29. FDA, FDA-TRACK AGENCY-WIDE PROGRAM FORMANCEhttp://www.fda.gov/AboutFDA/Transparency/track/.

30. II LEVINE, *supra* note 19, ¶ 1301.

31. 28 C.F.R. § 0.45(j).

32. *See* Scott Bass, *FDA Enforcement Powers*, in Food and Drug Law and Regulation 814 id G. Adams et al. eds., 2d ed. 2011) [hereinafter Bass, *FDA Enforcement Powers*] ("All ɛions of the FDCA are subject to civil or criminal enforcement—or both—based on FDA's DOJ's discretion.").

33. *See* U.S. DEP'T OF JUSTICE, CONSUMER PROTECTION BRANCH, NOGRAPH 2 (2011) [hereinafter CONSUMER PROTECTION BRANCH NOGRAPH], ://www.justice.gov/sites/default/files/civil/legacy/2011/09/06/CPB_Monograph.pdf.

34. *Id.* at 3, 5–7.

35. *Id.; see also* 28 U.S.C. § 547; Bass, *FDA Enforcement Powers, supra* note 32, at 814–15.

36. *See* 28 U.S.C. § 547; CONSUMER PROTECTION BRANCH MONOGRAPH, note 33, at 2–3.

37. II LEVINE, *supra* note 19, ¶ 1432.

38. GAO OCI REPORT, *supra* note 2, at 6.

39. *Id.* at 7.

40. *Id.* at 6.

41. *Cf.* U.S. DEP'T OF HEALTH AND HUMAN SERVS. AND U.S. DEP'T OF TICE, HEALTH CARE FRAUD AND ABUSE CONTROL PROGRAM, ANNUAL ORT FOR FISCAL YEAR 2016 1 2017) [hereinafter HHS-DOJ 2016 ANNUAL ORT], https://oig.hhs.gov/publications/docs/hcfac/FY2016-hcfac.pdf (describing number fendants "convicted for health care fraud-related crimes during the year" and number of iduals and entities excluded "for crimes related to Medicare and Medicaid" and other health ɛams).

42. *See generally* 42 U.S.C. § 1320a-7.

43. *See, e.g.*, Corporate Integrity Agreement Between the Office of Inspector Gen. of the t of Health and Human Servs. and Meadows Regional Medical Center, Inc. (Nov. 16,

),
://oig.hhs.gov/fraud/cia/agreements/Meadows_Regional_Medical_Center_Inc_11162017.p

44. *See* HHS-DOJ 2016 ANNUAL REPORT, *supra* note 41, at 8.
45. *Id.* at 8–9.
46. *Id.* at 10.
47. *Id.*
48. U.S. Dep't of Justice, June 2016 Takedown (Aug. 29, 2016),
://www.justice.gov/criminal-fraud/health-care-fraud-unit/june-2015-takedown.
49. *Id.*
50. U.S. Dep't of Justice, Owner of Two New York Medical Clinics Sentenced to 84
ths for Her Role in $55 Million Health Care Fraud Scheme (Sept. 15, 2017),
://www.justice.gov/opa/pr/owner-two-new-york-medical-clinics-sentenced-84-months-her-
55-million-health-care-fraud.
51. *Id.*
52. *Id.*
53. U.S. Dep't of Justice, HEALTH CARE FRAUD UNIT (Sept. 5, 2017),
://www.justice.gov/criminal-fraud/health-care-fraud-unit.
54. GAO OCI REPORT, *supra* note 2, at 16 n.48.
55. FDA, FY 2011 CONGRESSIONAL BUDGET REQUEST 236 (2011) (on file with
uthor).
56. *Id.*
57. Press Release, FDA, Drug Trafficking Organization Faces Indictment for Involvement in
ufacturing Fake Prescriptions Drugs with Fentanyl (May 31, 2017),
://www.fda.gov/ICECI/CriminalInvestigations/ucm561483.htm.
58. *Id.*
59. *See* 18 U.S.C. § 1365(g).
60. FDA, INVESTIGATIONS OPERATIONS MANUAL § 8.8.2 (2017) [hereinafter
INVESTIGATIONS OPERATIONS MANUAL],
://www.fda.gov/ICECI/Inspections/IOM/.
61. *Id.*
62. Memorandum of Understanding Between Fed. Trade Comm'n and Food & Drug
in., 36 Fed. Reg. 18,539 (Sept. 16, 1971); *see also* 21 U.S.C. § 378(a) (detailing, for
nce, FDA's duty to "notify in writing the Federal Trade Commission of the action [FDA]
oses to take respecting such food or advertising").
63. FDA INVESTIGATIONS OPERATIONS MANUAL, *supra* note 60, § 3.1.2.1.
64. 21 C.F.R. § 20.108; *see also* II LEVINE, *supra* note 19, ¶ 170.
65. 21 C.F.R. § 20.108(d).
66. *Id.*
67. GAO OCI Report, *supra* note 2, at 12 Table 1.
68. *Id.*

69. FDA INVESTIGATIONS OPERATIONS MANUAL, *supra* note 60, §§ 8.2, 8.4.3.4.

70. *Id.* § 8.9.1.3.

71. United States *ex rel.* Ryan v. Endo Pharm., Nos. 05-3450, 10-2039, 11-7767, 2015 WL 290, at *3–4 (E.D. Pa. July 15, 2015).

72. *See* II LEVINE, *supra* note 19, ¶ 1432.

73. GAO OCI Report, *supra* note 2, at 12, Table 1.

74. *See* United States v. R. Enters., Inc., 498 U.S. 292, 298 (1991) (quoting United States v. ıdra, 414 U.S. 338, 343 (1974)).

75. *See* FED. R. CRIM. P. 6(e)(2).

76. *See* FED. R. CRIM. P. 6(e)(3).

77. *See* 18 U.S.C. § 3486(a)(1)(A).

78. *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 10606, 124 119, 1006–09 (2010), *amended by* Healthcare and Education Reconciliation Act of 2010, L. No. 111-152, 124 Stat. 1029 (2010); *see also* 18 U.S.C. § 24(a)(2).

79. *See* 18 U.S.C. § 3486(a)(1)(B).

80. 21 U.S.C. § 333(f)(5)(A) ("In the course of any investigation, the Secretary may issue ɔenas requiring the attendance and testimony of witnesses and the production of evidence ɛlates to the matter under investigation.").

81. I MARK A. HELLER, GUIDE TO MEDICAL DEVICE REGULATION ¶ 1130 mpson Publ'g Grp. 2010).

82. *See* 31 U.S.C. § 3733(a)(1)(A)–(D).

83. *See* Redelegation of Authority of Assistant Attorney General, Civil Division, to Branch ːtors, Heads of Offices and United States Attorneys in Civil Division Cases, 75 Fed. Reg. 70, 14,072 (Mar. 24, 2010) (20 C.F.R. pt.0).

84. *See* 21 U.S.C. § 374.

85. *See* FDA INVESTIGATIONS OPERATIONS MANUAL, *supra* note 60, §§ 5.1–5.2; *so* II LEVINE, *supra* note 19, ¶ 302; FDA, WHAT DOES FDA INSPECT, //www.fda.gov/AboutFDA/Transparency/Basics/ucm194888.htm.

86. 21 U.S.C. § 374(a)(1).

87. Section 703 provides that "evidence obtained under this section, or any evidence which ectly or indirectly derived from such evidence, shall not be used in a criminal prosecution of erson from whom obtained." 21 U.S.C. § 373(a). Nevertheless, "[s]ection 703 has been ɔreted quite strictly to cover only inspections of common carriers and a few limited ories of persons receiving regulated products, thereby eliminating the vast majority of ctions that are conducted pursuant to section 704." Bass, *FDA Enforcement Powers, supra* 32, at 787 (citing United States v. Gel Spice Co., 601 F. Supp. 1214, 1220 (E.D.N.Y.)).

88. FDA INVESTIGATIONS OPERATIONS MANUAL, *supra* note 60, § 5.2.2.4.

89. *Id.*

90. *See, e.g.*, United States v. Jamieson-McKames Pharm., Inc., 651 F.2d 532, 537–39 (8th 1981) (explaining that "virtually every phase of the drug industry is heavily regulated"), *cert.*

d, 455 U.S. 1016 (1982).

91. 21 U.S.C. § 335; *see also* 21 C.F.R. § 7.84(a)(1).

92. 21 C.F.R. § 7.84(a)(1).

93. *See* FDA REGULATORY PROCEDURES MANUAL, *supra* note 4, § 657.

94. *See* 21 C.F.R. § 7.84(a)(2).

95. *See* 21 C.F.R. § 7.84(a)(3); *see also* FDA REGULATORY PROCEDURES MANUAL, note 4, § 657.

96. *See, e.g.*, United States v. Prigmore, 243 F.3d 1, 23 (1st Cir. 2001) (citing United States ɔtterweich, 320 U.S. 277, 279 (1943), and holding that defendants "are not entitled to issal of the prosecution" because of FDA's failure to provide section 305 notice and the rtunity to be heard).

97. FDA REGULATORY PROCEDURES MANUAL, *supra* note 4, § 651 (Mar. 2007).

98. *Cf.* FDA ENFORCEMENT STRATEGY 2010, *supra* note 1, at 1–2.

99. *See* FDA REGULATORY PROCEDURES MANUAL, *supra* note 4, § 653.

100. GAO OCI REPORT, *supra* note 2, at 16.

101. *See, e.g.*, Press Release, U.S. Dep't of Health and Human Servs., Departments of Justice Health and Human Services Announce over $27.8 Billion in Returns from Joint Efforts to bat Health Care Fraud (Mar. 19, 2015), https://www.justice.gov/opa/pr/departments-e-and-health-and-human-services-announce-over-278-billion-returns-joint (reporting that than $27.8 billion has been recovered since 1997, including $3.3 billion in fiscal year , and declaring that eliminating fraud remains a top priority); U.S. DEP'T OF HEALTH HUMAN SERVS. AND U.S. DEP'T OF JUSTICE, HEALTH CARE FRAUD AND SE PROGRAM, ANNUAL REPORT FOR FISCAL YEAR 2013 (Feb. 2014), //oig.hhs.gov/publications/docs/hcfac/FY2013-hcfac.pdf; Press Release, The White House, rtment of Justice Recovered a Record $5.6 Billion in Fraud in 2011 (Dec. 13, 2011), ://obamawhitehouse.archives.gov/realitycheck/the-press-office/2011/12/13/campaign-cut-e-vice-president-biden-announces-us-will-halt-productio.(stating that "[f]or every dollar on [federal anti-fraud enforcement in the healthcare industry], the Administration has ered seven dollars" and announcing the "next step in an aggressive campaign to crack down [edicare fraud").

102. CONSUMER PROTECTION BRANCH MONOGRAPH, *supra* note 33, at 3.

103. U.S. Dep't of Justice, Attorney General Jeff Sessions Delivers Remarks Announcing New s to Combat the Opioid Crisis (Nov. 29, 2017), ://www.justice.gov/opa/speech/attorney-general-jeff-sessions-delivers-remarks-announcing-tools-combat-opioid-crisis; FDA, Remarks from FDA Commissioner Scott Gottlieb, M.D., epared for Delivery at FDA OCI Meeting (Nov. 14, 2017), ://www.fda.gov/NewsEvents/Speeches/ucm584978.htm.

104. U.S. Dep't of Justice, Attorney General Sessions Announces Opioid Fraud and Abuse ction Unit (Aug. 2, 2017), https://www.justice.gov/opa/pr/attorney-general-sessions-unces-opioid-fraud-and-abuse-detection-unit.

105. U.S. Dep't of Justice, Attorney General Sessions Announces New Prescription

diction & Litigation Task Force (Feb. 28, 2018), https://www.justice.gov/opa/pr/attorney-al-sessions-announces-new-prescription-interdiction-litigation-task-force.

106. *Id.*

107. Press Release, U.S. Dep't of Justice, National Health Care Fraud Takedown Results in ges Against Over 412 Individuals Responsible for $1.3 Billion in Fraud Losses (July 13,), https://www.justice.gov/opa/pr/national-health-care-fraud-takedown-results-charges-st-over-412-individuals-responsible.

108. *Id.*

109. Ethan P. Davis, Deputy Assistant Attorney General, Remarks to the Food and Drug Law ute Enforcement, Litigation, and Compliance Conference (Dec. 7, 2017).

110. Press Release, U.S. Dep't of Justice, Pharmacy Owner and Director of Compliance ged with Defrauding United States and Distributing Adulterated Drugs (June 22, 2017).

111. *Id.*

112. *Id.*

113. *Id.*

114. Press Release, U.S. Dep't of Justice, Former Pharmacy Compliance Director Pleads y to Introducing Adulterated Drugs into Interstate Commerce and Conspiracy to Defraud Jnited States (Nov. 22, 2017).

115. GAO OCI REPORT, *supra* note 2, at 16.

116. U.S. DEP'T OF JUSTICE, U.S. ATTORNEYS' MANUAL, at 92.020 (1997) (changes ditions since 1997 are noted after affected sections), https://www.justice.gov/usam/united-attorneys-manual.

117. CONSUMER PROTECTION BRANCH MONOGRAPH, *supra* note 33, at 4.

118. *Id.*

119. *See, e.g.*, United States v. N.Y. Fish, Inc., 10 F. Supp. 3d 355, 372–74 (E.D.N.Y. 2014) ing the owner and president, vice president, and plant manager at a fish company liable for A violations); United States v. Mays, 69 F.3d 116, 119 (6th Cir. 1995) (affirming ictions of secretary/treasurer and operations manager of orange juice company); United s v. Beech-Nut Nutrition Corp., 871 F.2d 1181, 1184 (2d Cir. 1989) (discussing ictions of president/CEO and vice president of operations).

120. CONSUMER PROTECTION BRANCH MONOGRAPH, *supra*note 33, at 4.

121. Memorandum from Sally Quillian Yates, Deputy Attorney General, U.S. Dep't of e, to All U.S. Attorneys et al., Individual Accountability for Corporate Wrongdoing (Sept. 15) [hereinafter Yates Memo], https://www.justice.gov/archives/dag/file/769036/download.

122. *Id.* at 2.

123. *Id.* at 3.

124. *Id.* at 4.

125. *Id.* at 5.

126. *Id.* at 6.

127. Rod J. Rosenstein, Deputy Attorney General Rod Rosenstein Keynote Address on orate Enforcement Policy, NYU Program on Corporate Compliance & Enforcement (Oct.

17), https://wp.nyu.edu/compliance_enforcement/2017/10/06/nyu-program-on-corporate-liance-enforcement-keynote-address-october-6-2017/.

128. *Id.*

129. *See* Press Release, U.S. Dep't of Justice, Deputy Attorney General Rosenstein Delivers arks at the 34th International Conference on the Foreign Corrupt Practices Act (Nov. 29,), https://www.justice.gov/opa/speech/deputy-attorney-general-rosenstein-delivers-remarks-international-conference-foreign.

130. U.S. DEP'T OF JUSTICE, PRINCIPLES OF FEDERAL PROSECUTION OF INESS ORGANIZATIONS (portions updated Nov. 2017) [hereinafter DOJ, NCIPLES OF FEDERAL PROSECUTION OF BUSINESS ORGANIZATIONS], at 9-00, https://www.justice.gov/usam/usam-9-28000-principles-federal-prosecution-business-nizations; *see also* Mark R. Filip, Remarks Prepared for Delivery by Deputy Attorney ral Mark R. Filip at Press Conference Announcing Revisions to Corporate Charging elines (Aug. 28, 2008), https://www.justice.gov/archive/dag/speeches/2008/dag-speech-286.html.

131. *See generally* DOJ, PRINCIPLES OF FEDERAL PROSECUTION OF BUSINESS ANIZATIONS, *supra* note 130.

132. *See id.*

133. *Id.* at 9-28.720.

134. *Id.* at 9-28.710.

135. *Id.* at 9-28.730. *Cf.* United States v. Stein, 541 F.3d 130, 135–36 (2d Cir. 2008) ming order dismissing indictment against thirteen former accounting firm partners and oyees because the prosecutors deprived the defendants of their Sixth Amendment right to sel by pressuring the firm, KPMG, to limit its advancement of legal fees to the defendants).

136. *See* DOJ, PRINCIPLES OF FEDERAL PROSECUTION OF BUSINESS ANIZATIONS, *supra* note 130, at 8–11.

137. Yates Memo, *supra* note 121, at 3.

138. Memorandum from the Office of the Attorney General, U.S. Dep't of Justice, ibition of Improper Guidance Documents, at 1 (Nov. 16, 2017).

139. Memorandum from Rachel Brand, Associate Attorney General, U.S. Dep't of Justice, ed States Attorneys, Limiting Use of Agency Guidance Documents in Affirmative Civil rcement Cases, (Jan. 25, 2018).

140. *Id.* at 2.

141. *See* generally DOJ, PRINCIPLES OF FEDERAL PROSECUTION OF BUSINESS ANIZATIONS, *supra* note 130, at 9-28.100.

142. *Id.*

143. *See* Craig S. Morford, Memorandum for Heads of Department Components and United s Attorneys, at 1 n.2 (Mar. 7, 2008), www.justice.gov/criminal/pr/speeches/2012/crm-h-1209131.htmldag/morford-useofmonitorsmemo-03072008.pdf.

144. *Id.*

145. FDA Office of Criminal Investigations, Endo Pharmaceuticals and Endo Health

ions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing
ription Drug Lidoderm for Unapproved Uses (Feb. 21, 2014), https://wayback.archive-
/7993/20170406212731/https://www.fda.gov/ICECI/CriminalInvestigations/ucm387029.

146. Press Release, U.S. Dep't of Justice, Baxter Healthcare Corporation to Pay More Than
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://www.justice.gov/opa/pr/baxter-healthcare-corporation-pay-more-18-million-resolve-
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147. *Id.*

148. Press Release, U.S. Dep't of Justice, GNC Enters Into Agreement with Department of
e to Improve its Practices and Keep Potentially Illegal Dietary Supplements Out of the
etplace (Dec. 7, 2016), https://www.justice.gov/opa/pr/gnc-enters-agreement-department-
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149. *Id.*

150. *Id.*

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/7993/20170406212731/https://www.fda.gov/ICECI/CriminalInvestigations/ucm387029.

152. *Id.*

153. Honey Holding I, Ltd. DPA ¶¶ 5, 7, United States v. Honey Holding, I, Ltd., No. CR
Feb. 20, 2013), ECF No. 11.

154. Attorney General of the United States, Memorandum re Prohibition on Settlement
ients to Third Parties (June 5, 2017), https://www.justice.gov/opa/press-
e/file/971826/download.

155. Trevor N. McFadden, Acting Principal Deputy Assistant Attorney General, DOJ,
arks at the American Conference Institute's 19th Annual Conference on Foreign Corrupt
ices Act (Apr. 20, 2017), https://www.justice.gov/opa/speech/acting-principal-deputy-
ant-attorney-general-trevor-n-mcfadden-justice-department-s.

156. *Id.*

157. *See, e.g.*, United States v. Saena Tech Corp., 140 F. Supp. 3d 11, 31–34 (D.D.C. 2015).

158. Mem. and Order at 23–24, United States v. Aegerion Pharm., Inc., No. 1:17-cr-10288-
(Nov. 20, 2017), ECF No. 23.

159. United States v. Fokker Servs. B.V., 818 F.3d 733, 738, 747 (D.C. Cir. 2016).

160. United States v. HSBC Bank USA, N.A., No. 16-308(L), slip op. at 21–25 (2d Cir. July
017).

161. *Id.* at 2.

162. *Id.* at 6.

163. FDA, INSPECTIONS, COMPLIANCE, ENFORCEMENT, AND CRIMINAL
ESTIGATIONS, *supra* note 10.

164. *Id.*

165. FDA, CUMULATIVE NUMBER OF CONVICTIONS AT THE END OF THE ıRTER (2013), https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?:am=ora&id=ORA-OCI-Criminal-Convictions-and-Monies-Recovered&fy=2013.

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167. *See* FDA, CUMULATIVE NUMBER OF CONVICTIONS AT THE END OF THE ıRTER (2017), https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?:am=ora&status=public&id=ORA-OCI-Criminal-Convictions-and-Monies-vered&fy=2017.

168. *See generally* 21 U.S.C. § 331.

169. 21 U.S.C. § 321(e).

170. 21 U.S.C. § 331.

171. *Id.* § 331(a), (b), (c), (g).

172. *See, e.g.*, II LEVINE, *supra* note 19, ¶ 1310.

173. *See* 21 U.S.C. §§ 342, 351, 361.

174. *Id.*

175. 21 U.S.C. § 351(i).

176. *See* 21 U.S.C. §§ 343, 352(a), 362.

177. *See* 21 U.S.C. § 352(f).

178. 21 U.S.C. § 352(c).

179. 21 U.S.C. § 321(n).

180. *See generally* 21 U.S.C. § 352.

181. 21 U.S.C. § 331(d).

182. 21 U.S.C. § 352(a).

183. 21 U.S.C. § 352(f); *see also* 21 C.F.R. § 201.5.

184. *See* 21 U.S.C. § 352(a), (n).

185. 21 C.F.R § 1.21(a)(1)–(2).

186. FDA, GUIDANCE FOR INDUSTRY: INTERNET/SOCIAL MEDIA PLATFORMS H CHARACTER SPACE LIMITATIONS—PRESENTING RISK AND BENEFIT)RMATION FOR PRESCRIPTION DRUGS AND MEDICAL DEVICES 3 (June), //www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/1401087.pdf.

187. *Id.* at 1.

188. *Id.* at 5.

189. *Id.* at 6.

190. Agency Information Collection Activities; Proposed Collection; Comment Request; acter-Space-Limited Online Prescription Drug Communications, 81 Fed. Reg. 78,163

. 7, 2016).

191. FDA, WARNING LETTER NDA-021876 (Aug. 7, 2015), .fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/enforcementactivities u/warninglettersandnoticeofviolationletterstopharmaceuticalcompanies/ucm457961.pdf.

192. *Id.* at 2.

193. *See id.* at 1, 3.

194. *Id.* at 3.

195. *See* 21 U.S.C. § 331; *see also* 21 U.S.C. § 333.

196. 21 U.S.C. § 331(f) (prohibiting "[t]he refusal to permit entry or inspection as authorized ction 374"); *cf. id.* § 331(e) (prohibiting "[t]he refusal to permit access to or copying of any d as required by" various sections of the FDCA).

197. 21 U.S.C. § 331(h).

198. 21 U.S.C. § 331(i)(3).

199. 21 U.S.C. § 331(k).

200. 21 U.S.C. § 331(t); *see also* 21 U.S.C. § 353(c)(1) ("No person may sell, purchase, or or offer to sell, purchase, or trade any drug sample. For purposes of this paragraph and ction (d), the term 'drug sample' means a unit of a drug, subject to subsection (b), which is ntended to be sold and is intended to promote the sale of the drug.").

201. 21 U.S.C. § 331(v).

202. 21 U.S.C. § 331(tt).

203. 21 U.S.C. § 333(a)(2).

204. *See, e.g.*, United States v. Mitcheltree, 940 F.2d 1329, 1346–47 (10th Cir. 1991); *cf.* NSUMER PROTECTION BRANCH MONOGRAPH, *supra* note 33, at 3.

205. *See* CONSUMER PROTECTION BRANCH MONOGRAPH, *supra* note 33, at 3.

206. *See, e.g.*, United States v. Andersen, 45 F.3d 217, 220 (7th Cir. 1995) ("FDA represents ublic, and a deliberate attempt to mislead the FDA should be considered as clearly a fraud attempts to mislead customers or other individuals."); United States v. Arlen, 947 F.2d 143 (5th Cir. 1991) (holding that a defendant who sought to conceal steroid distribution federal regulators acted with "intent to defraud"); United States v. Bradshaw, 840 F.2d 874 (11th Cir. 1988) (same). *But cf.* Mitcheltree, 940 F.2d at 1347, 1349 ("The nment may premise criminal liability under § 333(a)(2) based upon an intent to mislead or ud not only natural persons, but also government agencies if there is evidence that a dant consciously sought to mislead drug regulatory authorities such as the FDA or similar nmental agency . . . . [But] there must be a demonstrated link between the § 331 violation n intent to mislead or defraud an *identifiable* drug regulatory agency involved in consumer ction. Distributing drugs in knowing violation of federal and state regulatory systems and is too general.") (emphasis in original).

207. *See, e.g.*, United States v. C.R. Bard, Inc., 848 F. Supp. 287, 289 (D. Mass. 1994); ited States v. Marcus, 82 F.3d 606, 607–08 (4th Cir. 1996) (affirming felony conviction onspiring to defraud the United States where defendant executive of drug manufacturer did eport to FDA alterations to drug formula).

208. *See* 21 U.S.C. § 333(a)(1).

209. *See, e.g.*, FDA, REGULATORY INFORMATION, ://www.fda.gov/RegulatoryInformation/default.htm.

210. United States v. Park, 421 U.S. 658, 670–71 (1975).

211. Hamburg Letter, *supra* note 26, at 2.

212. Tony West, Assistant Attorney General, Remarks at the 12th Annual Pharmaceutical latory and Compliance Cong. (Nov. 2, 2011), ://www.justice.gov/opa/speech/assistant-attorney-general-tony-west-speaks-12th-annual-naceutical-regulatory-and. One knows that the concept has permeated all ranks of the al enforcement agencies when an FDA OCI agent states to counsel representing a naceutical company that "the government is looking for a *Park* prosecution here," as one of uthors of this chapter has experienced. As knowledgeable as federal agents may be, they refer to Supreme Court cases other than *Miranda v. Arizona*, 384 U.S. 436 (1966).

213. United States v. Dotterweich, 320 U.S. 277, 281–85 (1943).

214. United States v. Wiesenfeld Warehouse Co., 376 U.S. 86, 91 (1964) (quoting *rweich*, 320 U.S. at 281).

215. *Dotterweich,* 320 U.S. at 285.

216. *Id.* at 284.

217. *Id.* at 285.

218. *Park*, 421 U.S. at 670.

219. *Id.* at 660.

220. *Id.* at 661.

221. *Id.* at 662.

222. *Id.* at 663.

223. *Id.* at 664.

224. *Id.*

225. *Id.* at 665 n.9.

226. *Id.* at 664–65.

227. *Id.* at 670.

228. *Id.*

229. FDA REGULATORY PROCEDURES MANUAL, *supra* note 4, § 653.

230. *Id.*

231. *Id.*

232. *Park*, 421 U.S. at 670.

233. *Id.* at 675.

234. Plea Agreement, United States v. Jensen, No. 13-mj-01138-MEH (D. Colo. Oct. 22,), ECF Doc. No. 32; Plea Agreement, United States v. Jensen, No. 13-mj-01138-MEH Colo. Oct. 22, 2013), ECF Doc. No. 34.

235. Plea Agreement § IV(5), United States v. Jensen, No. 13-mj-01138-MEH (D. Colo. 22, 2013), ECF Doc. No. 34.

236. *Id.* § IV(6).

237. *Id.* § IV(9); Press Release, U.S. Dep't of Justice, Eric and Ryan Jensen Charged with ducing Tainted Cantaloupe into Interstate Commerce (Sept. 26, 2013), ://www.justice.gov/usao-co/pr/eric-and-ryan-jensen-charged-introducing-tainted-loupe-interstate-commerce.

238. Plea Agreement § IV(7), United States v. Jensen, No. 13-mj-01138-MEH (D. Colo. 22, 2013), ECF Doc. No. 34.

239. *Id.* § II(A) n.1.

240. Press Release, U.S. Dep't of Justice, Former Executives of International Medical Device er Sentenced to Prison in Unlawful Clinical Trials Case (Nov. 21, 2011), ://wayback.archive-/7993/20170723081805/https://www.fda.gov/ICECI/CriminalInvestigations/ucm280937. Press Release, U.S. Dep't of Justice, Final Former Synthes Executive Sentenced in wful Clinical Trials Case (Dec. 13, 2011), https://wayback.archive-/7993/20180126095657/https://www.fda.gov/ICECI/CriminalInvestigations/ucm283692. Indictment at 2, United States v. Norian Corp., No. 2:09-cr-00403-LDD (June 16, 2009), No. 1.

241. Press Release, U.S. Dep't of Justice, Former Drug Company Executive Pleads Guilty in sized Drug Tablets Case (Mar. 10, 2011), https://www.justice.gov/opa/pr/former-drug-pany-executive-pleads-guilty-oversized-drug-tablets-case.

242. Press Release, U.S. Dep't of Justice, Dallas Compounding Pharmacy Owner Pleads y in Connection with Misbranded Drug Shipment (Apr. 24, 2012), ://www.justice.gov/opa/pr/dallas-compounding-pharmacy-owner-pleads-guilty-connection-randed-drug-shipment.

243. Press Release, U.S. Dep't of Justice, Former Executives of International Medical Device er Sentenced to Prison in Unlawful Clinical Trials Case (Nov. 21, 2011), ://wayback.archive-/7993/20170723081805/https://www.fda.gov/ICECI/CriminalInvestigations/ucm280937. Press Release, U.S. Dep't of Justice, Final Former Synthes Executive Sentenced in wful Clinical Trials Case (Dec. 13, 2011), https://wayback.archive-/7993/20180126095657/https://www.fda.gov/ICECI/CriminalInvestigations/ucm283692.

244. *See* Press Release, U.S. Dep't of Justice, Marc S. Hermelin, Former CEO of KV naceutical, Pleads Guilty to Misbranding Drugs and Agrees to Pay United States $1.9 on as Fines and Forfeiture (Mar. 10, 2011), https://archives.fbi.gov/archives/stlouis/press-es/2011/sl031011.htm; Plea Agreement 1–2, United States v. Friedman, No. 1:07-cr-9-JPJ (W.D. Va May 10, 2007), ECF No. 7; Plea Agreement 1–2, United States v. Udell, 1:07-cr-00029-JPJ (W.D. Va. May 10, 2007), ECF No. 8; Plea Agreement 1–2, United s v. Goldenheim, No. 1:07-cr-00029-JPJ (W.D. Va. May 10, 2007), ECF No. 9.

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on as Fines and Forfeiture (Mar. 10, 2011), https://archives.fbi.gov/archives/stlouis/press-es/2011/sl031011.htm.

246. *See* United States v. Ballistrea, 101 F.3d 827, 836 (2d Cir. 1996).

247. *Id.* at 835–36.

248. *Id.* at 836.

249. United States v. DeCoster, 828 F.3d 626, 636 (8th Cir. 2016).

250. *Id.* at 629.

251. *Id.* at 630.

252. *Id.* at 631.

253. *Id.* at 632–33.

254. *Id.* at 633 (internal quotations omitted).

255. *Id.*

256. *Id.* (internal quotations omitted).

257. Petition for Writ of Certiorari, DeCoster v. United States, No. 16-877 (Jan. 10, 2017).

258. *Id.*

259. Denial of Petition for Writ of Certiorari, DeCoster v. United States, No. 16-877 (May 017).

260. II LEVINE, *supra* note 19, ¶1330.

261. *See, e.g.*, United States v. Potter, 463 F.3d 9, 25 (1st Cir. 2006); United States v. mated Med. Labs, Inc., 770 F.2d 399, 407 (4th Cir. 1985).

262. FDA, WARNING LETTER FLA-14-13 (May 29, 2014), .fda.gov/iceci/enforcementactions/warningletters/2014/ucm402397.htm.

263. *Id.*

264. *See, e.g.*, FDA, WARNING LETTER WL: 320-15-14 (Aug. 6, 2015), .fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm458363.htm.

265. *Id.*

266. FDA, WARNING LETTER WL: 320-15-08 (Mar. 31, 2015), .fda.gov/ICECI/EnforcementActions/WarningLetters/ucm440966.htm.

267. 21 U.S.C. § 333(c).

268. 21 U.S.C. § 333(c)(1).

269. *See, e.g.*, United States v. H.L. Moore Drug Exch., Inc., 239 F. Supp. 256, 258–59 (D. ı. 1965).

270. *See id.* (quoting United States v. Levine, CCH Fed. Food, Drug & Cosmetic Rep. 7712 . Pa. 1948)).

271. 21 U.S.C. § 333(c)(2); *see also* 21 C.F.R. § 7.13(b) (providing "suggested forms of ınty or undertaking" compliant with section 303(c)(2) of the FDCA). A very similar defense under 21 U.S.C. § 333(c)(3) for defendants who receive in good faith a guarantee that a additive added to a product was "from a batch certified in accordance" with FDA ations.

272. 21 U.S.C. § 333(c)(4).

273. *See Park*, 421 U.S. at 673.

274. *Id.* (citing United States v. Wiesenfeld Warehouse Co., 376 U.S. 86, 91 (1964) (holding the defense involved factual proof that could not be raised in a motion to dismiss)).

275. *See id.; see also* United States v. New England Grocers Supply Co., 488 F. Supp. 230, 36 (D. Mass. 1980) (holding that *Park* permits an affirmative defense of impossibility). *But* nited States v. Gel Spice Co., 773 F.2d 427, 435 (2d Cir. 1985) (noting that even if the A does not require corporate officers to exercise extraordinary care to prevent violations, the ndant still failed to show that he was powerless to prevent a rodent infestation where the pany had passed five other inspections).

276. *See Park*, 421 U.S. at 673.

277. *See, e.g., Gel Spice Co.*, 773 F.2d at 435 ("Engel has . . . failed to introduce any evidence he was powerless to prevent the rodent infestation. Indeed, Gel Spice had passed an FDA ction in 1972 and five other inspections between 1973 and the July 1976 inspection.").

278. 21 U.S.C. § 333(a)(1).

279. 18 U.S.C. § 3571(b), (c).

280. 21 U.S.C. § 333(a)(2).

281. *See id.*

282. 18 U.S.C. § 3571(b), (c).

283. 18 U.S.C. § 3571(d).

284. U.S.S.G. § 2N2.1(c)(1).

285. *See* U.S.S.G. § 2B1.1.

286. CONSUMER PROTECTION BRANCH MONOGRAPH, *supra* note 33, at 5.

287. *See* 42 U.S.C. § 1320a7(a).

288. *See* 42 U.S.C. § 1320a7(a), (b).

289. *See* 42 U.S.C. § 1320a7(a), (c).

290. *See* 42 U.S.C. § 1320a7(c)(3)(D) (except in certain circumstances, "the period of the sion shall be 3 years, unless the Secretary determines in accordance with published ations that a shorter period is appropriate because of mitigating circumstances or that a r period is appropriate because of aggravating circumstances").

291. Vicki W. Girard, *Punishing Pharmaceutical Companies for Unlawful Promotion of oved Drugs: Why the False Claims Act is the Wrong Rx*, 12 J. HEALTH CARE L. & POL'Y 136–13 (2009) (quoting Christopher D. Zalesky, Pharmaceutical Marketing Practices: ıcing Public Health and Law Enforcement Interests; Moving Beyond Regulation-Through- ation, 39 J. HEALTH L. 235, 241 & n.27 (2006)).

292. *See* HHS-DOJ 2016 ANNUAL REPORT, *supra* note 41, at 1–2.

293. *See id.*

294. *See* 21 U.S.C § 335a(c)(1).

295. *See* 21 U.S.C § 335a(a), (b).

296. *See* 21 U.S.C § 335a(c)(2)(A)(i)-(ii).

297. *See* 21 U.S.C § 335a(c)(2)(A)(iii).

298. *See* Health Care Programs: Fraud and Abuse; Revisions to the Office of Inspector

ral's Exclusion Authorities, 82 Fed. Reg. 4100–118 (Jan. 12, 2017) (effective Mar. 21,
).

299. *Id.* at 4112.

300. *Id.* at 4104.

301. *Id.* at 4115.

302. 31 U.S.C. §§ 3729–3733.

303. *See* Press Release, U.S. Dep't of Justice, Johnson & Johnson to Pay More Than $2.2
n to Resolve Criminal and Civil Investigations (Nov. 4, 2013),
://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-
investigations.

304. *Id.*

305. FDA, INSPECTIONS, COMPLIANCE, ENFORCEMENT, AND CRIMINAL
ESTIGATIONS, *supra* note 10; *see also* 18 U.S.C. § 1365(g) ("In addition to any other
y which has authority to investigate violations of this section, the Food and Drug
inistration . . . ha[s] authority to investigate violations of this section involving a consumer
uct that is regulated by a provision of law such Administration . . . administers.").

306. *See* President Ronald Reagan, Statement on Signing the Federal Anti-Tampering Act
14, 1983), www.presidency.ucsb.edu/ws/?pid=40636; *see also* H.R. REP. NO. 93, 98th
. (1983); United States v. Gentry, 925 F.2d 186, 187 (7th Cir. 1991).

307. *See generally* 18 U.S.C. § 1365.

308. 18 U.S.C. § 1365(a).

309. 18 U.S.C. § 1365(b).

310. 18 U.S.C. § 1365(c)(1).

311. 18 U.S.C. § 1365(d).

312. 18 U.S.C. § 1365(e).

313. 18 U.S.C. § 1365(f)(1).

314. *See* 18 U.S.C. § 1365 (a), (b), (c)(1), (d), (e), (f)(1).

315. *See, e.g.*, United States v. Nukida, 8 F.3d 665, 670–73 (9th Cir. 1993).

316. 18 U.S.C. § 1365(h)(1)(A), (h)(1)(B); *see also*United States v. Walton, 36 F.3d 32, 34
Cir. 1994).

317. 18 U.S.C. § 1365(h)(2); *see also* 21 U.S.C. § 321(m).

318. *Walton*, 36 F.3d at 32.

319. *Id.* at 33.

320. *Id.*

321. *Id.*

322. *Id.* at 34–35.

323. U.S. DEP'T OF JUSTICE, U.S. ATTORNEYS' MANUAL, TAMPERING WITH
NSUMER PRODUCTS—PROSECUTIVE POLICY, § 9-63.1110 (last updated May
), www.justice.gov/usao/eousa/foia_reading_room/usam/title9/63mcrm.htm.

324. *See id.*

325. *Id.*

326. 18 U.S.C. § 1365(a)(2).

327. 18 U.S.C. § 1365(a)(3). The statute defines "serious bodily injury" as "(A) a substantial
of death; (B) extreme physical pain; (C) protracted and obvious disfigurement; or (D)
acted loss or impairment of the function of a bodily member, organ, or mental faculty." *Id.*
65(h)(3).

328. 18 U.S.C. § 1365(a)(1), (a)(4), (e).

329. 18 U.S.C. § 1365(b).

330. 18 U.S.C. § 1365(c)(1), (d).

331. *See* GAO OCI REPORT, *supra* note 2, at 6.

332. *See, e.g., Walton*, 36 F.3d at 33 (conspiracy, tampering, and mail fraud charges).

333. *See, e.g.*, 18 U.S.C. § 287 ("Whoever makes or presents to any person or officer in the
military, or naval service of the United States, or to any department or agency thereof, any
upon or against the United States, or any department or agency thereof, *knowing such*
to be false, fictitious, or fraudulent, shall be imprisoned not more than five years and shall be
ct to a fine in the amount provided in this title.") (emphasis added).

334. *See, e.g.*, 18 U.S.C. § 1505 ("Whoever *corruptly*, or by threats or force, or by any
tening letter or communication influences, obstructs, or impedes or endeavors to influence,
uct, or impede the due and proper administration of the law under which any pending
eding is being had before any department or agency of the United States, or the due and
er exercise of the power of inquiry under which any inquiry or investigation is being had by
r House, or any committee of either House or any joint committee of the Congress"
nits a crime punishable by as many as five years in prison.) (emphasis added).

335. *See, e.g.*, 18 U.S.C. § 1341 ("Whoever, having devised or intending to devise any scheme
ifice to defraud . . . .").

336. *See* 18 U.S.C. §§ 287, 1341, 1343.

337. Opp. to Pet. for Cert. 11–12, Natale v. United States, No. 13-744 (Mar. 14, 2014).

13

Pharmaceutical Price Reporting: The "ABCs" and "123s" of Compliance

Jeffrey L. Handwerker & Vicky G. Gormanly

One of the not so well-guarded secrets of the pharmaceutical business is the complexity of price reporting responsibilities. This is one of the more confusing and underappreciated areas of compliance, and the consequences of a mistake can be severe. Under penalties of the False Claims Act (FCA), manufacturers must calculate and report Average Manufacturer Price (AMP) and Best Price (BP) for Medicaid covered drugs; Average Sales Price (ASP) for Medicare Part B (physician-administered) drugs; non-Federal Average Manufacturer Price (non-FAMP) and Federal Ceiling Price (FCP) for covered drugs sold to the VA; and a 340B Ceiling Price for outpatient drugs sold to so-called "340B entities."

These metrics are generally weighted averages of all prices at which a drug is sold to certain classes of customers. They require tracking of: (a) class of trade; (b) discounts; (c) so-called "lagged price concessions"; and (d) units sold. Similar to a Form 10-K or other SEC filings, the manufacturer must certify to the accuracy of the prices reported in most instances. And, if a drug manufacturer gets it wrong, the law imposes stiff penalties. Given the complexities, it is not surprising that qui tam relators, the U.S. Department of Justice (DOJ), and other enforcement agencies have made price reporting a key focus of their enforcement activities. Drug manufacturers invest substantial time and dollars, both with internal and external resources, in making sure that they timely and accurately report this data to the government. This chapter describes these price reporting responsibilities of drug manufacturers, including some of the pitfalls, and discusses enforcement trends in the pricing area.

Price reporting requirements are a complex undertaking for drug manufacturers. The government has made rooting out noncompliance a focal point of its enforcement activities. The absence of clear guidance in this area has made it even more challenging for manufacturers to develop policies and methodologies that will mitigate their risks in this area. Given the uncertainties and the consequences of errors, we believe that development of good documentation, such as policies and reasonable assumptions, are critical

to avoiding charges of recklessness under the FCA. Companies that identify material mistakes in their calculations should promptly seek to correct them through routine restatements of their price calculations.

Federal Prescription Drug Programs: Pricing and Reporting Requirements

Medicaid Drug Rebate Program (MDRP)

Q 13.1 What is Medicaid?

Enacted in 1965, Medicaid offers medical coverage for low-income families and other categorically related individuals who meet eligibility requirements.[1] Medicaid is a federal-state partnership program that is administered on the federal level by the Centers for Medicare & Medicaid Services (CMS).[2] State Medicaid agencies receive financial assistance from the federal government (Federal Financial Participation or FFP) in exchange for agreeing to meet minimum statutory and regulatory program coverage.

The Medicaid programs in the states and the District of Columbia cover prescription drugs, but they vary dramatically in their prescription drug coverage. This is because states have considerable flexibility to limit the amount, duration, and scope of prescription drug coverage in their Medicaid programs while in compliance with broad federal guidelines applicable to state Medicaid prescription drug benefits.

Q 13.2 What is the MDRP?

The MDRP was established by section 4401 of the Omnibus Budget Reconciliation Act of 1990 (OBRA '90).[3] The MDRP, which became operational in the first quarter of 1991, requires "manufacturers" to sign a national rebate agreement with CMS under which the manufacturer agrees to pay a unit rebate amount (URA) for each of its "covered outpatient drugs" reimbursed by a state Medicaid agency.[4] The agreement also requires manufacturers to report specific pricing metrics to CMS on a quarterly basis.[5] A manufacturer's failure to execute the rebate agreement could disqualify its products from federal Medicaid matching fund eligibility.[6]

Q 13.3 Who is a "manufacturer" under the MDRP?

Current regulations define the term "manufacturer" to mean "any entity that holds the [National Drug Code] for a covered outpatient drug or biological product" and meets one of the following criteria: (1) the entity is engaged in the "production, preparation, propagation, compounding, conversion or processing of covered outpatient drug products, either directly or indirectly by extraction from substances of natural origin, or independently by means of chemical synthesis, or by a combination of extraction or chemical synthesis"; (2) the entity is engaged in the "packaging, repackaging, labeling, relabeling, or distribution of covered outpatient drug products"; (3) for authorized generic products, the entity is the original holder of the NDA; or (4) for drugs subject to private

labeling arrangements, the entity is the entity under whose own label or trade name the product will be distributed.[7] Wholesale distributors and retail pharmacies are excluded.[8] When there is doubt, CMS considers the manufacturer holding title to the National Drug Code, or "NDC,"[9] as the entity responsible for reporting pricing metrics and for paying rebates on a covered outpatient drug.[10]

Q 13.4 What does the MDRP require of pharmaceutical manufacturers?

Since 1991, subsequent federal legislation and regulations have revised the definitions for the various MDRP pricing metrics as well as the requirements for manufacturers that participate in the MDRP, including the Veterans Health Care Act of 1992 (VHCA),[11] the Omnibus Budget Reconciliation Act of 1993 (OBRA '93),[12] the Medicare Prescription Drug and Modernization Act of 2003 (MMA),[13] the Deficit Reduction Act of 2005 (DRA)[14] and its implementing regulations,[15] and, most recently, the Patient Protection and Affordable Care Act of 2010 (PPACA) and its implementing regulations, which were finalized in February 2016.[16]

At its core, the MDRP requires pharmaceutical manufacturers to pay each state a quarterly rebate for each unit of a covered outpatient drug paid for by a state Medicaid agency and dispensed to a Medicaid beneficiary. Generally, the amount of the rebate depends on whether the drug is an innovator drug or a generic, and is a function of manufacturer-reported pricing data, namely the "best price" (BP)[17] and average manufacturer price (AMP)[18] for each drug. The MDRP rebate formula for innovator drugs is equal to the greater of: (1) AMP - BP, or (2) 23.1% of AMP (the basic rebate). In order to protect the Medicaid program from price increases, manufacturers must pay an additional rebate if there are drug price increases at a greater pace than the rate of inflation for urban areas (CPI-U). The MDRP rebate formula for non-innovator multiple source drugs is: AMP less a discounted unit rebate amount (URA).[19] Effective January 1, 2017, non-innovator multiple source drugs also are subject to an additional rebate based on the CPI-U.[20]

Under current law, manufacturers are required to report BP and AMP for each covered outpatient drug to CMS within thirty days of the end of each rebate period (calendar quarter).[21] Manufacturers also must report an AMP within thirty days after the end of each month.[22] CMS uses the pricing information obtained at the end of each quarter to calculate the URA for each drug and provides that information to the states.[23] Each state determines its Medicaid utilization for each covered outpatient drug in the quarter and reports this information to the manufacturer within sixty days of the end of the quarter.[24] The manufacturer then computes and pays the rebate amount to each state within thirty days of receiving the utilization information.[25] States report rebate amounts received to CMS and share the rebates with the federal government based on their federal medical assistance percentage (FMAP).

Q 13.5 Have there been recent modifications to the MDRP pricing metrics?

As noted in Q 13.4, the MDRP pricing metrics have been subject to numerous changes since the implementation of the program. From 2007 until the March 2010 passage of PPACA, the calculation and reporting of MDRP pricing metrics, including the transactions included in and excluded from AMP and BP, were governed by the DRA and its implementing regulations (the "DRA Final Rule"). PPACA, however, made several important changes to the MDRP pricing metrics,[26] including:

- Requiring a separate AMP calculation for inhaled, infused, instilled, implanted, or injected drugs that are not generally dispensed through a retail community pharmacy ("5i products");
- Excluding from AMP calculation for drugs other than 5i products ("Non-5i products") sales and discounts made to mail-order pharmacies, nursing home pharmacies, long-term care facility pharmacies, hospital pharmacies, clinics, charitable or not-for-profit pharmacies, government pharmacies, or pharmacy benefit managers;
- Raising the minimum rebate percentage to 23.1% for most single-source and innovator multi-source products, and to 17.1% for such products that are blood clotting factors or are approved exclusively for pediatric indications;[27]
- Raising the minimum rebate percentage for non-innovator multiple-source drugs to 13%;
- Revising the Medicaid URA calculation for products identified as a "line extension" (a new formulation) of an existing solid oral dosage form drug;
- Extending Medicaid rebates to utilization covered by Medicaid Managed Care Organizations; and
- Limiting URA to 100% of AMP.

Shortly after the passage of PPACA, CMS withdrew the detailed AMP calculation regulations implemented in the DRA Final Rule (that is, 42 C.F.R. § 447.504 and most of § 447.510) and replaced them with an instruction simply to calculate AMP "based on section 1927(k)(1) of the Social Security Act," leaving manufacturers with no binding regulatory guidance on AMP implementation.[28] In rescinding its AMP regulations, CMS announced that manufacturers may not "rely" on those regulatory provisions that were withdrawn and, rather, must only make reasonable assumptions consistent with PPACA.[29]

CMS issued a Proposed Rule to implement the PPACA changes to the MDRP on February 2, 2012 (Proposed Rule).[30] While this Proposed Rule would implement PPACA's statutory mandates, CMS also proposed other significant changes to the operation of the MDRP. On February 1, 2016, CMS published in the *Federal Register* its Final Rule (the "PPACA Final Rule"), as discussed *infra* in Q 13.7. With certain exceptions, the Final Rule became effective on April 1, 2016. Prior to publication of the PPACA Final Rule,

manufacturers operated without guidance in many areas of the MDRP, including with respect to the calculation of AMP.

In addition to statutory and regulatory changes resulting from PPACA, the Bipartisan Budget Act of 2015 (H.R. 1314) modified the Medicaid rebate statute to provide that non-innovator drugs are subject to an additional rebate beginning with the first quarter of 2017.

The Medicaid rebate statute also was revised further under section 705 of the Comprehensive Addiction and Recovery Act of 2016 (CARA),[31] which modified the definition of "line extension" under 42 U.S.C. 1396r-8(c)(2)(C), effective October 1, 2016, to exclude "an abuse-deterrent formulation of the drug (as determined by the [HHS] Secretary), regardless of whether such abuse-deterrent formulation is an extended release formulation."[32] This clarification appears to address concerns that if the term "line extension" were construed to apply to abuse deterrent technologies, it would dissuade development of alternatives, running counter to other government policies aimed at curbing drug abuse.[33] Although CMS previously had collected comments regarding such concerns, CMS ultimately declined to exclude abuse-deterrent formulations from the definition of "line extension" in the PPACA Final Rule, urging manufacturers to instead rely on the statutory language and upon reasonable assumptions.[34]

Most recently, the Bipartisan Budget Act (BBA) of 2018 (H.R. 1892) amended the Medicaid rebate statute modifying how the URA is calculated for certain drugs. Prior to the BBA of 2018, the alternative URA was calculated by multiplying the highest additional rebate for any strength of the original drug as a percentage of the original drug's AMP by the AMP of the line extension drug. The BBA of 2018 corrected this calculation such that the aforementioned calculation is conducted, and that amount is added to the base rebate of the line extension drug. As a result, the alternative URA calculation for line extensions will be greater than it was prior to this legislative correction. This new modification will become effective on October 1, 2018.

Q 13.6 Without clear MDRP regulatory guidance, what have been some issues confronted by pharmaceutical manufacturers in their AMP and BP pricing calculations?

Notwithstanding the issuance of the Final Rule, which provides clear guidance on many rebate calculation issues, pharmaceutical manufacturers continue to face enforcement risks with regard to their AMP and BP calculations. In addition to general challenges in complying with the rules and accurately calculating pricing metrics, manufacturers face particular scrutiny with regard to their treatment of bona fide service fees; bundled sales; and coupon, voucher, and patient assistance programs in computing their MDRP pricing metrics. For these issues and others where the regulations are not clear or defined, CMS directs that manufacturers must memorialize their methodologies in written "reasonable assumption" documents, which are contemporaneous records reflecting the manufacturer's rationale for adopting a particular methodology. Additionally, CMS permits manufacturers to "restate" their AMP and Best Price calculations where mistakes are identified.

Restatements generally are limited to the prior three years, unless the manufacturer obtains CMS's consent to restate for prior periods.[35] Some issues that are the subject of assumptions, and potential enforcement actions, are described below.

Service Fees. Service fees are payments to customers for the rendering of a particular service, rather than a payment relating to the purchase of a drug (which are properly considered a discount). CMS formally addressed the treatment of service fees with regard to the MDRP in the PPACA Final Rule, which expressly excludes "*bona fide* service fees" (BFSFs) from AMP and BP pricing calculations.[36] A BFSF is "a fee paid by a manufacturer to an entity that represents fair market value for a bona fide, itemized service actually performed on behalf of the manufacturer that the manufacturer would otherwise perform (or contract for) in the absence of the service arrangement, and that is not passed on in whole or in part to a client or customer of an entity, whether or not the entity takes title to the drug."[37] Fees meeting this definition are excluded from both AMP and BP. However, PPACA contains a new provision that excludes from AMP any "BFSFs paid by manufacturers to wholesalers or retail community pharmacies, including, but not limited to, distribution service fees, inventory management fees, product stocking allowances, and fees associated with administrative services agreements and patient care programs (such as medication compliance programs and patient education programs)."[38] Until the publication of the PPACA Final Rule, CMS had not interpreted this PPACA provision.[39] The four-part DRA test continues to apply to BP, but AMP had been subject solely to the PPACA statutory provision. Failure to accurately identify BFSFs has been an enforcement area for both the government and *qui tam* relators under the False Claims Act.

Bundled Sales. Bundled sales arrangements are also relevant to AMP and BP calculations. Under the DRA Final Rule, a bundled sale was defined as:

> an arrangement regardless of physical packaging under which the rebate, discount, or other price concession is conditioned upon the purchase of the same drug or drugs of different types . . . or some other performance requirement . . . or where the resulting discounts or other price concessions are greater than those which would have been available had the bundled drugs been purchased separately or outside the bundled arrangement.[40]

Under the PPACA Final Rule, the definition of bundled sale is revised as follows:

> Bundled sale means an arrangement regardless of physical packaging under which the rebate, discount, or other price concession is conditioned upon the purchase of the same drug, drugs of different types (that is, at the nine-digit National Drug Code (NDC) level) or another product or some other performance requirement (for example, the achievement of market share, inclusion or tier placement on a formulary), or where the resulting discounts or other price concessions are greater than those which would have been available had the bundled drugs been purchased separately or outside the

> bundled arrangement. ~~For bundled sales~~, (1) T ~~the~~ discounts in a bundled sale, including those discounts resulting from a contingent arrangement, are allocated proportionally to the total dollar value of the units of all drugs or products sold under the bundled arrangement. (2) For bundled sales where multiple drugs are discounted, the aggregate value of all the discounts in the bundled arrangement must be proportionally allocated across all the drugs or products in the bundle.

CMS regulations require that bundled sales discounts be allocated proportionately to the dollar value of the units of each drug or product sold under the bundled arrangement. For bundled sales where multiple drugs or products are discounted, the aggregate value of all the drugs or products should be proportionately allocated across all drugs or products of the bundle.[41] Failure to do so may result in reporting inaccurate BPs, which in turn has been cited in FCA cases as an area of enforcement.[42]

Coupons, Vouchers, and Patient Assistance Programs. Under the DRA Final Rule, CMS permitted manufacturers to exclude the effects of coupon programs, voucher programs, and patient assistance programs from their AMP and BP calculations. However, in order to do so, the program cannot be contingent on a purchase requirement, the full value of the assistance must be passed through to the patient, and the administrator of the program (or the pharmacy processing the coupon or voucher) may receive only a BFSF payment. In other words, the vendor cannot receive anything additional beyond the fair market value of its services in processing any such program for a manufacturer.

In the PPACA Final Rule, CMS adopts somewhat different standards. In the preamble to the PPACA Final Rule, CMS agrees "with the commenters' assessment that a benefit provided to a patient, even if it is provided at the pharmacy counter, is not a discount, rebate, payment or other financial transactions received by or passed through to the retail community pharmacy that must be included in AMP in accordance with section 1927(k)(1)(B)(ii) of the Act."[43] CMS rejects requests made by some commenters that it "adopt one general provision specifying that discounts or benefits to patients are excluded from AMP and best price."[44] Specifically, CMS notes that "there are variations and nuances about how each program is treated within AMP and best price."[45] In CMS's view, each offering should be addressed by the separate exclusion standards. Also, CMS addresses key questions related to the administration of patient assistance programs and free goods. Specifically, CMS agrees that such transactions "generally do not affect the prices paid by wholesalers or retail community pharmacies and . . . should be excluded from AMP in accordance with section 1927(k)(1) of the Act."[46] However, CMS cautions that "the voucher or benefit provided by the PAPs or other manufacturer-sponsored program must not be contingent on any other purchase requirement to be consistent in our treatment of free goods within AMP."[47] Given recent enforcement scrutiny on these types of programs, this is another area where it is important for manufacturers to adopt reasonable assumptions.

Q 13.7 Has CMS Issued a Final Rule?

On February 1, 2016, CMS published in the *Federal Register* its long-awaited final rule implementing the Medicaid rebate provisions of PPACA and otherwise making changes to the MDRP (the "PPACA Final Rule").[48] With certain limited exceptions, the PPACA Final Rule was effective on April 1, 2016 and is not retroactive to periods prior to that date. The voluminous PPACA Final Rule contains important new guidance for Medicaid rebate calculations, and in many ways deviates from the Proposed Rule that CMS issued in February 2012. Below, we provide a high-level summary of some of the key provisions in the PPACA Final Rule.

- *Presumed Inclusion*. In the Proposed Rule, CMS departed from its longstanding policy that required manufacturers to include sales to wholesalers in AMP unless there was "adequate documentation" that the drugs were "subsequently resold to any . . . excluded entit[y]." This rule, commonly referred to as "presumed inclusion," required companies to include sales to wholesalers in AMP in the absence of "adequate documentation" about the ineligibility of the end user. Instead of presumed inclusion, CMS proposed to adopt a "buildup" approach that potentially would have required manufacturers to obtain data on the end user for all sales to wholesalers.[49] The PPACA Final Rule retains the presumed inclusion requirement. In particular, CMS was "persuaded" that calculating AMP based on "actual, documented sales to retail community pharmacies or wholesalers for drugs distributed to retail community pharmacies is a less practical approach, which would represent a significant change from the methodology manufacturers have traditionally used to calculate AMP."[50]
- *Inclusion of Territories in the MDRP*. Although the current Medicaid Rebate Agreement and CMS's current regulations define "States" as "the 50 States and the District of Columbia,"[51] CMS has adopted its proposal to expand the scope of the Medicaid Drug Rebate Program (MDRP) by expanding the definition of "States" to include "the Commonwealth of Puerto Rico, the Virgin Islands, Guam, the Northern Mariana Islands and American Samoa."[52] This change will require manufacturers to include sales to eligible customers in the United States territories (Puerto Rico, U.S. Virgin Islands, Guam, the Northern Mariana Islands and American Samoa) in AMP and Best Price, and to pay rebates on Medicaid drug utilization by beneficiaries in the territories. CMS asserts that its "authority to include the territories in the MDR program is based on section 1101(a)(1) of the Act."[53] In the PPACA Final Rule, CMS delayed the effective date for inclusion of the territories in the Medicaid rebate program until April 1, 2017, and noted that "[i]f the territories need additional time to implement the MDR program in accordance with the requirements, we would consider allowing them to use the existing waiver authority" not to participate in the MDRP.[54] However, on November 15, 2016, CMS issued an interim final rule with comment period

delaying the expansion of the MDRP to the territories until April 1, 2020.[55]

- *Bona Fide Service Fees*. Bona fide service fees (BFSFs) are excluded from AMP and Best Price. Thus, determining whether a fee to a customer (or vendor) constitutes a bona fide service fee is a critical component of price reporting. In the PPACA Final Rule, CMS's definition of BFSF—applicable to any entity—retains its longstanding, four-part test.[56] The four-part test requires that the fee represent fair market value for a bona fide, itemized service actually performed on behalf of the manufacturer that the manufacturer would otherwise perform (or contract for) in the absence of the service arrangement; and that is not passed on in whole or in part to a client or customer of an entity, whether or not the entity takes title to the drug.[57] Manufacturers "can apply the definition with regard to their calculation of both AMP and best price."[58] CMS asserts that "the four-part test remains a definitive test to qualify a payment as a bona fide service fee and that manufacturers are responsible for meeting all four parts of the definition before a fee can qualify as a bona fide service fee."[59] Regarding the "not passed on" element of the four-part test, CMS is permitting manufacturers "to presume, in the absence of any evidence or notice to the contrary, that the fee paid is not passed on to a client, or customer of any entity (if a fee paid meets the other elements of the definition of bona fide service fee)."[60] As to fair market value, CMS defers to manufacturers as to the level of evidence required, but requires that manufacturers obtain evidence of fair market value "contemporaneously" with the price-reporting treatment.[61]
- *Bundled Sales*. Since 2007, bundled sales have been defined as "any arrangement regardless of physical packaging under which the rebate, discount, or other price concession is conditioned upon the purchase of the same drug, drugs of different types (that is, at the nine-digit NDC level) or another product or some other performance requirement (for example, the achievement of market share, inclusion or tier placement on a formulary), or where the resulting discounts or other price concessions are greater than those which would have been available had the bundled drugs been purchased separately or outside the bundled arrangement."[62] The DRA Final Rule provided: "For bundled sales, the discounts are allocated proportionally to the total dollar value of the units of all drug[s] sold under the bundled arrangement. For bundled sales where multiple drugs are discounted, the aggregate value of all the discounts in the bundled arrangement shall be proportionally allocated across all the drugs in the bundle."[63] While the PPACA Final Rule adopted similar language, it provides in pertinent part that "the discounts in a bundled sale, *including those discounts resulting from a contingent arrangement*, are allocated proportionally to the total dollar value of the units of all drugs or products sold under the bundled arrangement."[64] This new wording could be read to suggest that manufacturers may allocate both contingent and

non-contingent discounts if they are part of the bundled arrangement (for example, if the discounts are greater than they otherwise would have been if negotiated separately outside of the bundle); however, CMS noted in the preamble that it did not intend a change in its longstanding bundling policy.[65]

- *Authorized Generics*. The PPACA Final Rule provides that a primary manufacturer's sales of an authorized generic drug to a secondary manufacturer may be included in the primary manufacturer's AMP if the secondary manufacturer meets the statutory definition of retail community pharmacy, that is, it must be "acting as a wholesaler." CMS does not state precisely when a manufacturer is acting as a wholesaler, but the regulations appear to provide that authorized generic transactions may be included in AMP if: (a) the secondary manufacturer is engaged in wholesale distribution of prescription drugs to retail community pharmacies; and (b) the secondary manufacturer does not re-label or repackage the product with its own or a different NDC.
- *Original NDA*. Medicaid rebate calculations vary depending upon the classification of the drug, with a minimum rebate amount of 23.1% applicable to single source drugs and innovator multiple source drugs, and a minimum rebate amount of 13% applicable to non-innovator multiple source drugs.[66] Both single source and innovator multiple source products turn on whether the product was originally marketed under an "original NDA." CMS proposed to define "original NDA," for purposes of determining whether a product qualifies as a single source drug or an innovator multiple source drug, by adding the following: "For purposes of the MDR program, an original NDA is equivalent to an NDA filed by the manufacturer for approval under section 505 of the FFDCA for purposes of approval by the FDA for safety and effectiveness."[67] CMS generally finalizes its proposed approach but creates a narrow exceptions process for manufacturers to request that a product approved under an NDA be classified as a non-innovator multiple source drug.[68] CMS allowed manufacturers until April 1, 2017 to make any necessary data changes before it would take any administrative action.[69]
- *Standard AMP*. Standard AMP applies to all drugs that are not so-called 5i products. See below for a discussion of AMP for 5i products. The PPACA Final Rule provides that "sales to home health care, home infusion and specialty pharmacies may be included in the [standard] AMP calculation but only to the extent that they meet the definition of retail community pharmacy at section 1927(k)(10) of the Act, which specifically excludes entities that dispense medications primarily through the mail."[70] CMS declined to define "specialty pharmacy," but stated that sales to specialty pharmacies (and home infusion pharmacies and home healthcare providers) should be included in the standard AMP calculation "when the pharmacies actually qualify as retail community pharmacies"[71] under the statutory definition. CMS states that manufacturers must

assess whether specialty pharmacies or home health pharmacies act as retail community pharmacies and do not primarily dispense through the mail.

- *5i Drugs*. The Medicaid rebate statute provides for a separate AMP calculation for inhalation, infusion, instilled, implanted, or injectable (5i) drugs that are "not generally dispensed through a retail community pharmacy."[72] In the PPACA Final Rule, CMS grants manufacturers the flexibility to determine whether their drugs qualify as 5i drugs.[73] To determine whether a 5i drug is "not generally dispensed" through a retail community pharmacy, CMS requires manufacturers to apply a monthly 70:30 test, such that "a 5i drug would be considered not generally dispensed through a retail community pharmacy when the manufacturer determined that 70 percent or more of its sales . . . are to entities other than retail community pharmacies."[74] This calculation must be done on a unit basis at the NDC-9 level. As noted below, CMS will allow manufacturers to apply a smoothing process in this monthly determination.
- *Oral Drugs Not Generally Dispensed Through Retail Community Pharmacies*. CMS received several comments regarding how manufacturers should treat oral drugs that are not dispensed through retail community pharmacies. Indeed, many oral non-5i products are sold exclusively through specialty pharmacies that dispense primarily through the mail, and thus are not retail community pharmacies. In those circumstances, the drug will have no AMP-eligible sales. In response to these comments, CMS cites the continued availability of the presumed inclusion approach for sales to wholesalers as a basis to believe that most or all drugs will have at least some AMP-eligible sales. CMS requires that "when there are any [standard] AMP eligible sales, the calculation should be made based on those sales to [retail community pharmacies]."[75] The PPACA Final Rule is unclear about what manufacturers should report in the event that there are no AMP-eligible sales, even after application of the presumed inclusion rule.
- *Smoothing*. In the PPACA Final Rule, CMS adopts a smoothing methodology for lagged price concessions (for example, rebates, chargebacks and other price concessions not known at the time of sale) that now makes explicit that smoothing should be performed at the NDC-9 level (meaning for each different dosage form or strength of a product), and that incorporates into the regulatory text the same details and level of specificity as the regulation on ASP smoothing in the Medicare Part B context.[76] In addition, CMS also permits, but does not require, two additional types of smoothing: (1) smoothing to estimate lagged ineligible sales in AMP; and (2) smoothing to determine whether a 5i drug is "not generally dispensed" through RCPs, and thus subject (or not) to the 5i AMP calculation.
- *Best Price Determination*. The PPACA Final Rule includes a list of Best Price–eligible transactions that corresponds precisely to the statute.[77] Because the statute does not include them, the PPACA Final Rule generally excludes direct sales to

patients from Best Price. This is a significant departure from the prior regulations, which had included these transactions in Best Price. However, if a sale to a patient is a free good contingent on a purchase requirement, the regulations provide that the transaction should come back into Best Price because contingent-free goods programs must be included in Best Price. Regarding Best Price eligibility of 340B covered entities, the PPACA Final Rule conforms to the statute and excludes "*any prices* charged to a covered entity described in [SSA] section 1927(a)(5)(B) . . . (including inpatient prices charged to hospitals described in section 340B(a)(4)(L) of the PHSA [Public Health Service Act])."[78] With respect to authorized generics, the primary manufacturer must include in Best Price the price of the authorized generic drug when sold to a "manufacturer, wholesaler, retailer, provider, HMO, non-profit entity, or governmental entity in the United States."[79]

- *Stacking for Best Price Determination*. The PPACA Final Rule addresses the concept of "stacking," that is, circumstances in which discounts from different transactions should be added together in the calculation of Best Price. Unfortunately, CMS leaves several issues to interpretation, which will necessitate manufacturers' adopting reasonable assumptions on the topic of stacking (among others).
- *Line Extensions*. Under PPACA, a "line extension" is subject to a higher rebate payment than other innovator drugs because the line extension will carry forward the base date AMP for the product that the line extension references. PPACA defines a "line extension" as "a new formulation of [an innovator drug in an oral solid dosage form], such as an extended release formulation."[80] Although CMS took clear positions regarding certain aspects of the definition, it did not finalize a definition, but instead decided to solicit additional comments for an extended sixty-day period. CMS informed manufacturers that "at this time, manufacturers are to rely on the statutory definition of line extension . . . and where appropriate, are permitted to use reasonable assumptions in their determination of whether their drug qualifies as a line extension drug."[81] As discussed above, CARA section 705 revised the definition of "line extension" to exclude "an abuse-deterrent formulation of the drug (as determined by the [HHS] Secretary), regardless of whether such abuse-deterrent formulation is an extended release formulation."[82] Additionally, the BBA of 2018 updated the line extension URA calculation such that the previous calculation (that is, the highest additional rebate for any strength of the drug as a percentage of the original drug's AMP, multiplied by the AMP of the line extension drug) will now be added to the base rebate of the line extension drug, which will result in higher URAs than under the original provision.
- *Restatements*. Manufacturers currently must report to CMS any revisions to AMP, Best Price, customary prompt pay discounts, or nominal prices for twelve quarters after the quarter in which the data were due.[83] CMS has now adopted (on a non-retroactive basis) five exceptions to the twelve-quarter restatement window, as

follows: (1) the change is a result of the drug category change or a market date change; (2) the change is an initial submission for a product; (3) the change is due to termination of a manufacturer from the MDR program for failure to submit pricing data and [the manufacturer] must submit pricing data to re-enter the program; (4) the change is due to a technical correction, that is, not based on any changes in sales transactions or pricing adjustments from such transactions; or (5) the change is to address specific rebate adjustments to states by manufacturers, as required by CMS or a court order, or under an internal investigation, or an OIG or Department of Justice (DOJ) investigation.[84] With respect to base date AMPs, CMS finalizes its proposal offering manufacturers the option to report a revised base date AMP to CMS within the first four full calendar quarters following the publication date of the PPACA Final Rule. Specifically, CMS agreed with commenters that it was important to permit manufacturers the ability to restate base date AMPs on a "product-by-product basis," and announced that it will permit manufacturers to report "an Affordable Care Act base date AMP."[85] As a condition of any such restatement, CMS requires manufacturers to have actual and verifiable documentation to support the restatement.[86] Moreover, CMS concludes that such restatements need not include the territories in the base date AMP "given the prospective nature of this rule."[87]

The PPACA Final Rule touches almost every aspect of the Medicaid rebate calculation, as well as reimbursement issues, such as the calculation and implementation of Federal Upper Limits (FULs) for multiple source drugs, and the requirement for Medicaid programs to reimburse for covered outpatient drugs (including single source drugs) based on the lower of (1) actual acquisition cost (AAC) plus a professional dispensing fee established by the state, or (2) providers' usual and customary charges to the general public.[88] Moreover, the PPACA Final Rule continues to underscore the importance of reasonable assumptions documentation, provided such interpretations are "consistent with the requirements and intent of Section 1927 of the Act and federal regulations . . . and consistent with the national rebate agreement."[89] Unlike the prior CMS regulations, this formulation notably no longer references "customary business practices" as a basis for a reasonable assumption.[90]

Where the rule is unclear or silent, it is a good practice for manufacturers to adopt and document assumptions explaining the basis for their interpretations of the statute and the rule. On November 9, 2016, CMS published a proposed notice announcing changes that would be made to the Medicaid Rebate Agreement.[91] Under the current Medicaid Rebate Agreement, manufacturers must "comply with the conditions of 42 U.S.C. 1396s [presumably an erroneous reference to the Medicaid rebate statute], changes thereto and implementing regulations as the Secretary deems necessary and specifies by actual prior notice to the manufacturer."[92] In the notice, CMS proposed to add a requirement for manufacturers to comply with CMS guidance, and proposed to eliminate the requirement to provide notice of incorporation of such guidance into the Medicaid Rebate

Agreement.[93] Specifically, under the proposal, manufacturers would agree to "comply with the conditions of 42 U.S.C. § 1396r-8, changes thereto, implementing regulations, agency guidance, and this agreement." This proposed change was among the subjects on which stakeholders commented.

The proposal also included a number of other changes. For example, CMS proposed replacing the current definition of "Medicaid Utilization Information" with "State Drug Utilization Data," defined as explicitly excluding 340B purchased drugs (the current definition does not address 340B drugs).[94] Also included was a change to the definition of "unit" for the purpose of calculating Medicaid rebates: "drug unit in the lowest *dispensable* amount" (as opposed to "identifiable amount," under the current wording).[95] The proposal also contained new provisions relating to consequences for manufacturers excluded from federal programs by OIG,[96] new requirements regarding transfers of manufacturer ownership,[97] and reporting requirements related to pricing on applicable NDCs and manufacturer bankruptcy filings.[98]

On March 23, 2018, CMS published a final notice containing the updated, finalized version of the Medicaid Rebate Agreement,[99] and responding to stakeholder comments. The changes noted above were finalized largely as proposed, with minor changes and corrections.[100] According to the final notice, manufacturers with an existing active agreement must sign and submit the updated agreement, which will become effective on October 1, 2018.[101]

340B Drug Discount Program ("340B Program")

Q 13.8 What is the 340B Program?

Following enactment of the MDRP in 1990, many pharmaceutical manufacturers discontinued discounting pricing to clinics and other healthcare providers serving low-income, uninsured or otherwise underserved populations because the MDRP failed to exempt such discounts from the BP calculation.[102] The 340B Program remedied this issue by allowing specified Public Health Service Act (PHS)-funded grantees and other safety net healthcare providers[103] to purchase prescription drugs at reduced prices that are exempt from Medicaid BP requirements.[104] The Health Resources and Services Administration (HRSA) administers the 340B Program, through the Office of Pharmacy Affairs (OPA).[105]

Q 13.9 What does the 340B Program require of pharmaceutical manufacturers?

The 340B Program requires pharmaceutical manufacturers to enter into a Pharmaceutical Pricing Agreement (PPA) with the Department of Health and Human Services (HHS) Secretary under which they must agree to sell their products to 340B "covered entities" at no more than the "340B ceiling price for covered outpatient drugs" in order to receive federal Medicaid and Medicare Part B reimbursement for those

products.[106] The 340B Ceiling Price is the difference between the AMP and the Medicaid URA. The 340B program incorporates the MDRP AMP and BP pricing metrics and, as a result, OPA does not require manufacturers separately to report AMP or BP data.[107] Unlike the MDRP, which requires manufacturers to pay retrospective rebates, the 340B program requires manufacturers to provide prospective discounts on the invoice price to participating covered entities.

Q 13.10 Are 340B covered entities subject to any restrictions?

Under the 340B Program, 340B covered entities are subject to two important restrictions, which are designed to protect manufacturers. First, they may not resell or otherwise transfer the discounted drugs to anyone other than their patients.[108] Failure to comply with this requirement constitutes diversion, which subjects the offender to serious penalties, potentially including exclusion from the 340B Program. Second, because manufacturers are required under the MDRP to pay rebates on outpatient drugs reimbursed by Medicaid, covered entities must comply with particular billing and reporting procedures to avoid "duplicate discounting" (that is, the application of both a 340B discount and a Medicaid rebate on the same drug).[109]

Q 13.11 How do 340B covered entities acquire drugs at the 340B price?

According to HRSA, covered entities who are properly registered in the 340B Program may obtain drugs at the 340B price either through their own pharmacies, and/or by contracting with one or more external retail pharmacies.[110] HRSA guidelines suggest a "ship to/bill to" process whereby the covered entity may purchase drugs, but require the manufacturer or wholesaler to ship them to an external contracted pharmacy, which then provides all pharmacy services related to the dispensing of the 340B Program drugs.[111] Under HRSA's approach, the contractor must provide the covered entity with financial statements, a detailed status report of collections, and a summary of receiving and dispensing records.[112] The contract pharmacy also must work with the covered entity to establish and maintain a tracking system to prevent diversion.[113] This methodology is not set out in the statute or regulations, but instead is an approach proposed by HRSA in guidance documents.

Q 13.12 Are 340B covered entities restricted on the number of its contract pharmacies?

Prior to April 5, 2010, HRSA guidance limited covered entities to one pharmacy per site.[114] Covered entities seeking to employ other types of pharmacy arrangements, or to implement both of the allowable methods of providing pharmacy services, were required to apply to OPA for an Alternative Method Demonstration Project (AMDP).[115] Based on subsequent HRSA guidance effective April 5, 2010, covered entities now may enter contracts with more than one external pharmacy to obtain the benefits of the 340B

Program.[116] This guidance has caused some controversy in light of the dramatic expansion of contract pharmacy networks that followed from its issuance. It may be the subject of review in the future.

Q 13.13 Have there been developments over time affecting the 340B Program?

In addition to the 2010 contract pharmacy guidance discussed above, legislative developments and related rulemaking and litigation have contributed significantly to the 340B Program's enhanced reach and visibility. In March 2010, PPACA amended the 340B statute to expand the number of entities who are eligible, as well as to strengthen oversight of covered entity and manufacturer compliance with the requirements of the program. With regard to manufacturers, PPACA requires the HHS Secretary to:

- Develop a system to verify the accuracy of ceiling prices calculated by manufacturers and charged to covered entities;
- Establish procedures for manufacturers to issue refunds to covered entities in the event of an overcharge;
- Develop a system to provide online access to applicable ceiling prices for covered drugs;
- Develop a mechanism by which rebates and other discounts provided by manufacturers to other purchasers are reported to the Secretary, and appropriate credits and refunds are issued to covered entities if necessary;
- Perform selective auditing of manufacturers and wholesalers to ensure the integrity of the 340B Program; and
- Impose civil monetary penalties against manufacturers that knowingly and intentionally overcharge covered entities (not to exceed $5,000 for each instance of overcharging a covered entity that may have occurred).[117]

With regard to covered entities, PPACA requires the HHS Secretary to:

- Develop procedures to enable and require covered entities to regularly update information maintained on the HHS website and a system for HHS to verify the accuracy of such information;
- Develop more detailed guidance describing acceptable methodologies and options for billing covered drugs to state Medicaid agencies in a manner that avoids duplicate discounts;
- Establish a single, universal, and standardized identification system by which manufacturers can identify covered entity sites; and
- Impose additional sanctions in appropriate cases as determined by the HHS Secretary, by one or more of the following: (1) requiring a covered entity that

> knowingly and intentionally violates prohibitions on diversion or duplicate discounts to pay a monetary penalty to manufacturers in the form of interest on sums for which the covered entity is found liable; (2) removing the covered entity from the discount program and disqualifying it from re-entry for a reasonable period of time (in the case of a violation that is systematic and egregious as well as knowing and intentional); and (3) referring matters to other appropriate federal authorities for appropriate action.[118]

On September 20, 2010, HRSA issued an advance notice of proposed rulemaking to carry out this mandate, inviting comments on how to implement the penalties;[119] and on June 17, 2015, HRSA published its proposed regulations.[120] The comment period for the proposed regulations was extended until May 9, 2016 to allow HRSA to solicit additional comments regarding alternatives to the proposed ceiling price calculation methodology and comments as to whether HRSA should more clearly define the "knowing and intentional" standard for violations.[121]

On January 5, 2017, HRSA published the final rule (CP/CMP Final Rule) regarding how manufacturers should calculate the 340B ceiling price and providing for civil monetary penalties (CMPs) against manufacturers that knowingly and intentionally charge a covered entity more than the ceiling price.[122] Below are highlights regarding some of the key areas addressed.

Penny Pricing. In the CP/CMP Final Rule, HRSA incorporates its longstanding—and somewhat controversial—penny pricing policy, which provides that in instances where the ceiling price formula would result in an amount less than $0.01, the ceiling price will be $0.01.[123] HRSA considered commenters' suggestions regarding alternatives (such as using the Federal Ceiling Price, the most recent positive ceiling price from previous quarters, and nominal price), but rejected these alternatives stating that they would be "inconsistent with the 340B ceiling price formula established in [the statute] and would raise the 340B ceiling prices above the statutory formula in ways that would be inconsistent with the statutory scheme."[124]

Ceiling Prices for New Covered Outpatient Drugs. The CP/CMP Final Rule replaces the guidelines HRSA's 1995 guidelines for estimating a ceiling price for new drugs and then making refunds in certain cases. Under the CP/CMP Final Rule, manufacturers must estimate a 340B ceiling price for new drugs "until an AMP is available, which should occur no later than the 4th quarter that the drug is available for sale."[125] That formula is "wholesale acquisition cost [WAC] minus the appropriate rebate percentage."[126] Once an AMP is available, then the manufacturer must "calculate the actual 340B ceiling price as described in [42 C.F.R. § 10.10(a)] and offer to refund or credit the covered entity the difference between the estimated 340B ceiling price and the actual 340B ceiling price within 120 days of the determination by the manufacturer that an overcharge occurred."[127] Unlike HRSA's 1995 guidelines on new drug price estimation, the manufacturer must take the initiative to offer this repayment to (or to credit) covered entities that purchased at an estimated ceiling price exceeding the "actual" ceiling price for the quarter in question,

instead of putting the burden on covered entities to request a repayment. Manufacturers must offer the repayment in all instances, including where the differential between the estimated and actual ceiling prices was de minimis, and without any offsets for inadvertent undercharges. Citing the new regulatory text in 42 C.F.R. § 10.11 on CMPs, HRSA states that "if a manufacturer refuses to refund covered entities after it has been determined covered entities were overcharged during the time the 340B ceiling price was estimated, that could meet the knowingly and intentionally [intent] standard to apply a CMP.[128]

Civil Monetary Penalties. HRSA defers to the HHS Office of Inspector General (OIG) for a case-by-case analysis of when the "knowing and intentional" overcharge standard is met (declining even to define "knowing and intentional" so as to provide the OIG with flexibility). The preamble to the CP/CMP Final Rule does, however, provide a non-exhaustive list of circumstances where HRSA would assume that a manufacturer did not "knowingly and intentionally" overcharge a covered entity.[129] The CP/CMP Final Rule also provides that specific intent to violate the 340B statute is not necessarily required to warrant an application of the penalty provision.[130] Further, HRSA suggests in the CP/CMP Final Rule that manufacturers could face CMP risk if they do not affirmatively recalculate 340B prices and refund covered entities if Medicaid rebate metrics are restated in the routine course. In addition, manufacturers are not permitted to offset reductions in 340B ceiling prices that result from Medicaid rebate restatements with increases in 340B ceiling prices resulting from restatements (thus requiring that a manufacturer provide a refund to a 340B covered entity even in circumstances where the net amount it owes to the entity is zero or negative).

The CP/CMP Final Rule originally was slated to become effective March 6, 2017, but because the effective date falls in the middle of a quarter, HRSA had planned to begin enforcing the rule's requirements at the start of the next quarter (April 1, 2017). However, as of March 17, 2017, the effective date of the CP/CMP Final Rule has been delayed three times. First, in response to a memorandum published by the Trump administration entitled "Regulatory Freeze Pending Review," HRSA published a final rule on March 6, 2017 delaying the effective date to March 21, 2017. HRSA explained, "the temporary delay . . . is necessary to give Department officials the opportunity for further review and consideration of new regulations, consistent with the Assistant to the President and Chief of Staff's memorandum."[131] Second, on March 17, 2017, HRSA issued an interim final rule further delaying the effective date of the CP/CMP Final Rule to May 22, 2017, and inviting comments on whether a longer delay to October 1, 2017 would be more appropriate.[132] In the interim final rule, HRSA explains the revised effective date is necessary to "consider questions of fact, law, and policy raised in the rule, consistent with the 'Regulatory Freeze Pending Review' memorandum" and to provide affected parties sufficient time to comply with the CMP Final Rule's requirements. HRSA also points to President Trump's January 20, 2017 Executive Order entitled "Minimizing the Economic Burden of the Patient Protection and Affordable Care Act Pending Repeal," explaining that an effective date of March 21, 2017 "does not allow for a sufficient amount of time to

consider the regulatory burdens that may be posed by this issuance and does not provide regulated entities sufficient time to come into compliance with the requirements of the rule." Finally, on August 21, 2017, HRSA solicited comments on further delaying the effective date of the CP/CMP Final Rule to July 1, 2018, and, after considering the comments submitted, HHS issued a final rule implementing this further delay.[133]

PPACA also requires the HHS Secretary to promulgate regulations to establish and implement an administrative dispute resolution process to address any allegations of overcharging by manufacturers or violations of the program integrity requirements by covered entities.[134] On August 12, 2016, HRSA released a proposed rule governing the 340B Administrative Dispute Resolution (ADR) process, with comments due in October of 2016).[135] The proposed ADR process would replace the current process for resolving disputes between manufacturers and covered entities and implement key 340B program integrity provisions added under PPACA.[136] Under the proposed rule, a 340B ADR Panel would review (1) covered entity claims of manufacturer overcharges and (2) post-audit manufacturer claims against covered entities for violations of duplicate discount or diversion provisions.[137] The panel would decide each case based on written submissions, including the original claims and covered entity information requests, which require a manufacturer response.[138] Potentially concerning aspects of the proposed rule for either manufacturers or covered entities include the short time frame allowed manufacturers for responses to covered entity information requests (twenty days), and also the proposal by HRSA that final Panel decisions could be the basis for imposing sanctions against either manufacturers or covered entities, though the sanctions would not be determined in the ADR process itself and the proposed rule does not clarify what steps would be taken to actually impose the sanctions.[139] This proposed rule, however, was withdrawn on August 1, 2017.

Also, on August 28, 2015, HRSA issued proposed "omnibus" guidance, addressing numerous important topics, such as the definition of a "patient," duplicate discounts, diversion, contract pharmacies, the "must offer" provision, among many other topics.[140] Shortly after publication of HRSA's omnibus guidance, it published an Information Collection Request regarding amending the PPA via an addendum to incorporate the "must offer" provision and quarterly manufacturer reporting of calculated ceiling prices.[141] Comments were submitted in October 2015. The guidance had been pending review at OMB, but on January 30, 2017, was withdrawn, presumably, in light of the Regulatory Freeze Pending Review memorandum discussed above.[142]

Several other recent 340B developments are noteworthy. First, on November 7, 2016, HRSA finalized an addendum to the PPA that incorporates the statutory "must offer" provision (requiring manufacturers to represent they will offer covered outpatient drugs at or below the reported 340B ceiling price) and ceiling price reporting requirements. Participating manufacturers were required to return the executed addendum by December 31, 2016.[143] The provisions included in the addendum implement PPACA section 7102(a), which tasks HHS with adding the two new requirements to the PPA.[144] Second,

HRSA has continued its auditing efforts in keeping with requirements under the Public Health Services Act.[145] HRSA has published results from over 100 audits of covered entities in 2016, and over 160 in 2017. In addition, HRSA has performed audits of manufacturers. As of April 22, 2018, the HRSA website has published results from eleven manufacturer audits, none of which included any adverse findings.[146]

Second, in the Medicare proposed outpatient prospective payment system (OPPS) rule for 2018,[147] CMS proposed OPPS payment rate reductions for certain drugs purchased by certain types of hospitals under the 340B program.[148] Affected hospitals will be required to include a new modifier on claims for a drug acquired under the 340B program.[149] CMS finalized its proposal in the OPPS CY 2018 final rule.[150] Effective January 1, 2018, OPPS payments for separately payable 340B drugs changed from 106% of ASP to ASP minus 22.5%. This ASP minus 22.5% payment applies to both innovator and generic drugs. In response to the OPPS final rule, a group of three hospital systems and three hospital trade associations have filed suit against HHS (i) alleging that these 340B cuts violate the statute, and (ii) seeking an injunction preventing HHS from implementing the reduced reimbursement rate.[151] Specifically, plaintiffs have alleged that the rate reduction for 340B drugs is arbitrary and capricious, and as such, it should be struck down pursuant to the Administrative Procedures Act. The U.S. District Court for the District of Columbia dismissed the plaintiffs' complaint because they had not yet filed a claim for reimbursement (nor had the reimbursement rate taken effect), and as such, they failed to meet a jurisdictional requirement set forth by 42 U.S.C. § 405(g) for judicial review of Medicare rulemakings. Rather than wait for a final determination before filing an amended complaint, the plaintiff hospitals have appealed to the D.C. Circuit. As of February 23, 2018, this appeal is pending before the circuit court. Third, there are legislative proposals currently under consideration in Congress that would reform the 340B Program. Rep. Larry Bucshon (R-IN) has introduced the 340B Protecting Access for the Underserved and Safety-net Entities (PAUSE) Act (H.R. 4710) that would implement a two-year moratorium on certain new 340B hospital covered entities and child sites, and also require certain data reporting. A similar proposal in the Senate, the Helping Ensure Low-Income Patients Have Access to Care and Treatment (HELP) Act (S. 2312), would institute a two-year moratorium on the registration of certain hospitals and associated child sites, create new eligibility requirements for hospitals and child sites participating in the program, and add new reporting requirements. In addition to the HRSA activities described above, a major development occurred on May 23, 2014, when the U.S. District Court for the District of Columbia issued a memorandum opinion in *Pharmaceutical Research & Manufacturers of America v. United States Department of Health & Human Services*, vacating the first rule that HRSA had ever issued to implement the 340B Program—the orphan drug exclusion rule—because, according to the court, the rule exceeded the scope of HRSA's rulemaking authority relative to the 340B Program.[152] Specifically, this case involved a carve-out from 340B eligibility added by PPACA, under which "drugs designated as orphan drugs" by the FDA were carved out of the obligation to sell at the

340B price to certain categories of entities added by PPACA. On July 22, 2014, HRSA issued a putative interpretive rule interpreting this provision to apply only when the drug was used for the orphan indication; when an orphan drug was used for a non-orphan indication, the manufacturer still would be obligated to sell at the 340B price. On October 15, 2015, the court struck down HRSA's rule on the merits that the rulemaking was outside of HRSA's rulemaking authority under the statute, and the government chose not to appeal the decision. In so holding, the court limited HRSA's 340B Program rulemaking authority to three specific areas: (1) the establishment of an administrative dispute resolution process; (2) the "regulatory issuance" of precisely defined standards of methodology for calculation of ceiling prices; and (3) the imposition of monetary civil sanctions.[153] As a result of this decision, the scope of the agency's future rulemaking authority concerning various aspect of the 340B program is at best uncertain, and is likely limited.

Q 13.14 What key topics are addressed in the proposed omnibus guidance for the 340B program?

As noted in Q 13.13, HRSA's omnibus guidance addresses numerous topics.[154] Below are highlights regarding some of the key areas addressed.

Definition of "Patient." The guidance proposes that an "individual will be considered a patient of a covered entity, on a prescription-by-prescription or order-by-order basis" if the following six criteria are met: (1) "[t]he individual receives a health care service at a facility or clinic site which is registered for the 340B Program and listed on the public 340B database"; (2) "[t]he individual receives a health care service provided by a covered entity provider who is either employed by the covered entity or who is an independent contractor for the covered entity, such that the covered entity may bill for services on behalf of the provider"; (3) "[a]n individual receives a drug that is ordered or prescribed by the covered entity provider as a result of the service described in (2); (4) "[t]he individual's health care is consistent with the scope of the Federal grant, project, designation, or contract"; (5) "[t]he individual's drug is ordered or prescribed pursuant to a health care service that is classified as outpatient"; and (6) "[t]he individual's patient records are accessible to the covered entity and demonstrate that the covered entity is responsible for care."[155]

The guidance would supersede the definition of patient set forth by HRSA in 1996.[156] The definition of patient is crucial because the statutory prohibition against diversion (discussed below) hinges on whether the individual receiving a drug is a patient of a covered entity.[157] The proposed guidance notes that exceptions to the definition may arise in the event of an HHS-declared public health emergency, though it is unclear what criteria would be used for emergency patient designations.[158]

Duplicate Discounts. The proposed guidance would expand the 340B Medicaid Exclusion File, the online list published by HRSA of covered entities that use 340B drugs for Medicaid patients (or as the guidance states, "Medicaid FFS [Fee-for-Service] patients"[159]). Under the guidance: "[A] covered entity will be listed on the public 340B database if it

notifies HHS at the time of registration whether it will purchase and dispense 340B drugs to its Medicaid FFS patients (carve-in) and bill the State, or whether it will purchase drugs for these patients through other mechanisms (carve-out)."[160] Carve-in entities will have their Medicaid billing number, National Provider Identifier (NPI) or both listed in the Exclusion File.[161] However, the proposed guidance asserts that:

> The covered entity may make a different determination regarding carve-in or carve-out status for MCO [Managed Care Organization] patients than it does for FFS patients. An entity can make different decisions by covered entity site and by MCO, but must provide to HRSA identifying information of the covered entity site, the associated MCO, and the decision to carve-in or carve-out. This information may be made available on a 340B Medicaid Exclusion File.[162]

In the guidance, HRSA sought comments as to whether covered entities should be allowed "to take a more nuanced approach to purchasing, for example, only using 340B drugs for Medicaid FFS and MCO patients when appropriate for service delivery," and other alternatives.[163] Finally, in lieu of directly establishing a single identification system for tracking claims, HRSA "encourage[s] covered entities, States, and Medicaid MCOs to work together to establish a process to identify 340B claims."[164]

Diversion. The proposed guidance suggests that covered entities would be "expected to work with manufacturers regarding repayment within 90 days of identifying the violation" and that a "covered entity must notify HHS and each affected manufacturer of diversion and is expected to document notification attempts in auditable records."[165] A manufacturer may use discretion as to whether to request repayment "based on its own business considerations," so long as the manufacturer continues to comply with applicable law (e.g., the federal anti-kickback statute).[166] However, the guidance does not clarify how declining to seek repayment from a covered entity would affect CMS price reporting requirements under the statutory exclusion from Best Price of "any prices" charged to covered entities.[167]

Contract Pharmacies. In the proposed guidance, HRSA asserts that although the 340B statute "does not specify how a covered entity may provide or dispense" drugs to 340B patients, the statute nevertheless "does not prohibit the use of contract pharmacies."[168] Under the guidance, "[a] covered entity may contract with one or more licensed pharmacies to dispense 340B drugs to the covered entity's patients, instead of or in addition to an in-house pharmacy."[169] The covered entity also "may contract with one or more pharmacies on behalf of its child sites" and "a child site may contract directly with a pharmacy."[170] According to HRSA, covered entities may contract with pharmacy corporations to include multiple locations, although the guidance cautions that covered entities should be mindful of how the federal anti-kickback statute could apply to potential arrangements.[171]

The guidance also proposes a process for registration of contract pharmacies. HRSA "only lists contract pharmacy locations on a covered entity's 340B database record once a

written contract exists between the covered entity and the contract pharmacy and the covered entity registers those arrangements."[172] The contract must enumerate the requirements contained in the proposed guidance and "should include all locations of a single pharmacy company the covered entity plans to use and all child sites that plan to use the contract pharmacies."[173] Groups or networks may not register contract pharmacy arrangements on behalf of covered entity members—only individual covered entities may register these arrangements, and only registration by covered entities will be accepted.[174] The guidance states broadly that required documentation "would include a series of compliance requirements and a covered entity's attestation regarding its arrangement with the contract pharmacy."[175] Manufacturers and wholesalers must ship only to "authorized shipping addresses listed for the covered entity in the public 340B database."[176] The guidance also allows covered entities to request additional contract pharmacy locations in the event a public health emergency is declared by HHS.[177]

The proposed guidance also warns of the particular need to ensure compliance for contract pharmacy arrangements. HRSA reiterates a recommendation from its 2010 contract pharmacy guidance that covered entities should use independent auditors for annual audits.[178] Moreover, HRSA states, covered entities should compare 340B prescribing records with the contract pharmacy's 340B dispensing records on at least a quarterly basis.[179]

Department of Veterans Affairs (VA) Drug Discount Program

Q 13.15 What is the VA drug discount program?

Like the 340B Program, the VA "Big Four" drug discount program was established by the Veterans Health Care Act of 1992 (VHCA)[180] and was intended to address manufacturer price increases to federal purchasers that resulted from the MDRP's BP provisions. The VA National Acquisition Center (NAC) administers the Federal Supply Schedule (FSS) program, which is the principal mechanism by which the federal government procures pharmaceuticals for customers eligible to purchase from the FSS. Although the FSS program has been in effect for several decades, the VHCA fundamentally changed the method by which Big Four FSS prices are determined.[181]

Q 13.16 What does the VA drug discount program require of pharmaceutical manufacturers?

Under section 603 of the VHCA, pharmaceutical manufacturers must enter into a "Master Agreement" and a "Pharmaceutical Pricing Agreement" (PPA)[182] with the VA with respect to all of their FSS covered drugs.[183] Entry into such agreements is a condition to federal reimbursement of the manufacturer's products under the Medicaid programs, VA, the Department of Defense (DoD), the Public Health Service, including the Indian Health Service (PHS), or any entity that receives funds under the Public Health Service

Act.[184] Manufacturers must also execute an FSS contract.[185] The VA Master Agreement imposes on manufacturers the following three principal requirements:

(1) Manufacturers must make available for procurement each of its "covered drugs" on the FSS[186] and must set prices for FSS-covered drugs at no greater than the prices charged to their most favored commercial customers for the same products under comparable terms and conditions pursuant to their FSS contract;[187]

(2) Manufacturers must agree not to charge state-operated Veterans Homes a price for their product that exceeds the FSS list price for that product;[188] and

(3) With respect to covered drugs procured by VA, DoD, PHS, or the Coast Guard (collectively, the "Big Four") that are either purchased via depot-contracting or listed on the FSS, manufacturers are required to enter into an annual (one-year) PPA with VA under which they are precluded from selling their products to the Big Four in excess of the "federal ceiling price" (FCP or "Big Four Price").[189]

The FCP formula is a function of two components. Specifically, the VA limits a manufacturer's FCP to 76% of the Non-Federal AMP (Non-FAMP) for the one-year period ending one month prior to the effective date of manufacturer's current PPA less an "additional discount," that is, (annual Non-FAMP x 0.76)—any additional discount.[190] The Non-FAMP is defined as the weighted average price paid by "wholesalers" for the manufacturer's product, including any discounts or similar price concessions but not including account prices paid by 340B program-covered entities and the federal government or "nominal" prices.[191] The "additional discount," which is analogous to the "additional rebate" under the MDRP, applies if the non-FAMP in the third quarter of the current year is higher than the non-FAMP from the third quarter of the prior year adjusted by the CPI-U.[192] In the first two to five years of a contract, the manufacturer must take the additional step of comparing the calculated FCP to the FSS price as of September 30 of the calendar year, adjusted for inflation. The lower of the two prices is deemed the FCP for the product for the following calendar year. This is known as the "FSS Max Cap," and applies only after the first year of a multi-year FSS contract.

Manufacturers are required to calculate and report the non-FAMP to the VA both quarterly and annually.[193] A manufacturer's annual VA price report, which is due to the VA no later than November 15 of each year, must include an annual Non-FAMP, a prior-year, third-quarter Non-FAMP, and an annual FCP for each covered drug.

The FSS contract permits manufacturers to choose either Single or Dual Pricing for their FSS drugs. Under Single Pricing, manufacturers agree to sell each covered drug to all FSS customers at one price, which cannot exceed the FCP. Under Dual Pricing, a manufacturer agrees to assign two prices for each covered drug:

(1) An FSS price applicable to the Big Four that does not exceed the FCP; and

(2) An FSS price applicable to Other Government Agencies (OGAs) authorized to

purchase on the FSS, which is not limited to the FCP and is negotiated between the manufacturer and the VA based on the above-described commercial "most favored customer" pricing concept, including an option for economic price adjustments.[194]

FSS contracts require pharmaceutical manufacturers to disclose to the VA commercial product pricing information that the VA utilizes to negotiate for most favored customer pricing.[195] The FSS typically runs for a five-year term. Manufacturer FSS pricing disclosures must contain current, accurate, and complete data or run the risk of violating the Truth in Negotiations Act and/or the False Claims Act.[196] Using this information, the VA and the manufacturer then identify a "tracking customer" whose pricing will set the VA OGA price for the life of the FSS contract.

The FSS contract's Price Reductions Clause (PRC) requires the manufacturer to disclose any price reductions offered to the tracking customer for a product in a timely fashion and to make that discounted price available under the FSS.[197] If the manufacturer is a Single Pricer, then the lower of the tracking customer price or the statutory FCP will be the FSS price for all purchasers. If the manufacturer is a Dual Pricer, then the Big Four price will be the lower of the calculated FCP or the tracking customer price. OGA purchasers will receive the tracking customer price.

Q 13.17 What kind of pharmaceutical products are covered under the VA drug discount program?

The VA program generally applies to the same pharmaceutical products that are covered under the MDRP and 340B programs with three exceptions.[198] First, VA program covered drugs are limited to innovator multiple source drugs and single source drugs.[199] Non-innovator multiple source drugs (that is, generics) are not subject to the VHCA. Second, vaccines are covered products under the VA program.[200] Third, and unlike the MDRP and 340B, the VA program does not limit its drug discounting and reporting requirements to "covered *outpatient* drugs" as defined by the federal Medicaid statute.[201] Under the VA program, manufacturers are obligated to report and charge no higher than the FCP for products administered or dispensed in connection with inpatient hospital, hospice, dental services, physician, outpatient, emergency room, skilled nursing facility, laboratory and x-ray, and renal dialysis services, if such products are sold through wholesalers. Until recently, under general procurement policy, manufacturers could not offer products that were not compliant with the Trade Agreements Act (TAA) (such as products or API manufactured in China or India) on their FSS contracts.[202] However, in April 2016, the VA released a mass modification to its FSS contracts for pharmaceutical products (Schedule 65 I B).[203] Under the change, manufacturers now are required to list *all* covered drug products, regardless of TAA compliance.[204] In order to procure non-TAA compliant products under an FSS contract, the VA Contracting Officer may make an individual non-availability determination, based on whether: "1) information provided by the offeror that neither the

offered 42-2A [covered] product items nor similar or like items are mined, produced or manufactured in the United States or a designated country in sufficient quantity to fulfill the requirements, and 2) in light of the requirement set forth in 38 U.S.C. § 8126(a)(1) that manufacturers shall make available for procurement on the Federal Supply Schedule of the General Services Administration each covered drug of the manufacturer."[205]

Notably, if a pharmaceutical company falsely represents a product as TAA-compliant, it continues to face not only the loss of its FSS contract, but also the prospect of penalties under the False Claims Act, suspension and debarment, and even criminal charges.

Q 13.18 Are pharmaceutical manufacturers subject to other associated programs for veterans or other military personnel?

Related to the VA program, pursuant to section 703 of the National Defense Authorization Act for Fiscal Year 2008[206] as implemented by a DoD Final Rule, manufacturers must pay refunds for drugs utilized under the TRICARE Retail Pharmacy (TRRx) Program.[207] TRICARE is the health system for active duty military officials and military retirees. In general, manufacturers may calculate TRRx rebates as either (i) the difference between annual Non-FAMP and the FCP for a drug, or (ii) the difference between the FCP for the drug and the direct commercial contract sales price specifically attributable to the drug, if known.[208] The TRRx Program allows TRICARE beneficiaries to purchase drugs directly from a retail pharmacy instead of through a military hospital or mail order. Because TRRx is a federal program, sales of drugs dispensed to TRICARE beneficiaries pursuant to the TRRx Program are deducted from Non-FAMP calculations. Manufacturers receive invoices from TRICARE at the end of each quarter that set forth the total TRRx utilization for each of their covered drugs. They must reconcile the data against their own records and pay rebates on the amounts actually dispensed to TRICARE beneficiaries through DoD network retail pharmacies.

Medicare Part B: Average Sales Price

Q 13.19 What is Medicare?

Medicare provides government-backed health coverage for people age sixty-five or older, people under age sixty-five with certain disabilities, and people of all ages with end-stage renal disease.[209] Medicare Part D covers outpatient prescription drugs provided by stand-alone prescription drug plans (PDPs) and Medicare Advantage Prescription Drug Plans (MA-PDs).[210] Medicare Part B ("Part B") covers drugs that are primarily administered in physicians' offices, hospital outpatient departments, and dialysis clinics.[211]

Q 13.20 What kinds of drugs are covered by Part B?

As stated above, Part B covers drugs that are primarily administered in physicians' offices, hospital outpatient departments, and dialysis clinics. Part B drugs include injectable

drugs administered by a physician and certain drugs that are typically self-administered under a physician's supervision, such as oral anti-cancer drugs and immunosuppressive drugs, blood clotting factors for patients with hemophilia, infused drugs used in conjunction with durable medical equipment, and some vaccines.[212]

Q 13.21 What is the Part B prescription drug reimbursement procedure?

Physician practices and hospitals (for outpatient settings) typically purchase Part B drugs through wholesalers or directly from the drug manufacturer.[213] Medicare then reimburses Part B providers for the administration of Part B-covered drugs "incident to" provider services.[214]

Until 2005, Medicare reimbursed providers for Part B-covered drugs based on the product's manufacturer-reported average wholesale price (AWP).[215] Although AWP was the first generally accepted, industry-standard pricing benchmark for prescription drug reimbursement, by 2005, it had long-suffered criticism that it was unreliable, subject to manipulation, and not representative of the actual purchase price for pharmaceuticals.[216] The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA)[217] revised the Part B prescription drug reimbursement methodology. Specifically, the MMA required CMS to pay for most Part B drugs based on their average sales price (ASP), not AWP, effective starting January 1, 2005.[218] In addition, the MMA obligates manufacturers that participate in the MDRP to provide CMS with the ASP and volume of sales for each of their national drug codes (NDC) on a quarterly basis, with submissions due thirty days after the close of each quarter.[219]

Q 13.21.1 What is the ASP and how is it calculated?

The MMA defines ASP as "the manufacturer's sales to all purchasers [excluding exempt sales[220]] in the United States for such drug or biological in the calendar quarter divided by . . . the total number of such units of such drug or biological sold by the manufacturer in such quarter [excluding exempt sales]."[221] The MMA requires manufacturers to include in their ASP calculations "price concessions," including "volume discounts, prompt pay discounts, cash discounts, free goods that are contingent on any purchase requirement, chargebacks, and rebates" (other than MDRP rebates under the MDRP).[222] Moreover, because certain price concessions, such as rebates and chargeback data, are not available within thirty days of the end of each calendar quarter, the MMA and CMS guidance require manufacturers to calculate a twelve-month rolling average "price concession percentage" to estimate the lagged "price concession discount amount" for the reporting quarter.[223] The basic premise of this "smoothing" methodology is that the true sales cycle is better reflected over a longer period incorporating cyclical or ad hoc sales patterns. By utilizing a price concession smoothing methodology, the manufacturer is better equipped to generate more accurate and consistent pricing data.

Because Part B reimbursement for outpatient drugs is based on Healthcare Common

Procedure Coding System (HCPCS) codes rather than NDCs and more than one NDC may meet the definition of a particular HCPCS code, CMS has developed a file (the ASP background file) that "crosswalks" manufacturers' NDCs to HCPCS codes. CMS uses information in this file to calculate volume-weighted ASPs for covered HCPCS codes based on the data from the relevant NDCs.

ASP-based reimbursement rates for Part B drugs vary dependent on whether the drug is classified as a multiple source or single source drug.[224] Part B-covered single source drugs are generally reimbursed at the lower of 106% of ASP or 106% of Wholesale Acquisition Cost (WAC).[225] Part B-covered multiple source drugs are generally reimbursed at 106% of the volume-weighted average ASP for all drugs sharing the same reimbursement code.[226] Moreover, pursuant to the MMA and its implementing regulations, if the HHS OIG concludes that a product's ASP exceeds "widely available market data" (WAMP) or AMP by 5%, CMS is entitled, at its discretion, to substitute the lower of WAMP or 103% of AMP as the product's actual reimbursement rate.[227] The OPPS CY 2018 final rule, discussed above in Q 13.13, modifies its OPPS drug payment methodology for CY 2018 by reducing payment for separately payable, non- pass-through outpatient drugs purchased under the 340B program to ASP minus 22.5%.[228] As of February 23, 2018, there is pending litigation brought by a group of three hospital systems and three hospital trade associations seeking to enjoin the implementation of the reduced reimbursement rate.[229] This lawsuit is also discussed in further detail above, in Q 13.13.

Government Program Pricing and Reporting: Compliance Risks

Generally

Q 13.22 What are the repercussions to a pharmaceutical manufacturer who does not comply with federal healthcare program pricing and reporting obligations?

As explained above, the MDRP relies on timely and accurate reporting of pharmaceutical manufacturer AMP and BP data in order to calculate state Medicaid program rebates.[230] Similarly, Medicare Part B relies on timely and accurate reporting of manufacturer ASP data to determine Part B drug reimbursement rates. Pharmaceutical manufacturer noncompliance with federal healthcare program pricing and reporting obligations potentially implicates various Civil Monetary Penalties (CMPs) statutes as well as the False Claims Act.

CMPs and Administrative Sanctions

Q 13.23 What noncompliance penalties are assessed by the MDRP?

Section 1927 of the Social Security Act authorizes HHS to impose CMPs and other administrative sanctions on pharmaceutical manufacturers that fail to comply with their price reporting obligations under the MDRP and 340B programs (AMP and BP metrics).[231] Manufacturers that fail to report MDRP-required price metrics to CMS within thirty days of the end of the rebate period could face CMPs in the amount of $10,000 per item overdue per day.[232] Moreover, manufacturers that still fail to report those metrics within ninety days of end of the rebate period may be suspended from Medicaid participation until they come into compliance.[233] Finally, manufacturers that knowingly provide false information to CMS may be fined up to $100,000 for each item of false information submitted.[234] Section 1927's price reporting noncompliance penalties and sanctions are equally applicable to manufacturer reporting obligations under the VA drug pricing program (Non-FAMP and FSS metrics) and the Medicare Part B drug benefit program (ASP and sales volume metrics). Moreover, section 1847A of the Social Security Act provides that manufacturers who make a misrepresentation in ASP reporting may be fined up to $10,000 for each price misrepresentation for each day in which each price misrepresentation was applied.[235] The statute implementing the 340B Program similarly contains a separate penalty provision specific to 340B Program price reporting, including that a manufacturer who overcharges a covered entity may be fined up to $5,000 for each instance of overcharging.[236]

OIG Price Reporting Enforcement Initiatives

In years past, OIG published an annual public-facing Work Plan to identify its changing priorities and its plans to respond to these priorities with the resources available.[237] Effective June 15, 2017, OIG announced that, in order to enhance transparency, it will instead update its Work Plan on a monthly basis.[238] As of April 22, 2018, there are six monthly updates available on the OIG website: October 2017, November 2017, December 2017, January 2018, February 2018, and March 2018.[239] These monthly updates describe a number of new and continuing studies and reports on pharmaceutical issues to be conducted by OIG's Office of Evaluations and Inspections, including several government program price reporting initiatives as follows:

Medicare Part D Rebates Related to Drugs Dispensed by 340B Pharmacies: In its FY 2017 Work Plan, OIG indicated that it would assess what savings could be realized for the federal government if rebate requirements similar to those under the MDRP were adopted by the Medicare Part D Program.[240] OIG will determine the upper bound of possible savings if pharmaceutical manufacturers were required to pay rebates dispensed through Medicare Part D at 340B covered entities and contract pharmacies. The expected issue date for this report is in 2018.[241]

Specialty Drug Pricing and Reimbursement in Medicaid: When setting Medicaid pharmacy reimbursement amounts, states use CMS's national average drug acquisition cost to set Medicaid pharmacy reimbursement amounts.[242] However, this does not include the cost of drugs sold at specialty pharmacies.[243] In its FY 2017 Work Plan,[244] OIG indicated that it would determine how states define specialty drugs, how much they paid for specialty drugs, how they determine payment methodologies for specialty drugs, and the differences in reimbursement amounts for these drugs among states.[245] The expected issue date for this report is in 2018.[246]

Treatment of Authorized Generic Drugs: In its FY 2017 Work Plan, OIG indicated that it would review how manufacturers treat sales of authorized generics in calculating AMP for MDRP.[247] OIG will determine whether manufacturers include sales of authorized generics to secondary manufacturers in their AMP calculations.[248] Although the Work Plan and monthly updates indicate that the report was set for completion in 2017, the report has yet to be published.[249]

Accuracy of Drug Classification Data Used to Collect Medicaid Rebates: In order to receive federal payments for Medicaid-covered outpatient drugs, drug manufacturers must enter into rebate agreements with HHS and pay quarterly rebates to states. The rebate amount for a drug is based, in part, on its classification. In December 2017, OIG published a report entitled, "Potentially-Misclassified

Drugs May Have Led to $1 Billion in Lost Medicaid Rebates." The report reviewed the Medicaid drug rebate classification systems and evaluated the accuracy of innovator and non-innovator classifications for drugs.[250] The report also reviewed procedures CMS has in place to ensure that manufacturers are in compliance with the requirements of the Medicaid Drug Rebate Program.[251]

FDA-Approval Status of Drugs in the Medicaid Drug Rebate Program: With certain exceptions, drugs generally must be FDA-approved for safety and effectiveness to qualify for to qualify for federal payments under Medicaid. Under the Medicaid Drug Rebate Program, a manufacturer must provide CMS with its FDA-assigned labeler code and a complete list of drugs marketed by the company. In June 2017, OIG indicated that, at the request of the Congress, it will review the FDA approval status of drugs covered under the MDRP and determine what steps CMS takes to review FDA approval status of drugs and prevent inappropriate payments for unapproved drugs under the MDRP.[252] The expected issue date for this report is in 2018.[253]

Increase in Prices for Brand-Name Drugs Under Part D: In its FY 2017 Work Plan, OIG indicated that it would evaluate the extent to which pharmacy reimbursement for brand-name drugs under Medicare Part D changed between 2011 and 2015 and compare the rate of change in pharmacy reimbursement for brand-name drugs under Medicare Part D to the rate of inflation for the same period.[254] The expected issue date for this report is in 2018.[255]

Reasonable Assumptions in Manufacturer AMP Reporting: In June 2017, OIG indicated that, in response to a congressional request, it will estimate how many manufacturers make reasonable assumptions and identify the major issues for which assumptions are being made.[256] OIG also will examine CMS's oversight of the reasonable assumptions process and explore whether manufacturers believe that CMS's recent final rule clarified issues for which manufacturers previously made assumptions.[257] To this end, many manufacturers received this summary in late 2017 and were asked to return the survey in early 2018. The expected issue date for this report is in 2018.[258]

Federal False Claims Act (FCA)

Q 13.24 What is the FCA?

The FCA[259] imposes liability where "any person" (a) "knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval,"[260] (b) "knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim,"[261] or (c) "conspires to commit a violation of another subsection of the

FCA."[262] The FCA applies not only when a person causes the government to pay money that it should not pay, but also applies when a person misrepresents a fact that in turn causes the government to receive an underpayment of an amount owed to it.[263] This is known as a "reverse false claim." Failure to report accurate pricing information to the government, which in turn results in an underpayment of Medicaid rebates, qualifies as a reverse false claim.

Q 13.25 What do the terms "knowing" and "knowingly" mean under the FCA?

The terms "knowing" and "knowingly" in the FCA context mean that a person must, with respect to a particular claim: (1) have actual knowledge of the information; (2) act in deliberate ignorance of the truth or falsity of the information; or (3) act in reckless disregard of the truth or falsity of the information.[264] Congress specifically added this definition of scienter to the FCA, to make "firm . . . its intention that the act not punish honest mistakes or incorrect claims submitted through mere negligence";[265] it was meant to reach the situation where an individual has "buried his head in the sand" and failed to make basic inquiries which would alert him that false claims are being submitted.[266] Consistent with Congress's intent, courts have construed the "deliberate indifference/reckless disregard" standard to be a form of gross negligence.[267] In the context of the above price reporting regulations, which in many instances are complex, ambiguous, or incomplete, application of this scienter standard presents unique challenges.

Q 13.26 What are the penalties for violation of the FCA?

The FCA penalties include civil penalties for each violation, treble damages, and attorneys' fees.[268] Until 2016, civil penalties ranged from $5,500 to $11,000 per violation.[269] However, DOJ adjusted these amounts in June 2016 pursuant to an interim final rule with request for comments (comments closed on August 29, 2016).[270] Under the rule, civil penalties assessed after August 1, 2016 for violations that occurred after November 2, 2015 are subject to higher inflation-adjusted penalties ranging from $10,781 to $21,563.[271] Regardless of the penalty amount at stake, it is critical to note that penalties are awarded on a per-violation basis. Thus, where a manufacturer may be reporting prices for hundreds or even thousands of products per period, each separate line item on each separate price report could qualify as an independent false claim. Accordingly, the FCA penalties can accumulate quickly upon establishment of a false price reporting scheme.

Q 13.27 Has there been litigation involving government price reporting under the FCA?

In part due to the penalties discussed in Q 13.26 above, pharmaceutical manufacturer price reporting to government programs have historically received close scrutiny by both federal and state law enforcement agencies. In fact, several government investigations into

such price reporting have triggered civil lawsuits alleging FCA liability, many of which were ultimately resolved by significant civil settlement agreements. A quick synopsis of certain of these lawsuits concerning key government pricing compliance risk areas follows below.

Nominal Pricing/Bundled Sales

On April 27, 2016, Pfizer, Inc. ("Pfizer") agreed to a $784.6 million dollar settlement with the government to resolve claims related to two FCA whistleblower lawsuits in the District of Massachusetts.[272] The DOJ and sixteen states had intervened in May 2009 in both suits, contending that the company's Wyeth unit defrauded government health programs by improperly reporting price discounts for its Protonix® Oral and Protonix® IV acid-reflux drugs.[273] Specifically, DOJ alleged that, from 2000 to 2006, Wyeth sold the two medicines to thousands of hospitals at a deep discount for purchasing the drugs together in a bundled package called the Protonix Performance Agreement.[274]
In its press release, the DOJ stated: "Wyeth created the Protonix bundle so they could increase their market share at the expense of the Medicaid program—a program to provide the least advantaged Americans with necessary medical care and services . . . . By offering massive discounts to hospitals, but then hiding that information from the Medicaid program, we believe Wyeth caused Medicaid programs throughout the country to pay much more for these drugs than they should have."[275] In arguing that Wyeth characterized the discount contracts as "bundles," DOJ pointed to several strategic documents and high-level committee meetings.[276]

Recklessness

In 2005, King Pharmaceuticals, Inc. ("King") entered into a $124 million civil settlement with the government to resolve allegations that it had violated the FCA by overcharging various federal and state entities for its drug products as a result of its knowing "fail[ure] to report accurately the average manufacturer price (AMP) and best price (BP) for its Medicaid-reimbursed drugs from 1993 through 2002."[277] According to the DOJ, King allegedly failed to collect and analyze pricing information that ensured accurate MDRP price reporting calculations, failed to adequately train its staff with regard to MDRP price reporting, and consistently included inappropriate customers in its "retail class of trade" sales, thereby resulting in false AMP and BP price reports across its entire product line.[278] The *King* case is illustrative of the benefits of having good compliance controls and policy documentation regarding price reporting methodologies.

Timely Price Reporting

Since 2015, several smaller settlements between OIG and manufacturers, in amounts ranging from $60,000 to $2.89 million, have continued to demonstrate the importance of timely filing of AMP data.[279] In 2016, for example, Coloplast Corporation ("Coloplast") entered into a $600,000 settlement with OIG to resolve allegations that it failed to submit certified monthly and quarterly AMP data to CMS for certain months and quarters in 2013, 2014, and 2015.[280] Other settlements with OIG from 2015– 2016 have involved manufacturers in New Jersey (Glenmark Pharmaceutical Incorporated, USA; Ascend Laboratories, LLC; Seton Pharmaceuticals), Florida (Nephron Pharmaceuticals Corporation), South Carolina (Cipher Pharmaceuticals US LLC), and Kansas (B.F. Ascher & Company, Inc.).[281]

Classification Under the MDRP

On October 7, 2016, Mylan N.V. announced an agreement in the amount of $465 million to resolve allegations that its EpiPen Auto-Injector products were misclassified as non-innovator (generic) drugs under the MDRP, resulting in underpayments of Medicaid rebates.[282] The products in question had been classified as non-innovator drugs since before Mylan acquired them in 2007 and had continued to be classified as generic based on guidance from the federal government.[283] Although this settlement came under criticism, the Department of Justice finalized the settlement on August 17, 2017.[284] The settlement includes a five-year corporate integrity agreement that requires, among other things, an independent review organization to annually review multiple aspects of Mylan's practices relating to the Medicaid drug rebate program. Additionally, on December 16, 2016, Mylan announced that it would begin to offer a generic version of EpiPen Auto-Injector at a more than 50% discount.[285]

Repackaging/Relabeling

In 2009, Aventis Pharmaceuticals, Inc. ("Aventis") entered into a $95.5 million settlement agreement with the DOJ to resolve allegations that it had violated the FCA by knowingly misreporting Best Prices for the steroid-based anti-inflammatory nasal sprays in order to reduce its MDRP and 340B Program obligations.[286] Specifically, the government claimed that "[i]n order to avoid triggering a new best price that would obligate it to pay millions of dollars in additional drug rebates to Medicaid, Aventis entered into 'private label' agreements with the HMO Kaiser Permanente that simply repackaged Aventis's drugs under a new label. As a result, Aventis underpaid drug rebates to the Medicaid program and overcharged certain Public Health Service entities for these products."[287]

Service Fees/Discounts

In June 2015, AstraZeneca LP agreed to pay approximately $45.5 million to resolve allegations that it had improperly treated fees paid to wholesalers for inventory management as discounts in its AMP calculation.[288] The AstraZeneca settlement was announced at the same time as a $7.5 million dollar settlement between the United States and Cephalon to resolve similar allegations.[289] The litigation related to how the drug manufacturers classified fees to wholesalers for inventory management services for government price reporting purposes (i.e., bona fide service fees versus price concessions). The government asserted that because AstraZeneca and Cephalon had treated the fees as price concessions, they under-reported AMP.[290] Another complaint recently unsealed in the Northern District of Illinois raises the same allegations against certain drug companies regarding wholesaler fees.[291]

In 2012, Sanofi-Aventis U.S. Inc. and Sanofi-Aventis U.S. ("Sanofi") executed a $109 million government settlement to resolve allegations that it had violated the FCA by giving physicians free units of Hyalgan®, a knee injection, allegedly to induce them to purchase and prescribe the product, and submitted false average sales price (ASP) reports for Hyalgan® that it had failed to account for free units distributed contingent on Hyalgan® purchases.[292] According to the government, Sanofi's "false ASP reports, which were used to set reimbursement rates, caused government programs to pay inflated amounts for Hyalgan and a competing product."[293] This case supports the assertion that the government will argue that for product programs that offer value to customers, in the form of a free or a reduced price product, such value should be included in price reporting.

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1. Kaiser Family Foundation, Medicaid, A Primer: Key Information on the Nation's th Coverage Program for Low-Income People (Mar. 2013), http://kff.org/medicaid/issue-medicaid-a-primer/.

2. An overview of Medicaid and all other programs administered by CMS is available at .cms.hhs.gov. The federal government also maintains a Medicaid-specific website, which is ıble at www.medicaid.gov/.

3. Omnibus Budget Reconciliation Act of 1990, Pub. L. No. 101-508 (Nov. 5, 1990), *ding* Social Security Act § 1927, codified at 42 U.S.C. § 1396r-8.

4. Notice, "Medicaid Program, Drug Rebate Agreement," 56 Fed. Reg. 7049, 7049–50 21, 1991) ("Under this agreement, a manufacturer must provide the States with quarterly es [and] a manufacturer must supply information concerning average manufacturer price P) and, as appropriate, best price for its covered outpatient drugs to HHS on a quarterly "). It is important to note that most states negotiate separate, supplemental Medicaid ription drug rebates with pharmaceutical manufacturers over and above those required r federal law. CMS has interpreted SSA section 1927(a)(1) as express authority for states to

tiate supplemental rebates so long as such agreements achieve drug rebates equal to or er than the drug rebates set forth in the Secretary's national rebate agreement with drug ıfacturers."

5. *Id.*

6. 42 U.S.C. § 1396r-8(a).

7. 42 C.F.R. § 447.502.

8. 42 U.S.C. § 1396r-8(k)(5). *See also* 42 C.F.R. § 447.502 (explicitly excluding wholesale butors and retail pharmacies from the category of manufacturers that engage in "packaging kaging, labeling, relabeling, or distribution of covered outpatient drug products").

9. An NDC is a number assigned by the FDA to each pharmaceutical. There are eleven in total, the first five of which identify the manufacturer, the next four of which identify osage form and strength of the drug, and the last two of which identify the drug's package

10. *See* 81 Fed. Reg. 5170, 5197 (Feb. 1, 2016) (to be codified at 42 C.F.R. pt. 447).

11. Veterans Health Care Act of 1992, Pub. L. No. 102-585 (Nov. 4, 1992).

12. Omnibus Budget Reconciliation Act of 1993, Pub. L. No. 103-66 (Aug. 10, 1993).

13. Medicare Prescription Drug and Modernization Act of 2003, Pub. L. No. 108-173 . 10, 2003).

14. Deficit Reduction Act of 2005, Pub. L. No. 109-171 (Feb. 8, 2006).

15. Medicaid Program; Prescription Drugs, 72 Fed. Reg. 39,142 (July 17, 2007).

16. Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148 (Mar. 23,), *as amended by* the Health Care and Education Reconciliation Act of 2010 (HCERA), L. No. 111-152 (Mar. 30, 2010) (collectively "PPACA").

17. Best Price is the lowest manufacturer price available from the manufacturer to any ıaser (defined by the Medicaid statute as "any wholesaler, retailer, provider, health tenance organization (HMO), or nonprofit or government entity" with some exceptions, as, for example, certain direct government purchasers, that is, Departments of Defense and ans Affairs. 42 U.S.C. § 1396r-8(c)(1)(C). Best Price is required to reflect all discounts, es, and other price concessions that lower the actual price at which the drug was sold. 45 R. § 447.505.

18. AMP is the average price paid to the manufacturer by or for retail community nacies including independent or chain pharmacies and excluding, among others, mail-order ıursing home pharmacies. PPACA § 2503(a)(2), *amending* 42 U.S.C. § 1396r-8(k)(1).

19. 42 U.S.C. § 1396r-8(c)(3).

20. 42 U.S.C. § 1396r-8(c)(3)(C). *See also* Dep't of Health & Human Servs., Ctrs. for care & Medicaid Servs., Release No. 97, New Additional Inflation-Adjusted Rebate irement for Non-Innovator Multiple Source Drugs (April 15, 2016).

21. 42 U.S.C. § 1396r-8(b)(3); 42 C.F.R. § 447.510(a).

22. 42 C.F.R. § 447.510(d).

23. 42 U.S.C. § 1396r-8(b)(2).

24. *Id.*

25. *Id.* § 1396r-8(b)(3).

26. Prior to PPACA, Medicaid rebates for innovator drugs equaled the greater of AMP s Best Price, or 15.1% of AMP, plus an additional rebate and non-innovator drugs' rebates ed 11% of AMP.

27. CMS has compiled a list drugs that are clotting factors and drugs approved exclusively ediatric indications, and posts such lists on the Bulletin Page in the DDR application for and labeler use. *See* https://www.medicaid.gov/medicaid-chip-program-information/by-s/prescription-drugs/downloads/bcfandpedguidance.pdf.

28. CMS stated that "[manufacturers] may not rely on regulatory provisions and language ıave been withdrawn. Until a subsequent rule is issued and finalized, manufacturers should ɔn section 1927 of the Act, as amended by the Affordable Care Act, and regulations (except regulations or portions thereof that have been withdrawn)." *See* 75 Fed. Reg. at 69,594.

29. *Id.*

30. Proposed Rule, Medicaid Program; Covered Outpatient Drugs, 77 Fed. Reg. 5318 (Feb. 12).

31. Comprehensive Addiction and Recovery Act of 2016, Pub. L. No. 114-198 (July 22,).

32. 42 U.S.C. 1396r–8(c)(2)(C) (2016).

33. *See* 81 Fed. Reg. at 5265 (addressing commenters' concerns that inclusion of abuse rent formulations within the definition of "line extension" would run contrary to other ies aimed at ending the national drug abuse problem).

34. *Id.*; 77 Fed. Reg. at 5338–39.

35. 42 C.F.R. § 447.510(b)(i)–(v), (d)(3) (2016). Under the PPACA Final Rule, CMS will consider requests for revisions outside of the twelve-quarter period where the change is: (i) esult of a change in drug category or market date; (ii) an initial submission for a product, lue to termination of a manufacturer from the MDRP for failure to submit pricing data re such manufacturer must submit pricing data to reenter the program); (iv) due to a ıical correction ("that is, not based in sales transactions or pricing adjustments from such actions"); or (v) "to address specific rebate adjustments to States by manufacturers, as red by CMS or court order, or under an internal investigation, or an OIG or Department stice (DOJ) investigation." 42 C.F.R. § 447.510(b)(1)(i)–(v). "A manufacturer must report ed AMP within the 12-quarter time period, except when the revision would be solely as a of data pertaining to lagged price concessions." 42 C.F.R. § 447.510(b)(2).

36. 42 C.F.R. § 447.504(h); 42 C.F.R. § 447.505(d)(12) (Oct. 1, 2007).

37. 42 C.F.R. § 447.502.

38. 42 U.S.C. § 1396r-8(k)(1)(B)(i).

39. 42 U.S.C. § 1396r-8(k)(1)(B)(i)(II).

40. 42 C.F.R. § 447.502 (2007).

41. 42 C.F.R. § 447.502 (2016).

42. HHS OIG issued an advisory opinion providing guidance and clarification regarding the al anti-kickback statute's discount safe harbor in connection with "bundled discounts" as

ed to device and pharmaceutical manufacturers. OIG Adv. Op. 13-07 (July 1, 2013), ://oig.hhs.gov/compliance/advisory-opinions/#2013.

43. 81 Fed. Reg. at 5235.

44. 81 Fed. Reg. at 5233.

45. *Id.*

46. *Id.*

47. 81 Fed. Reg. at 5234.

48. 81 Fed. Reg. 5170 (Feb. 1, 2016).

49. 77 Fed. Reg. at 5329.

50. 81 Fed. Reg. at 5210.

51. 42 C.F.R. § 447.502; *see also* Medicaid Rebate Agreement § I(aa).

52. 81 Fed. Reg. at 5349 (codified at 42 C.F.R. § 447.502). The PPACA Final Rule also zes a definition of "United States" that mirrors the definition of "States." 81 Fed. Reg. at (codified at 42 C.F.R. § 447.502).

53. 81 Fed. Reg. at 5203.

54. *Id.* at 5204.

55. 81 Fed. Reg. 80,003 (Nov. 15, 2016).

56. 81 Fed. Reg. at 5347 (42 C.F.R. § 447.502).

57. *Id.*

58. 81 Fed. Reg. at 5177.

59. 81 Fed. Reg. at 5178.

60. *Id.*

61. 81 Fed. Reg. at 5180.

62. 42 C.F.R. § 447.502 (2016).

63. 72 Fed. Reg. at 39,240.

64. 42 C.F.R. § 447.502 (2016) (emphasis added).

65. *See* 81 Fed. Reg. at 5182.

66. Although historically only single source and innovator multiple source drugs have been ct to an additional, inflation-based rebate payment on top of the applicable base rebate ntage, the Balanced Budget Act of 2015 amended the Social Security Act to include an ion-based rebate for non-innovator drugs. Those provisions took effect in the first quarter 17.

67. 77 Fed. Reg. at 5360, 5361 (proposed) (Feb. 2, 2012) (to be codified at 42 C.F.R. 7.502).

68. *See* 81 Fed. Reg. at 5348–49 (42 C.F.R. § 447.502).

69. *See* 81 Fed. Reg. at 5192.

70. 81 Fed. Reg. at 5221.

71. *Id.*

72. 42 U.S.C. § 1396r-8(k)(1)(B)(i)(IV).

73. *See* 81 Fed. Reg. at 5237.

74. 81 Fed. Reg. at 5239.
75. 81 Fed. Reg. at 5250.
76. 81 Fed. Reg. at 5284–86 (42 C.F.R. § 447.510(d)(2)).
77. 42 C.F.R. § 447.505(c).
78. 81 Fed. Reg. at 5352 (42 C.F.R. § 447.505(c)(2)) (emphasis added).
79. 81 Fed. Reg. at 5352 (42 C.F.R. § 447.506(c)).
80. 42 U.S.C. § 1396r-8; § 1927(c)(2)(C).
81. 81 Fed. Reg. at 5265.
82. 42 U.S.C. 1396r-8(c)(2)(C).
83. 42 C.F.R. § 447.510(b)(1). Revisions that would result solely from data pertaining to d price concessions are outside this rule. *Id.* § 447.510(b)(2).
84. 42 C.F.R. § 447.510(b)(1)(i)-(v) (2016).
85. 81 Fed. Reg. at 5281–82.
86. *Id.*
87. *Id.*
88. 42 C.F.R. § 447.512(b). For more discussion on reimbursement issues, including rements for states, please see Arnold & Porter Kaye Scholer, LLC's Advisory CMS Releases Medicaid Rebate Rule (Jan. 2016), .apks.com/en/perspectives/publications/2016/1/cms-releases-final-medicaid-rebate-rule.
89. 81 Fed. Reg. at 5174. *See also id.* at 5237 (suggesting such documentation ought to be ten or electronic" in order to be adequate).
90. *But see* 72 Fed. Reg. at 39,166–67 (July 17, 2007) ("In the absence of specific guidance, nufacturer may make reasonable assumptions in its calculations, consistent with the general rements and the intent of the Act, Federal regulations, *and its customary business practices*") hasis added).
91. Medicaid Program; Announcement of Medicaid Drug Rebate Program National Rebate ement, 81 Fed. Reg. 78,816 (Nov. 9, 2016).
92. Medicaid Program; Drug Rebate Agreement, 56 Fed. Reg. 7049, 7052 (Feb. 21, 1991).
93. 81 Fed. Reg. at 78,819 (proposed section II(g)).
94. 81 Fed. Reg. at 78,818 (proposed section I(t)).
95. 81 Fed. Reg. at 78,818 (proposed section I(w)).
96. 81 Fed. Reg. at 78,820 (proposed section VII(a)).
97. 81 Fed. Reg. at 78,820 (proposed section VIII(c)).
98. 81 Fed. Reg. at 78,818–19 (proposed section II).
99. 83 Fed. Reg. 12,770 (Mar. 23, 2018).
100. *See id* at 12,784–86.
101. *See id* at 12,770–71.
102. 58 Fed. Reg. 27,289, 27,290–91 (May 7, 1993).
103. The program results in significant savings on prescription drugs for entities, including rally Qualified Health Centers, Disproportionate Share Hospitals, children's hospitals, r hospitals, critical access hospitals, sole community hospitals, rural referral centers, the

n Health Service, and Centers for Disease Control, treating sexually transmitted diseases uberculosis. *See* 42 U.S.C. § 256b(a)(4).

104. *Id.* Healthcare providers eligible for the 340B Program, which include ten types of al grantees and six types of hospitals that meet specified standards, are deemed "covered es." Sub-regulatory guidance also permits certain outpatient facilities of a 340B hospital to ɔipate in the 340B Program so long as they are "integral" to the hospital (i.e., are listed as ɔursable on the hospital's Medicare cost report). 59 Fed. Reg. 47,884, 47,885–86 (Sept. 19,).

105. 58 Fed. Reg. at 27,293.

106. 442 U.S.C § 256b(a)(1); General Instructions for Completing the Pharmaceutical ıg Agreement (PPA), ://www.hrsa.gov/sites/default/files/opa/manufacturers/pharmaceuticalpricingagreement.pdf.

107. 58 Fed. Reg. at 27,292.

108. 42 U.S.C § 256b(a)(5)(B).

109. 42 U.S.C § 256b(a)(5)(A).

110. Notice Regarding 340B Drug Pricing Program—Contract Pharmacy Services, 61 Fed. 43,549 (Aug. 23, 1996).

111. *Id.*

112. *Id.*

113. *Id.*

114. *Id.*

115. *Id.*

116. Notice Regarding 340B Drug Pricing Program—Contract Pharmacy Services, 75 Fed. 10,272 (Mar. 5, 2010).

117. 42 U.S.C. § 256b(d)(1)(B).

118. 42 U.S.C. § 256b(d)(2)(B).

119. Advance Notice, 340B Drug Discount Program, Manufacturer Civil Monetary lties, 75 Fed. Reg. 57,230 (Sept. 20, 2010); Unified Agenda, 340B Civil Monetary lties for Covered Entities (Spring 2011).

120. 80 Fed. Reg. 34,583 (June 17, 2015).

121. 81 Fed. Reg. 22,960, 22,960–61 (Apr. 19, 2016); Unified Agenda, 340B Civil etary Penalties for Covered Entities (proposed Fall 2016).

122. 82 Fed. Reg. 1210 (Jan. 5, 2017).

123. 82 Fed. Reg. at 1229.

124. 82 Fed. Reg. at 1215.

125. 82 Fed. Reg. at 1229.

126. 82 Fed. Reg. at 1229.

127. 82 Fed. Reg. at 1229.

128. 82 Fed. Reg. at 1218.

129. *See* 82 Fed. Reg. at 1221.

130. 82 Fed. Reg. at 1222.
131. 82 Fed. Reg. 12,509 (Mar. 6, 2017).
132. On September 28, 2017, HRSA issued another final rule delaying the effective date of CP/CMP Final Rule to July 1, 2018, ://www.federalregister.gov/documents/2017/09/29/2017-20911/340b-drug-pricing-am-celing-price-and-manufacturer-civil-monetary-penalties-regulation.
133. 82 Fed. Reg. 45,511 (Sept. 29, 2017).
134. 42 U.S.C. § 256b(d)(3).
135. 340B Drug Pricing Program; Administrative Dispute Resolution, 81 Fed. Reg. 53,381 . 12, 2016) (to be codified at 42 C.F.R. pt. 10); Unified Agenda, 340B Drug Pricing am; Administrative Dispute Resolution Process (Fall 2016).
136. 81 Fed. Reg. at 53,382.
137. *Id.* at 53,383.
138. *Id.* at 53,388 (proposed section 10.22).
139. *Id.* At 53,384–85.
140. 80 Fed. Reg. 52,300 (Aug. 28, 2015).
141. 80 Fed. Reg. 63,560 (Oct. 20, 2015).
142. Unified Agenda, 340B Omnibus Guidance (Fall 2016); Office of Mgmt. & Budget, e of Info. & Regulatory Affairs, RIN 0906-AB08, "Pending EO 12866 Regulatory w."
143. *See* Dep't of Health & Human Services, Health Res. & Servs. Admin., Healthcare Sys. au, OMB No. 0915-0327, "Pharmaceutical Pricing Agreement Addendum," .hrsa.gov/opa/manufacturers/ppa_addendum.pdf.
144. 42 U.S.C. § 256b.
145. *See* 42 U.S.C. § 256b(d)(1)(B)(v).
146. U.S. Dep't of Health & Human Services, Health Res. & Servs. Admin., "FY16 ufacturer Audit Results," .hrsa.gov/opa/programintegrity/auditresults/fy16manufactureraudit results.html; U.S. Dep't ealth & Human Services, Health Res. & Servs. Admin., "Program Integrity: FY16 Audit lts,"www.hrsa.gov/opa/programintegrity/auditresults/fy16results.html.
147. 82 Fed. Reg. 33,558 (July 20, 2017).
148. *Id.*
149. *Id.*
150. 82 Fed. Reg. 53,256 (Nov. 13, 2017).
151. Am. Hosp. Ass'n v. Hargan, Case No. 17-cv-02447, 2017 WL 6734176 (D.D.C. Jan. 018).
152. Pharm. Research & Mfrs. of Am. v. U.S. Dep't of Health & Human Servs., 43 F. Supp. 3 (D.D.C. 2014).
153. *Id.* at 43.
154. 80 Fed. Reg. 52,300 (Aug. 28, 2015). The omnibus guidance also addresses the statutory t offer" provision, which now has been included in the PPA via an addendum as discussed

13.13.

155. *Id.* at 52,306–07.

156. *See id.* at 52,306; 61 Fed. Reg. 55,156, 55,157 (Oct. 24, 1996).

157. *See* 42 U.S.C. § 256(a)(5)(B); 80 Fed. Reg. at 52,306.

158. 80 Fed. Reg. at 52,307–08.

159. 80 Fed. Reg. 52,308. This distinction is consistent with a December 2014 Program
se that also appears to limit the List to Medicaid Fee-for-Services (MFFS). *See* Dep't of
h & Human Servs., Health Res. & Servs. Admin., Release No. 2014-1, Clarification on
f the Medicaid Exclusion File (Dec. 12, 2014),
.hrsa.gov/opa/programrequirements/policyreleases/clarificationmedicaidexclusion.pdf.

160. 80 Fed. Reg. 52,308.

161. *Id.* at 52,309.

162. *Id.*

163. *Id.*

164. *Id.*

165. *Id.* at 52,308.

166. *Id.*

167. 42 U.S.C. § 1396r–8(c)(1)(C)(i)(I).

168. 80 Fed. Reg. at 52,310.

169. *Id.*

170. *Id.*

171. *Id.*

172. *Id.*

173. *Id.*

174. *Id.*

175. *Id.*

176. *Id.*

177. *Id.* at 52,311.

178. *Id.*

179. *Id.*

180. Pub. L. No. 102-585 (Nov. 4, 1992), codified at 38 U.S.C § 8126.

181. *Id.*

182. The pharmaceutical pricing agreement is an addendum to the master agreement that
ins a complete list of a manufacturer's covered drugs and a federal ceiling price (FCP) for
drug. By signing the document the manufacturer certifies the accuracy of all specified
.

183. 38 U.S.C. § 8126(a).

184. 38 U.S.C. § 8126(a)(4).

185. Manufacturers who enter into a FSS contract with the VA may also enter into a Blanket
ase Agreement (BPA). A BPA is "a simplified method of filling anticipated repetitive needs

ıpplies or services by establishing 'charge accounts' with qualified sources of supply." FAR 303-1(a). The government may use a BPA when there is a need for a wide variety of items, he exact items, quantities, and delivery requirements are not known in advance; when there eed for commercial source of supply for offices that do not have purchase authority; or to :e the administrative burden of writing numerous purchase orders. FAR § 13.303-2. In ;, the contractors may offer additional volume-based discounts. Moreover, the contractor nter into a BPA with a VA hospital, one of the Veterans Integrated Service Networks Ns), or the entire system. *Id.*

186. 38 U.S.C. § 8126(a)(1).

187. 48 C.F.R. § 538.270.

188. 38 U.S.C. § 8126(a)(2). The Amended Master Agreement also requires manufacturers to ı all relevant price reporting record for no less than five years pursuant to the VA's audit ɔrity at 38 U.S.C. § 8126(e)(3). Amended Master Agreement § II(D). Pursuant to its audit ɔrity, the VA is entitled to "unrestricted access" of the records and information necessary to mine the accuracy of price reports. 38 U.S.C. § 8126(e)(3).

189. 38 U.S.C. § 8126(a)(3), (b). Manufacturers are permitted to offer a higher price to all federal agencies so long as that price is consistent with its other obligations under cable government contracting principles. 38 U.S.C. § 8126(d).

190. 38 U.S.C. § 8126(a)(2).

191. 38 U.S.C. § 8126(h)(5). The term "nominal price" is defined in the VA master ment as "any price less than 10% of the Non-FAMP in the previous quarter from a sale lly below cost) designed to benefit the public by financially aiding disadvantaged, not-for- t covered drug dispensaries or researchers using a drug for an experimental or non-standard ɔse." Non-FAMP is net of all cash discounts, *e.g.*, prompt payment and similar price :tions, including rebates, administrative fees, free goods contingent on a purchase rement (excluding bona fide samples under 21 U.S.C. § 353), chargebacks, and incentive ased reductions or credits where a buyer realizes a net reduced price with increased ation of a product.

192. 38 U.S.C. § 8126(c).

193. 38 U.S.C. § 8126(e)(1). While the statute requires manufacturers to report Non-FAMP n thirty days of the end of the quarterly reporting period, the VA has issued sub-regulatory ınce in the form of "Dear Manufacturer Letters" that require manufacturers to report Non- P within forty-five days of the end of the quarterly reporting period.

194. 48 C.F.R. § 538.270.

195. *Id.* 48 C.F.R. §§ 515.408, 515.2. FSS contracts are multi-year (minimum of five years) nultiple award contracts, which means multiple companies supplying comparable products ervices, at varying prices, are awarded contracts.

196. *Id.* Manufacturers are further required to "certify" that their required price disclosures :urrent, accurate, and complete."

197. 42 C.F.R. § 552.215-72.

198. 38 U.S.C. § 8126(h)(2).

199. *Id.*

200. *Id.*

201. *Id.*

202. Federal agency acquisitions are subject to the requirements of the Trade Agreements Act
), 19 U.S.C. §§ 2501 *et seq.*, and its related regulations, which limit the countries of origin
which federal agencies may purchase supplies.

203. U.S. Dep't of Veterans Affairs, Mass Modification No. 0004, Schedule 65 I B (April
), www.va.gov/oal/business/fss/massmods.asp.

204. U.S. Dep't of Veterans Affairs, "TAA—Non-Availability Determinations under 65 I B"
5), www.va.gov/oal/business/fss/taa.asp#65ib.

205. *Id.*

206. National Defense Authorization Act for Fiscal Year 2008, Pub. L. No. 110,181 (Jan. 28,
), codified at 10 U.S.C. § 1074g(f).

207. 75 Fed. Reg. 63,383, codified at 32 C.F.R. § 199.21(q).

208. 32 C.F.R. § 199.21(q)(3)(ii).

209. *See, e.g.*, CMS Medicare, www.cms.gov/Medicare/Medicare-General-
mation/MedicareGenInfo/index.html.

210. *See, e.g.*, OIG, OEI-03-07-00350, Comparing Pharmacy Reimbursement: Medicare Part
Medicaid (Feb. 2009), http://oig.hhs.gov/oei/reports/oei-03-07-00350.pdf.

211. 42 U.S.C. § 1395x(s).

212. *Id.*

213. OIG, OEI-12-12-00260, Medicare Could Collect Billions If Pharmaceutical
ıfacturers Were Required to Pay Rebates for Part B Drugs (Sept. 2013), at 1–2.

214. 42 U.S.C. § 1395x(s)(2)(A).

215. *See, e.g.*, 63 Fed. Reg. 58,905 (Nov. 2, 1998), *as amended by* 69 Fed. Reg. 1116 (Jan. 7,
).

216. *See, e.g.*, U.S. Gov't Accountability Office, Prescription Drugs: Expanding Access to
ːal Prices Could Cause Other Price Changes, GAO/HEHS-00-118, at 9 (Aug. 7, 2000),
.gao.gov/assets/240/230510.pdf ("AWP is typically less than the retail price, which will
de the pharmacy's own price markup. AWP is referred to as a sticker price because it is not
ːtual price that large purchasers normally pay."). Moreover, AWP is not government-
ated pricing benchmark because is not defined in any federal statue or regulation.

217. Medicare Prescription Drug and Modernization Act of 2003, Pub. L. No. 108-173
. 10, 2003), codified at 42 U.S.C. § 1395w-3a.

218. Certain Part B covered drugs and biologics, including certain vaccines (such as
mococcal and Hepatitis B vaccine) and blood products, are exempt from the ASP
ɔursement methodology. 42 U.S.C. § 1395u(o)(1).

219. 42 U.S.C. § 1395w-3a(b)(3)(A)(iii).

220. Exempt sales include "all sales exempt from inclusion in the determination of 'best
'" and "nominal sales" as defined by the Medicaid statute. 42 U.S.C. § 1395w-3a(c)(2)(A)
).

221. MMA § 3139.
222. *Id.*; 42 U.S.C. § 1395w-3a(c)(3).
223. 71 Fed. Reg. 69,624 (Dec. 1, 2006).
224. 42 U.S.C. § 1395w-3a.
225. 42 U.S.C. § 1395w-3a(b)(1)(A). Wholesale acquisition cost (WAC) is defined in the care statute as "the manufacturer's list price for the drug or biological to wholesalers or t purchasers in the United States, not including prompt pay or other discounts, rebates or ctions in price, for the most recent month for which the information is available, as reported olesale price guides or other publications of drug or biological pricing data." 42 U.S.C. 95w-3a(6)(B).
226. 42 U.S.C. § 1395w-3a(b)(1)(B).
227. 42 C.F.R. § 414.90476(d)(3); 76 Fed. Reg. 73,026, 73,293 (Nov. 28, 2011). The MMS es "widely available market price" or WAMP "the price that a prudent physician or supplier d pay for the drug or biological . . . taking into account the discounts, rebates, and other concessions routinely made available to such prudent physicians or suppliers for such drugs ological." 42 U.S.C. § 1395w-3a(b)(5)(A).
228. 82 Fed. Reg. 53,256.
229. Am. Hosp. Ass'n v. Hargan, Case No. 17-cv-02447, 2017 WL 6734176 (D.D.C. Jan. 018).
230. The federal upper limit (FUL) program also relies on AMP reporting data to calculate Medicaid FUL applicable to brand name covered outpatient drugs.
231. SSA § 1927(b)(3)(C), codified at 42 U.S.C. 1396r-8(b)(3)(C).
232. 42 U.S.C. 1396r-8(b)(3)(C)(i).
233. *Id.*
234. 42 U.S.C. § 1396r-8(b)(3)(C)(ii).
235. 42 U.S.C. § 1395w-3a(d)(4).
236. 42 U.S.C. § 256b(d)(1)(B)(iv).
237. *See, e.g.*, Dep't of Health & Human Servs., Office of the Inspector General, Work Plan iscal Year 2017 (Nov. 10, 2016), https://oig.hhs.gov/reports-and-cations/archives/workplan/2017/HHS%20OIG%20Work%20Plan%202017.pdf.
238. Dep't of Health & Human Servs., Office of the Inspector General, Work Plan, ://oig.hhs.gov/reports-and-publications/workplan/index.asp.
239. Dep't of Health & Humans Servs., Office of the Inspector General, Archives-Work https://oig.hhs.gov/reports-and-publications/archives/workplan/index.asp.
240. Dep't of Health & Human Servs., Office of the Inspector General, Work Plan for Fiscal 2017 (Nov. 10, 2016), https://oig.hhs.gov/reports-and-cations/archives/workplan/2017/HHS%20OIG%20Work%20Plan%202017.pdf.
241. Dep't of Health & Human Servs., Office of the Inspector General, Archives-Work Plan, ://oig.hhs.gov/reports-and-publications/archives/workplan/index.asp, Report No. W-00-5789.
242. Dep't of Health & Human Servs., Office of the Inspector General, Work Plan for Fiscal

2017 (Nov. 10, 2016), https://oig.hhs.gov/reports-and-cations/archives/workplan/2017/HHS%20OIG%20Work%20Plan%202017.pdf.

243. *Id.*

244. *Id.*

245. *Id.*

246. Dep't of Health & Human Servs., Office of the Inspector General, Archives-Work Plan, ://oig.hhs.gov/reports-and-publications/archives/workplan/index.asp, Report No. OEI-03-)430.

247. Dep't of Health & Human Servs., Office of the Inspector General, Work Plan for Fiscal 2017 (Nov. 10, 2016), https://oig.hhs.gov/reports-and-cations/archives/workplan/2017/HHS%20OIG%20Work%20Plan%202017.pdf.

248. *Id.*

249. Dep't of Health & Human Servs., Office of the Inspector General, Active Work Plan s, Treatment of Authorized Generic Drugs (Report No. W-00-17-31499), ://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000023.asp visited Feb. 22, 2018).

250. Dep't of Health & Human Servs., Office of the Inspector General, OEI-03-17-00100, ıtial Misclassifications Reported by Drug Manufacturers May Have Led to $1 Billion in Medicaid Rebates, https://oig.hhs.gov/oei/reports/oei-03-17-00100.pdf.

251. *Id.*

252. Dep't of Health & Human Servs., Office of the Inspector General, Active Work Plan s, FDA-Approval Status of Drugs in the Medicaid Drug Rebate Program (Report No. OEI-7-00120), https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-214.asp.

253. *Id.*

254. Dep't of Health & Human Servs., Office of the Inspector General, Active Work Plan s, Increase in Prices for Brand-Name Drugs Under Part D (Report No. OEI-03-15-00080), ://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000151.asp.

255. *Id.*

256. Dep't of Health & Human Servs., Office of the Inspector General, Active Work Plan s, Reasonable Assumptions in Manufacturer AMP Reporting (Report No. OEI-12-17-0), https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-216.asp.

257. *Id.*

258. *Id.*

259. 31 U.S.C. §§ 3729–33.

260. 31 U.S.C. § 3729(a)(1)(A).

261. 31 U.S.C. § 3729(a)(1)(B).

262. 31 U.S.C. § 3729(a)(1)(C).

263. 31 U.S.C. § 3729(a)(1)(G).

264. 31 U.S.C. § 3729.

S. REP. NO. 99-345, at 7 (1986), *reprinted in* 1986 U.S.C.C.A.N. 5266, 5272.

United States v. Kaman Precision Prods., Inc., No. 6:09-cv-1911-Orl-31GJK, 2011 WL 569 (M.D. Fla. Aug. 20, 2011) (discussing legislative history).

See, e.g., United States v. King-Vassel, 728 F.3d 707, 713 (7th Cir. 2013) (observing eckless disregard had been variously described as those who act with gross negligence or e to make such inquiry as would be reasonable and prudent under the circumstances; sion of gross negligence of extreme version of ordinary negligence and concluding that think these are all apt and useful descriptions of the concept of reckless disregard.").

31 U.S.C. § 3729(a).

Id.

Civil Monetary Penalties Inflation Adjustment, 81 Fed. Reg. 42,491, 42,494 (June 30,) (to be codified at 28 C.F.R. pt. 85.3(a)(9)).

Id.

Press Release, U.S. Dep't of Justice, Wyeth and Pfizer Agree to Pay $784.6 Million to ve Lawsuit Alleging That Wyeth Underpaid Drug Rebates to Medicaid (Apr. 27, 2016), .justice.gov/usao-ma/pr/wyeth-and-pfizer-agree-pay-7846-million-resolve-lawsuit-alleging-underpaid-drug.

Press Release, U.S. Dep't of Justice, U.S. and 16 States Join Suits Against naceutical Giant, Wyeth (May 18, 2009), www.justice.gov/opa/pr/2009/May/09-civ- ıtml.

Id.

Id.

See Second Amended Complaint of the United States, U.S. *ex rel.* Kieff v. Wyeth, No. cv-11724-DPW (D. Mass. filed Feb. 11, 2016).

Press Release, U.S. Dep't of Justice, King Pharmaceuticals to Pay U.S. $124 Million for caid Rebate Underpayments & Overcharging for Drug Products (Nov. 1, 2005), .justice.gov/opa/pr/2005/November/05_civ_581.html.

Id.

U.S. Dep't of Health & Human Servs., Office of the Inspector General, "Civil Monetary lties and Affirmative Exclusions," https://oig.hhs.gov/fraud/enforcement/cmp/cmp-ae.asp.

Id.

Id.

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14

The Foreign Corrupt Practices Act and Its Impact on the Pharmaceutical Industry

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The U.S. Foreign Corrupt Practices Act (FCPA) is a far-reaching U.S. anti-bribery law that has been a major enforcement priority for U.S. r (non-FAMP) and egulators since at least 2009, when the U.S. government announced an industry-wide investigation into pharmaceutical sales abroad. Enforcement remains a priority today; indeed, 2016 saw the largest criminal fine ever imposed against a pharmaceutical company for FCPA violations. In short, the FCPA prohibits multinational companies with a U.S. connection (and their officers, directors, employees, and third-party agents) from bribing non-U.S. government officials in order to win or keep business, or obtain some other business advantage. The FCPA contains two main components: (1) the anti-bribery provisions, which prohibit certain persons and companies from making corrupt payments to non-U.S. government officials to obtain or retain business;[2] and (2) the accounting provisions, which require that U.S. exchange-listed companies maintain accurate books and records, and devise and maintain adequate internal accounting controls.[3]

In the pharmaceutical context, the FCPA governs most company interactions with individual healthcare professionals (HCPs) and government officials outside of the United States, particularly in countries with publicly funded healthcare systems. Such interactions include those related to research and development of new products, clinical trials, training seminars and educational conferences, grants and donations, fellowships, marketing and promotional activities, travel, gifts and hospitality, hospital tenders, product regulatory approvals and certifications, and product imports/exports, just to name a few.

As the U.S. Department of Justice (DOJ) warned in 2009, U.S. regulators are, and indeed have been, "intensely focused on rooting out foreign bribery" in the "high-risk" pharmaceutical industry.[4] Since then, U.S. regulators have settled FCPA cases with over twenty pharmaceutical and medical device companies, generating approximately $980 million in fines, penalties, and disgorgement of profits. Other healthcare companies are still under

investigation in the United States, and government regulators have indicated that the pharmaceutical industry remains in its crosshairs.[5] In fact, the DOJ recently announced a new partnership between the Healthcare Fraud Unit's Corporate Strike Force and the FCPA Unit. The two groups will work together to investigate and prosecute domestic and foreign bribery in the healthcare sector.[6]

In light of the significant increase in FCPA enforcement against life sciences companies—and the expenses associated with investigations, fines, and penalties—it has never been more critical that pharmaceutical companies take care to ensure compliance with the FCPA.

In the discussion below, all amounts are in U.S. dollars, unless otherwise specified.

FCPA Basics

Q 14.1 What FCPA basics should the pharmaceutical industry know?

Multinational pharmaceutical companies—particularly those that maintain significant operations outside the United States—should have an understanding of the FCPA, including the law's elements and components, its jurisdictional provisions, and possible penalties and collateral consequences. Managers and others whose responses to FCPA challenges will be the first line of protection for their employers must be armed with this knowledge.

Q 14.2 Which U.S. regulators enforce the FCPA?

The DOJ and U.S. Securities and Exchange Commission (SEC) share responsibility for FCPA enforcement.

The DOJ is responsible for criminal enforcement of the FCPA. Within the DOJ, the Criminal Division, Fraud Section in Washington, D.C., maintains primary responsibility for enforcement. The Fraud Section often works with local U.S. Attorneys' offices throughout the country to prosecute FCPA violations.

The SEC is responsible for civil enforcement of the FCPA with respect to issuers. The SEC established a dedicated FCPA Unit in 2010, which has primary responsibility for all FCPA matters.

Q 14.3 Who is covered by the FCPA?

The FCPA's anti-bribery provisions cover three groups:

- *Issuers* (that is, companies whose securities are traded on a U.S. exchange) and certain individuals acting on their behalf that "make use of the mails or any means or instrumentality of interstate commerce."[7] For example, a non-U.S. pharmaceutical company that has American Depositary Receipts traded on the New York Stock Exchange is an "issuer."[8]
- *Domestic concerns* (that is, U.S. citizens, nationals, residents, or companies organized under the laws of the United States or with a principal place of business in the United States) and certain individuals acting on their behalf that "make use of the mails or any means or instrumentality of interstate commerce."[9] For example, a privately owned U.S. pharmaceutical company is a domestic concern.[10]
- *Anyone other than an issuer or domestic concern* that "make[s] use of the mails or any means or instrumentality of interstate commerce" or otherwise acts in furtherance of proscribed conduct "while in the territory of the United States."[11] For example, a non-U.S. pharmaceutical representative who, while traveling in the United

States, engages in conduct that violates the FCPA falls within this category.[12] This jurisdictional basis is very broad and is largely untested.[13]

By contrast, the FCPA's accounting provisions apply only to "issuers."[14] However, the FCPA extends to the books of such companies' subsidiaries and affiliates where their books roll up into the parent's books. In other words, companies traded on U.S. exchanges have an obligation to ensure that their subsidiaries—both inside and outside of the United States—comply with the FCPA's accounting provisions.[15]Moreover, certain individuals also may face personal liability for the acts of foreign subsidiaries that affect the company's books and records based on a theory of "control person" liability.[16]

Each of the three categories above (that is, issuers, domestic concerns, and other persons) also includes "any officer, director, employee, or agent" of such entity.[17] Accordingly, the FCPA's jurisdictional embrace reaches beyond U.S. borders to include entities such as non-U.S. subsidiaries of a U.S. company, or under certain circumstances, non-U.S. joint venture partners not otherwise subject to the FCPA.

Q 14.4 What do the FCPA's anti-bribery provisions prohibit?

The FCPA's anti-bribery provisions prohibit:

- Offering, promising, authorizing, or paying;
- Money or anything of value;
- Directly or indirectly;
- To a "foreign official" or non-U.S. political party, party official, or candidate;
- When such offers, promises, authorizations, or payments are made corruptly;
- To obtain or retain business, or to gain some other business advantage.[18]

The DOJ and SEC have taken a broad view of the definition of "foreign official" to encompass employees of non-U.S. government-owned or operated entities, including doctors, pharmacists, and lab technicians. Employees of public international organizations are also considered foreign officials. According to the DOJ, "it is entirely possible, under certain circumstances and in certain countries, that nearly every aspect of the approval, manufacture, import, export, pricing, sale and marketing of a drug product in a foreign country will involve a foreign official within the meaning of the FCPA."[19]

It is unlawful under the FCPA to make payments or provide benefits to third parties—including distributors, dealers, carrying and forwarding agents, travel agents, conference organizers, design institutes, medical associations, and foundations—knowing that some or all of those payments or benefits will be provided to foreign officials in violation of the FCPA. "Knowing" is defined as actual knowledge or conscious disregard of facts indicating a high probability that improper conduct will occur.[20] In other words, pharmaceutical executives and employees cannot evade FCPA liability by putting their "heads in the sand" and ignoring "red flags," or facts or circumstances that indicate a probable risk, possible

violation, or actual violation of the FCPA.

Q 14.5 Does the FCPA contain any affirmative defenses?

Yes. The FCPA contains two affirmative defenses relative to the anti-bribery provisions. The first affirmative defense applies to payments, gifts, offers, or promises of anything of value that are lawful under the written laws in the foreign official's country.[21] This affirmative defense matters little because it is illegal to bribe government officials in every country.

The second is an affirmative defense for reasonable and bona fide expenditures that are directly related to the (1) promotion, demonstration, or explanation of the company's products or services, or (2) execution or performance of a contract with a non-U.S. government or government agency.[22] Reasonable and bona fide expenditures may take many forms, and the analysis is necessarily fact specific. The DOJ has explicitly acknowledged that certain expenditures, when appropriate in size and directly related to the promotion or demonstration of products, or performance of a contract, do not create criminal liability under the FCPA. For example, the DOJ has stated that, depending on the circumstances, the following expenditures may be appropriate:

- Travel and expenses for non-U.S. officials to visit company facilities or operations;[23]
- Travel and expenses for non-U.S. officials to receive training;[24] and
- Product demonstration or other promotional activities, including travel and reasonable expenses to attend meetings.[25]

Q 14.6 Does the FCPA contain any exceptions?

The FCPA contains one exception under the anti-bribery provisions for "facilitating payments," which are small payments made to foreign officials for the purpose of expediting or securing the performance of a routine governmental action.[26] Examples of routine government action include providing mail services, utilities, or processing visa applications. They do not include acts that are within a foreign official's discretion.[27] The purpose of the payment may help determine whether it is truly a facilitating payment.

Facilitating payments often present unique and difficult challenges for companies because analyzing whether a payment may qualify as a facilitating payment is particularly complex. Moreover, although the FCPA provides an exception for facilitating payments, such payments are not expressly permitted under other anti-bribery or local laws. For example, the U.K. Bribery Act does not contain an exception for facilitating payments.[28] As a result, many multinational pharmaceutical companies have prohibited making facilitating payments in their compliance policies.

Q 14.7 What do the FCPA's accounting provisions require?

The FCPA's accounting provisions require "issuers" to maintain accurate books and records, and to have internal controls adequate to detect and prevent violations of the law.[29] In many cases, it is easier for U.S. enforcement authorities to prove a civil violation of the accounting provisions because there is no requirement to establish knowledge or intent. "Knowing" or intentional violations of the books and records and internal controls provisions can be enforced criminally.[30]

Q 14.8 What fines and penalties may be assessed for FCPA violations?

The FCPA carries significant fines and penalties. Corporations and other business entities are subject to fines of up to $2 million for each violation of the anti-bribery provisions,[31] and up to $25 million for each violation of the accounting provisions.[32] Individuals are subject to fines of up to $250,000 and imprisonment for up to five years for violations of the anti-bribery provisions,[33] and fines of up to $5 million and imprisonment for up to twenty years for violations of the accounting provisions.[34] Fines up to twice the benefit that the defendant obtained through the corrupt payment may be imposed in some instances.[35]

In practical terms, fines, penalties, and disgorgement of profits have ranged greatly based on the unique circumstances of each case. The largest penalty ever imposed by U.S. enforcement authorities under the FCPA was in 2008, when Siemens AG and its subsidiaries agreed to pay $800 million in fines, penalties, and disgorgement.[36] In 2016, Odebrecht S.A. and its affiliate Braskem S.A. agreed to pay $3.5 billion in connection with a global settlement with authorities in the United States, Brazil, and Switzerland. Since the start of the pharmaceutical industry sweep in late 2009, fines, penalties, and disgorgement paid by healthcare companies have ranged from $375,000 to $519 million.[37]

Q 14.9 What collateral consequences might arise from an FCPA violation?

One potential consequence associated with FCPA violations is the imposition of an independent compliance monitor as part of a negotiated settlement with U.S. regulators. A corporate compliance monitor is an independent third party that assesses a company's adherence to the ongoing compliance requirements set forth in settlement agreements. Although not appropriate in all circumstances, the DOJ has issued internal guidance suggesting that appointment of a monitor may be appropriate where a company's existing compliance program is unsatisfactory or where internal controls need to be significantly tightened.[38] The SEC similarly can require a company to retain an independent compliance consultant or monitor.[39] In circumstances where both the DOJ and SEC require a company to retain a monitor, the agencies have coordinated their requirements so the company may retain one monitor to fulfill both sets of requirements.[40]

Corporate monitorships can be extremely expensive and disruptive for companies, as they strain internal company resources, and monitors report directly to the government without oversight from company personnel. Over the past several years, the government

has imposed corporate monitorships in a number of settlements,[41] while other companies have managed to avoid monitorships all together. In the settlements where a monitor has not been imposed, the government has touted the companies' remedial actions, improvements to their compliance programs and internal controls, and specific compliance undertakings in settlement agreements.[42]

Other potential collateral consequences include: enhanced compliance obligations, debarment, cross-debarment by multilateral development banks, loss of export privileges, dilution of share price, loss of talent, and reputational damage.[43]

Q 14.10 What other laws are used in conjunction with the FCPA?

The DOJ also may bring anti-corruption cases under the Travel Act, which generally prohibits individuals and companies from using communications and travel facilities to commit U.S. state or federal crimes. More specifically, the Travel Act provides, in relevant part, that any entity or person who:

> travels in interstate or foreign commerce or uses the mail or any facility in interstate or *foreign commerce*, with the intent to—(1) distribute the proceeds of any unlawful activity; or (2) commit any crime of violence to further any unlawful activity; or (3) otherwise promote, manage, establish, carry on, or facilitate the promotion, management, establishment, or carrying on, of any unlawful activity . . . and thereafter performs or attempts to perform an act [described above in paragraphs (1), (2), or (3)]

is subject to criminal liability.[44] The statute describes "unlawful activity" to include violations of state commercial bribery laws.[45] This is a useful tool for the government where, for example, it may be difficult to determine whether an individual qualifies as a foreign official but bribery has occurred. In 2004, the DOJ indicted a number of healthcare executives for violations of the FCPA and Travel Act in connection with bribes paid to the Director General of a Saudi foundation that built and administered a hospital.[46]

Other laws that may be used in conjunction with the FCPA include anti-money laundering statutes, mail and wire fraud statutes, certification or reporting violation statutes, and tax statutes.[47]

Anti-Bribery Provisions in Detail

Anything of Value

Q 14.11 What does the phrase "anything of value" mean?

While the FCPA specifically prohibits bribes in their most common forms (for example, money and gifts), the statute also contains a catch-all clause to address "anything of value." Congress included this language recognizing that bribes may be disguised as any number of improper benefits, and can range in value to the recipient. Moreover, items or payments that might appear relatively benign in the United States may be considered more significant in a foreign country. The prohibition on "anything of value" under the FCPA has been construed broadly by the DOJ and SEC, but necessarily is dependent on the facts and circumstances of each case. Regardless of the form of payment, it should be noted that the statute requires corrupt intent before criminal liability will attach.

Q 14.12 How have cash and cash equivalents featured in FCPA actions?

When most people imagine bribes, they envision a bad actor passing a bag or briefcase of cash to the recipient. Although cash payments may not always occur in quite so dramatic a fashion, cash and cash equivalents remain the most obvious forms of "value" that can be passed to foreign officials. A number of FCPA enforcement actions in the healthcare industry have centered on cash payments to HCPs and other foreign officials.[48] For example:

- A healthcare company's Taiwanese subsidiary provided sealed envelopes of cash to HCPs at public hospitals to encourage product sales and patient referrals;[49]
- A medical device company made payments in cash and stock options to an HCP at a public hospital center that were "proportional to purchases made by the public hospital" and intended to increase sales;[50] and
- A healthcare company allegedly provided a personal loan to an HCP that was never repaid.[51]

In most cases, the source of the cash is disguised in an effort to avoid detection from the business or auditors. For example, cash payments may be made by providing HCPs with "rebates" or "commissions" equivalent to a percentage of the HCP's total purchases, which is in reality a disguised kickback to the HCP for purchasing the company's products. In several cases, distributors have made cash payments to HCPs after obtaining product rebates or discounts from pharmaceutical or medical device companies.[52]

Q 14.13 Are travel and entertainment considered "anything of value"?

Yes. U.S. enforcement authorities have brought FCPA enforcement actions based on the provision of travel, lodging, meals, and other expenses to foreign officials. Travel, lodging, meals, and related expenses have featured in FCPA enforcement actions involving the healthcare industry.[53] Some of the more common risk areas that have been targeted by U.S. regulators include travel upgrades, international travel unrelated to legitimate business activities, travel provided for spouses or other companions, and repeat international travel for the same individual.[54] Examples include:

- Allegedly providing international travel to HCPs (either directly or through third parties) to influence prescriptions, provide hospital formulary listing, or obtain unfair advantages;[55]
- Reportedly agreeing to provide international travel to HCPs based on the HCPs' promises to prescribe the company's products;[56]
- Sending an official on a "motivational trip" in order for certain products to be included on the government's list of reimbursable medications;[57]
- Allegedly providing travel packages to public hospital employees in order to secure contracts;[58]
- Allegedly providing travel for HCPs to tourist locations rather than to the locations of legitimate education activities, and including their family members;[59] and
- Reportedly sending an official and her spouse for a six-day stay in New York City that included two Broadway shows, followed by a five-day stay in Aruba, in connection with a single-day site tour in New Jersey.[60]

One particular danger is that entertainment and travel expenses may be falsified easily to create cash funds. For example, in two cases, employees of major healthcare companies allegedly submitted fake receipts and travel itineraries to seek reimbursement for improper expenses.[61]

It should also be noted that companies are, in fact, permitted to provide legitimate travel, lodging, and related expenses. In the absence of corrupt intent, many expenses are perfectly acceptable. Moreover, many expenses may fall under the affirmative defense for bona fide expenditures (see Q 14.5 above). Nonetheless, healthcare companies must remain vigilant about the risks associated with these activities, and familiarize themselves with travel guidelines contained in relevant pharmaceutical codes (see Q 14.43 below).

Q 14.14 Are gifts considered "anything of value"?

The DOJ and SEC have targeted companies that provided gifts to HCPs in order to improperly influence them. In many instances, improper gifts are part of a larger scheme or are symptomatic of other FCPA issues. In one action, the SEC noted that the dollar amount of each alleged gift was relatively small, but the volume of improper payments was significant.[62] The DOJ and SEC have brought enforcement actions against companies that

reportedly directly, or through third-party distributors and/or sales representatives, provided gifts to HCPs, including:

- Wine and specialty foods;[63]
- Jewelry;[64]
- Meals;[65]
- Visits to bathhouses, spas, and karaoke bars;[66]
- Publication fees;[67]
- Televisions, laptops, and appliances;[68]
- Car leases;[69]
- "Points" based on the number of prescriptions issued, which were redeemable for items ranging from medical books to cell phones, reading glasses, and tea sets;[70]
- "Miles" that could be redeemed for personal travel;[71]
- English language classes;[72] and
- Shopping excursions.[73]

Q 14.15 Are sponsorships and trainings considered "anything of value"?

In the life sciences industry, companies often provide training to or sponsor training for HCPs. The DOJ and SEC have brought enforcement actions where companies provide international travel for training that is tied to the purchase or use of company products,[74] or based on activities undertaken in connection with otherwise legitimate sponsorship or training activities for HCPs, such as side trips, sightseeing activities, and other non-business-related entertainment activities.[75]

In one enforcement action, a healthcare company reached a $77 million combined settlement based on improper conduct that included travel sponsorships for HCPs that "contributed significantly to [the company's tender] win" and was a "fulfillment of the post tender obligations."[76]

Q 14.16 Are clinical trials and observational studies considered "anything of value"?

Yes. Clinical trials and observational studies present particularly significant corruption risks for healthcare companies because government officials are involved in nearly every aspect of the clinical development process, from giving regulatory approval to conducting the trials and studies. Moreover, a significant amount of the clinical trials conducted for FDA-regulated products are conducted in foreign countries. These arrangements can present particularly significant corruption risks as companies may select and engage particularly influential HCPs to conduct trials or studies in an effort to influence their

purchasing or prescribing decisions. Moreover, the risk of consulting arrangements where the HCP is paid in excess of fair market value only heightens the scrutiny that these arrangements should receive.

Clinical trials and observational studies have received increased regulatory attention in the past several years. The DOJ and SEC have brought enforcement actions against a number of healthcare companies based, in part, on improper payments to HCPs that have facilitated or participated in clinical trials. For example, the DOJ has entered into deferred prosecution agreements with major medical device and pharmaceutical companies based on:

- Improper payments for "observational studies" in order to influence HCPs to purchase the company's products;[77]
- Improper payments made to Polish HCPs through "civil contracts" to conduct, among other things, clinical trials, in an effort to influence tender awards;[78] and
- Improper payments for medical studies that lacked scientific value and were designed to reward the purchase of company products.[79]

Q 14.17 Are employment and/or consulting agreements considered "anything of value"?

Yes. HCPs can be engaged legitimately pursuant to employment or consulting agreements for a variety of purposes. However, the DOJ and SEC have examined employment and consulting arrangements with HCPs and other non-U.S. government officials to determine whether the contractual arrangements are being used to disguise the flow of improper benefits. A number of enforcement actions have centered on agreements with HCPs whereby the HCPs were paid more than fair market value for their services, or conducted little, if any, legitimate work for the company in exchange for payment. In one matter, a company allegedly provided stock options to members of its scientific advisory board who also were employed by public hospitals. There, the value of the stock options exceeded the value of the services provided.[80] The company also made payments to a physician at a university hospital center under a consulting agreement for services that were not performed.[81]

Speaker fees have also been a focus of recent enforcement actions. In one matter, the company allegedly paid speaker fees to HCPs in connection with events that never occurred.[82] In another matter, a company did not ensure that limits on what could be paid to speakers were followed, which allowed employees to use otherwise legitimate speaker fees to improperly influence HCPs.[83]

A recent enforcement action dealt with paying HCPs recognized as "Key Opinion Leaders" (KOLs) to manage training centers. According to the settlement papers, the KOLs who managed the company's training centers received an annual salary, a 50% discount on the company's equipment, a $30,000 budget for "VIP Management," and "miles" that could be redeemed for personal travel.[84]

Companies should remain aware of the dichotomy between HCPs as customers and as consultants, and the potential appearance that HCP consultants are being paid or rewarded (for example, through travel, meals, and entertainment) in exchange for the purchase, recommendation, or prescription of products.

Q 14.18 Are charitable donations considered "anything of value"?

Yes. The DOJ and SEC carefully scrutinize charitable donations to ensure that charitable donations are not being made for the benefit of foreign officials. In one recent matter, a company's Chinese subsidiary allegedly made a $154,000 donation to a charity selected by a Chinese Communist Party Official in order to influence a pending investigation against the company. Anti-corruption language suggested by the company's outside counsel was removed from the final version of the donation agreement. Two days after making the donation, the company learned that it would not be charged or fined in connection with the investigation.[85]

In another matter, a pharmaceutical company reportedly gave approximately $39,000 in donations to a small charitable organization that restored castles in Poland. However, the charitable organization was "founded and administered by the head of one of the regional government health authorities," and the donations allegedly were made "at the same time that [the company] was seeking the official's support for placing [the company's] drugs on the government reimbursement list."[86] Moreover, according to the SEC, the purpose of the payments was falsely described in the company's books and records.[87]

Certain internal controls can be put in place to minimize the risk that charitable donations will be used improperly. See Q 14.37 below. For example, in one Opinion Procedure Release,[88] the DOJ indicated that it did not intend to take enforcement action with respect to a proposed donation of 100 sample medical devices and related items to a series of hospitals in a foreign country, in part because the products would be provided to the foreign government rather than to individual foreign officials.[89] Moreover, the company described a thorough and transparent patient selection process that would mitigate the risk of corruption.[90]

Third Parties

Q 14.19 How do third parties pose FCPA risks?

For purposes of the FCPA, third parties such as distributors, dealers, sales agents, carrying and forwarding agents, and consultants are considered "agents" of the company. There are many instances in which companies have settled FCPA actions based on the alleged conduct of these third parties.[91] The FCPA prohibits payments to third parties if the company *knew* or *should have known* that the third party corruptly passed on all or part of the payments directly or indirectly to a foreign official.[92] Knowledge is defined very broadly to include conscious disregard or deliberate ignorance, so that purposely turning a blind eye to corruption can constitute knowledge.[93] As such, there are significant FCPA

and anti-corruption risks associated with (1) these third parties' interactions with foreign officials, and (2) the company's and its subsidiaries' interactions with third parties who, themselves, might be considered foreign officials (for example, physician consultants or physician-owned distributors).

Many enforcement actions are brought by the DOJ and SEC based on the actions of a company's third-party agents. For example, a pharmaceutical company's subsidiary in Russia allegedly paid off-shore companies for "services" that rarely were provided so that distributors and government officials would purchase drugs. The SEC specifically noted that "[i]n some instances, the off-shore entities appear to have been used to funnel money to government officials or others with influence in the government in order to obtain business for the subsidiary."[94] In another example, a Mexican subsidiary of a medical device company allegedly paid bribes to third-party entities that were each controlled by Mexican government officials in return for agreements with the entities and their hospitals to purchase millions of dollars of the company's products.[95]

Companies should remain skeptical of third parties specifically selected or recommended by foreign officials with whom the company wishes to do business or from whom the company is seeking approvals. For information on how to mitigate FCPA risk presented by third parties, see Q 14.44 below.

Q 14.20 Do joint venture partners pose FCPA risks?

Yes. Under the anti-bribery provisions, joint venture partners may be liable for their partners' illicit activities if they have actual or constructive knowledge of the activities. Although the level of ownership or control in the joint venture does not specifically determine the level of liability, it may be relevant in determining whether a joint venture partner knew or should have known about its partners' activities.

Companies should undertake appropriate due diligence on all prospective joint venture partners to ensure that there have been no past corruption issues that may result in liability for the entire joint venture, confirm that the joint venture agreement contains audit rights, and consider whether including an exit clause (in the event that FCPA issues are discovered) is appropriate.

Under the FCPA's accounting provisions, majority owners of joint ventures can be held liable for violations by the joint venture.[96] Minority owners are still liable for the joint venture's books and records and internal controls, but may avoid liability if they demonstrate good faith efforts to cause the joint venture to comply with the accounting provisions.[97]

Q 14.21 Do local agents and consultants pose FCPA risks?

Yes. Many companies rely on local agents to navigate regional regulations and bureaucracy, and to interface with customers and foreign officials. In some instances, laws and regulations require the use of local agents for various tasks. Because companies may be held criminally liable for the acts of third parties acting on their behalf, local agents can

pose significant FCPA risks. One of the more common examples of local agents that present significant risk for the healthcare industry is customs brokers. In one case, the Brazilian subsidiary of a dietary supplement company allegedly made payments to customs brokers who in turn paid customs officials to allow the importation of unregistered products.[98]

Local sales agents also present significant FCPA risks. For example, a healthcare company settled with the SEC based on the alleged actions of a local sales agent. In that case, the company's Italian subsidiary reportedly offered cash to a hospital director through a local sales agent to influence his upcoming decision regarding whether to renew his hospital's contract for supplies.[99] According to the SEC, the sales agent described the payment as "overdue compensation" for a conference.[100]

Companies may enter into consulting agreements with third parties for any number of legitimate reasons, including research and development, scientific advice, and sales and marketing. Like other third-party agents, companies must take care to ensure that consultants comply with the FCPA and other relevant laws, or else they risk opening themselves up to FCPA liability. For example, a life sciences company recently settled an enforcement action related to improper payments made by an agent the company had hired to help register, license, and distribute one of its treatments in Russia.[101] Similarly, a pharmaceutical company recently settled an enforcement action based, in part, on a consulting arrangement with a high-ranking government official who assisted with product registrations in Ukraine.[102] In another enforcement action, a major multinational company allegedly made a number of improper payments to various government officials via several local consultants, including:

- Payments to the Vietnamese Ministry of Health through a Hong Kong consultant;
- Payments through consultants to government-owned hospital employees, and lavish "study trips" for physicians at state-owned hospitals in China; and
- Payments through consultants to government-owned customers in Russia.[103]

Q 14.22 Do distributors present unique FCPA risks?

Yes. Many companies utilize a distributor business model for purposes of efficiency or, in some cases, to comply with local laws and regulations. For example, it is common or required in some countries for local distributors to hold product registrations. The DOJ and SEC have demonstrated an interest in the relationship between companies and distributors.[104] For example, a life sciences company agreed to a $22.2 million combined settlement with the DOJ and SEC in 2012 to resolve charges that subsidiaries had bribed government-employed doctors in Greece.[105] According to the SEC complaint, from 1997 to 2008, company subsidiaries used agents, affiliates, and employees to sell products to a Greek distributor at list price, after which they paid the distributor a rebate into an off-shore account.[106] These funds then allegedly were used by the distributor to pay cash or offer gift incentives to government-employed Greek HCPs in order to induce them to use

the company's products.[107]

A number of enforcement actions have centered on allegations related to company distributors:

- A producer of ultrasound equipment allegedly made $20 million in improper payments to third parties through distributors, and created fictitious invoices reflecting inflated sales prices to hide the payments;[108]
- A pharmaceutical company allegedly sold certain drugs at "unusually large discounts" to its Brazilian distributor so that the distributor could use approximately 6% of the purchase price to bribe Brazilian government officials to purchase the company's product;[109]
- A pharmaceutical company selected an exclusive distributor that reportedly funneled money to government officials to obtain product registrations in Kazakhstan;[110]
- A medical device company's distributor paid cash kickbacks to physicians with authority to make purchasing decisions at a public hospital in China, on a per-product-purchased basis;[111]
- A company's distributor in China made payments to patent officials to speed up the patent review process, "solve some problems" with the relevant applications, and ultimately obtain patent approvals;[112]
- A pharmaceutical company's Russian distributors allegedly made direct payments to hospital administrators and doctors for purchasing products, and falsely recorded the payments as "discounts" in the company's books and records;[113]
- A medical device company's Greek distributor paid cash incentives to orthopedic surgeons in the Greek public health system[114] and a 35% commission in advance of all purchases by the Greek distributor to an Isle of Man-registered company;[115] and
- The Colombian distributor of a diagnostic testing kit manufacturer made payments to the manager of a government-run healthcare entity that were disguised as payments for consulting services.[116]

Q 14.23 Are there FCPA risks associated with travel agents and conference organizers?

Travel agencies, in particular, have been used to create "slush funds" through which improper payments have been made. Several companies have settled with U.S. regulators based on improper payments through travel agents. For example, one pharmaceutical company reportedly:

- Reimbursed distributors for improper expenses by instructing travel agencies and

conference organizers to pay distributors and obtain reimbursement from the company by submitting false invoices for continuing medical education activities in Indonesia;[117] and

- Generated funds by paying vendors' falsified invoices, including travel agencies that submitted false or inflated invoices related to "large-scale consumer education events," and receiving cash kickbacks in Pakistan and China.[118]

More recently, a pharmaceutical company entered into a settlement with the SEC to resolve allegations that its employees colluded with third-party vendors to fund improper payments to HCPs by having the third parties inflate expenses for travel and event planning services and submitted invoices for events that never occurred.[119] Another pharmaceutical company also settled with the SEC based on similar conduct.[120]

Q 14.24 Do medical foundations and societies present FCPA risks?

Yes. Pharmaceutical companies regularly work with, present to, and provide educational grants and donations to foundations and other medical societies. These foundations and societies are often led by, and/or are comprised of, practicing physicians who may, in the ordinary course, purchase, recommend, or prescribe certain company products. As a result, there is a risk that U.S. enforcement authorities might perceive a grant or donation to be an inducement or reward for purchasing company products. In one case, officers of a large healthcare provider were prosecuted for paying the Director General of a Saudi Arabian foundation responsible for hospital contracting $500,000 per year in exchange for securing major hospital contracts.[121]

This topic has also become an area of focus for non-U.S. governments. For instance, China recently strengthened its laws surrounding donations to healthcare entities including medical societies and foundations.[122]

Foreign Officials

Q 14.25 What is a "foreign official" for purposes of the FCPA?

The FCPA defines a "foreign official" to include any officer, employee, or person acting on behalf of "a foreign government or any department, agency, or instrumentality thereof."[123] The statute thus applies to a broad range of individuals, including any official or employee regardless of his or her rank or title. Examples range from professors at public universities to customs and immigration officials.

The term "instrumentality" has been construed by U.S. enforcement authorities to include wholly or partially state-owned or controlled enterprises, including state-owned or controlled hospitals.[124] Whether an institution qualifies as an instrumentality of a non-U.S. government is not always obvious, and often requires investigation and a fact-specific analysis. The U.S. government has taken a broad view of the term's meaning despite recent challenges in federal court.

Depending on the circumstances, providing anything of value—including education, travel, lodging, meals, and incidental expenses—to HCPs employed by or affiliated with public hospitals or universities could trigger the FCPA.[125] The DOJ has explicitly warned healthcare companies:

> As important for your clients, consider the possible range of "foreign officials" who are covered by the FCPA: Some are obvious, like health ministry and customs officials of other countries. But some others may not be, such as the doctors, pharmacists, lab technicians and other health professionals who are employed by state-owned facilities. Indeed, it is entirely possible, under certain circumstances and in certain countries, that nearly every aspect of the approval, manufacture, import, export, pricing, sale and marketing of a drug product in a foreign country will involve a "foreign official" within the meaning of the FCPA.[126]

Q 14.26 Are HCPs foreign officials?

Yes, depending on the circumstances. Over the past several years, the DOJ and SEC have advanced the theory that HCPs employed by non-U.S. public hospitals, medical facilities, or universities qualify as foreign officials for purposes of the FCPA.

The DOJ and SEC have brought enforcement actions against a number of companies based on improper payments to HCPs.[127] Doctors and surgeons have been cited as the most obvious examples of HCPs for purposes of the FCPA. However, there are a multitude of other medical professionals or hospital/university employees that may also qualify.

Q 14.27 Are pharmacists foreign officials?

Yes, depending on the circumstances. The DOJ explicitly identified pharmacists as possible foreign officials in announcing the pharmaceutical sweep in 2009.[128]

Q 14.28 Are laboratory technicians foreign officials?

Yes, depending on the circumstances. If laboratory technicians are employed by public hospitals or facilities, they would likely be considered "foreign officials" by the DOJ and SEC. The DOJ and SEC settled one case, in part, based on cash commission payments made to laboratory technicians at state-owned hospitals.[129]

Q 14.29 Are hospital administrators and employees foreign officials?

Yes, depending on the circumstances. If a hospital administrator or employee works in a public hospital or medical facility, he or she is likely to be considered a "foreign official" by U.S. regulators.[130] In one recent case, a medical equipment manufacturer settled with the SEC, agreeing to pay over $4.5 million, based on alleged cash payments to hospital administrators to help secure tender awards.[131]

Q 14.30 Are healthcare regulators foreign officials?

Yes. The DOJ and SEC have indicated that healthcare regulators are foreign officials for purposes of the FCPA. Healthcare regulators often are responsible for tasks such as product approval and registration, approval of product pricing in-country, product reimbursement rates, and product placement regulations. For example, one company allegedly entered into an improper consulting arrangement with a high-ranking official within the Ukrainian Ministry of Health to assist the company in securing product registrations,[132] while another company allegedly made improper payments to a registration official in Croatia to influence the registration of its products.[133] Companies operating outside the United States should take great care to ensure that third parties engaged to interface with healthcare and other relevant regulators are aware of the anti-corruption risks, and are compliant with the FCPA and other anti-bribery laws and regulations.

Corrupt Intent

Q 14.31 When are offers, promises, authorizations, or payments made corruptly?

At its most basic level, the word "corruptly" means with an intent to improperly influence the recipient of a payment. It is not defined in the statute. However, in enacting the FCPA in 1977, the U.S. Congress explicitly noted:

> [t]he word "corruptly" is used in order to make clear that the offer, payment, promise, or gift, must be intended to induce the recipient to misuse his official position; for example, wrongfully to direct business to the payor or his client, to obtain preferential legislation or regulations, or to induce a foreign official to fail to perform an official function. The word "corruptly" connotes an evil motive or purpose . . . .[134]

The FCPA criminalizes the intent to make an improper payment. The FCPA *does not* require that an improper payment be successfully made. Moreover, it is the intent to make the improper payment that is relevant, rather than the intent to violate the FCPA.

Criminal liability only will attach where a defendant acts "willfully," a term that is not defined in the FCPA. Courts have generally construed the term to mean an act committed purposefully and with improper purpose, and have noted that the government is not required to prove that a defendant was specifically aware of the FCPA.[135] Rather, a defendant must know generally that his conduct is unlawful to trigger criminal liability. Accordingly, even if an agent or employee was unaware of the FCPA, the company and individual still may be held criminally liable for the agent or employee's improper payments.

It is important to note that corrupt intent, like all of the FCPA's anti-bribery elements, can be proven circumstantially. Thus, in the absence of direct evidence of corrupt intent

the DOJ often will conclude that corrupt intent existed if the surrounding circumstances suggest that payments or things of value were given to improperly influence an HCP.

Business Purpose

Q 14.32 What does it mean to obtain or retain business?

The requirement that payments must be intended to influence a foreign official to use his or her position to assist in retaining or obtaining business is known as the "business purpose test." Unsurprisingly, the business purpose test has been broadly construed to include everything from securing government contracts,[136] to reducing taxes or customs duties,[137] to preventing competitors from entering a market.[138] The key takeaway of this element is that it can include a wide range of business advantages.

Accounting Provisions in Detail

In General

Q 14.33 What do the accounting provisions require?

The accounting provisions require that U.S. exchange-listed companies maintain accurate books and records, and devise and maintain adequate internal accounting controls.

Books and Records

Q 14.34 What is the books and records provision?

The books and records provision requires issuers to "make and keep books, records, and accounts, which, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the issuer."[139] In short, this means that issuers may not mischaracterize the true nature of transactions. Companies have faced books and records charges when, for example:

- Improper payments to customs brokers were described as "importation advances";[140]
- Improper cash, gifts, and travel expenses were recorded as cash advances, training and promotional expenses, meetings and congresses;[141]
- Improper payments allegedly were described as promotional activities, marketing, training, travel and entertainment, clinical trials, freight, conferences, and advertising;[142]
- Cash payments and payments to secure sales were described as advertising and promotional expenses;[143]
- Improper international "incentive trips" reportedly were recorded as educational or charitable support;[144]
- The purpose of a payment was described as a donation rather than an improper payment to influence a government official;[145]
- The true nature of improper payments purportedly was concealed with the assistance of distributors and vendors;[146]
- A company maintained fictitious invoices issued to and received from distributors in its books, records, and accounts;[147]
- Company executives allegedly wrote checks to themselves to secure money for improper payments and described them as cash advances;[148] and

- There reportedly was no supporting documentation for improper cash payments.[149]

Internal Controls

Q 14.35 What is the internal controls provision?

The internal controls provision requires issuers to:

> devise and maintain a system of internal accounting controls sufficient to provide reasonable assurances that—

(i) transactions are executed in accordance with management's general or specific authorization;

(ii) transactions are recorded as necessary (I) to permit preparation of financial statements in conformity with generally accepted accounting principles or any other criteria applicable to such statements, and (II) to maintain accountability for assets;

(iii) access to assets is permitted only in accordance with management's general or specific authorization; and

(iv) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences . . . .[150]

In practice, this means that issuers must implement effective anti-corruption compliance programs (see Q 14.39 below); implement policies and procedures regarding financial controls (for example, approvals, authority matrix, and segregation of duties); conduct risk assessments; and monitor and audit transactions on an ongoing basis.[151] Companies must tailor their internal controls to the unique nature of their business and to the environment in which their business operates.

Successor Liability

Q 14.36 Does an acquiring company assume a target's liability under the FCPA's anti-bribery provisions?

The text of the FCPA does not provide for successor liability, but the DOJ and SEC have indicated that "[s]uccessor liability applies to all kinds of civil and criminal liabilities, and FCPA violations are no exception."[152] In other words, according to the government, an acquiring company assumes liability for an acquired company's FCPA violations. The DOJ and SEC typically only take action against successor companies in cases "involving egregious and sustained violations or where the successor company directly participated in the violations or failed to stop the misconduct from continuing after the acquisition."[153]

Q 14.37 What limitations are there on successor liability?

There must be FCPA jurisdiction over the target's improper conduct in order for successor liability to apply. The DOJ and SEC have stated:

> Successor liability does not . . . create liability where none existed before. For example, if an issuer were to acquire a foreign company that was not subject to the FCPA's jurisdiction, the mere acquisition of that foreign company would not retroactively create FCPA liability for the acquiring issuer.[154]

Analyzing whether there is jurisdiction over a target's actions can be a complicated inquiry. Companies and individuals need not be aware that they are making "use of the mails . . . [or] interstate commerce" in furtherance of improper conduct in order for jurisdiction to attach. This could happen, for example, when wire transfers are made through correspondent bank accounts or when email is routed through the United States.[155]

Separate from jurisdiction, the structure of the transaction may limit successor liability. Under U.S. law, a corporation does not inherit the liabilities of another corporation in an asset purchase unless: (1) the purchasing company expressly or impliedly agrees to assume the other company's liabilities; (2) the transaction was fraudulent; (3) there was a de facto merger or consolidation of the companies; or (4) the purchasing company was a mere continuation of the selling company.[156] Asset purchasers should remain wary of misconduct that continues after the purchase and could trigger FCPA liability.

Q 14.38 What can an acquiring company do to protect itself from successor liability?

As discussed in Q 14.40 below, an acquiring company should conduct thorough pre-

transaction anti-corruption due diligence (or post-transaction due diligence if pre-transaction due diligence is not possible), timely integrate the acquired company into the acquirer's anti-corruption compliance program, and conduct risk assessments of the newly acquired entity as necessary and appropriate.

The DOJ and SEC have indicated that, when possible, they are more likely to pursue enforcement against a predecessor company rather than the acquirer, "particularly when the acquiring company uncovered and timely remedied the violations."[157] In one case, a healthcare company discovered potentially improper payments made to doctors at state-owned hospitals by a target's foreign subsidiaries during pre-transaction anti-corruption due diligence. It promptly notified the target and the target began an investigation.[158] Ultimately, the target's foreign subsidiary pleaded guilty and the target settled with the SEC.[159] The acquirer avoided FCPA liability altogether.

In another matter, a pharmaceutical company had disclosed potentially improper conduct to the DOJ and SEC, and was cooperating in an investigation. When it acquired a target several years later, it conducted risk-based due diligence, identified improper payments to HCPs at government hospitals, and reported its findings to the government. The pharmaceutical acquirer integrated the target's operations into its anti-corruption compliance program. When the acquirer settled with the government, the acquired company—which had been maintained as a separate subsidiary—came to a resolution with the SEC for pre-transaction conduct.[160]

Anti-corruption due diligence is also an important component in assessing the value of a target company. One medical device company discovered "irregular sales practices" in an acquired entity's overseas operations shortly after the acquisition. Upon announcing its discovery and that its full year sales would be reduced by $100 million, the acquirer's share price dropped 13%.[161] Ultimately, the acquirer reached an agreement with the vendors of the acquired entity to reduce the previous purchase price.[162]

Mitigating FCPA Risk and Anti-Corruption Compliance Programs

Q 14.39 How can effective anti-corruption compliance programs help companies mitigate FCPA risk?

In the words of the DOJ and SEC, "an effective compliance program is a critical component of a company's internal controls and is essential to detecting and preventing FCPA violations."[163] The government considers the efficacy of a company's anti-corruption compliance program when evaluating the scope of its investigation, whether the case can be resolved through a deferred prosecution agreement or non-prosecution agreement, whether a monitor should be imposed, and the amount of penalties imposed.[164]

Q 14.40 What does the government expect to see in an anti-corruption compliance program?

The DOJ and SEC expect companies to institute anti-corruption compliance programs that are "tailored to the company's specific business and the risks associated with that business," and "are dynamic and evolve as the business and the markets change."[165] While they are careful to stress that there are "no formulaic requirements,"[166] the DOJ and SEC have consistently emphasized certain baseline requirements:

- A corporate policy against FCPA violations and violations of other anti-corruption laws;
- Compliance standards and procedures designed to address violations of the FCPA; other applicable anti-corruption laws; and the company's compliance policy that are applicable to directors, officers, employees and, "where necessary and appropriate, outside parties acting on behalf of [the company] in a foreign jurisdiction, including but not limited to, agents, consultants, representatives, distributors, teaming partners, and joint venture partners (collectively, 'agents and business partners')," and include:
    - Gifts;
    - Hospitality, entertainment, and expenses;
    - Customer travel;
    - Political contributions;
    - Charitable donations and sponsorships;
    - Facilitating payments; and
    - Solicitation and extortion;[167]

- Assigning one or more senior corporate executives to oversee implementation of the anti-corruption compliance policies, standards, and procedures, and giving them authority to report directly to the board of directors or an appropriate committee of the board of directors;[168]
- Mechanisms to ensure that anti-corruption policies, standards, and procedures are effectively communicated, including: (1) periodic training for directors, officers, employees, and, where necessary, business partners; and (2) annual certifications by directors, officers, employees, and, where necessary and appropriate, agents and business partners;
- A system for reporting violations and suspected violations of anti-corruption laws and/or compliance policies, standards, and procedures, such as a hotline;
- Disciplinary procedures to address violations of anti-corruption laws and the company's compliance policies, standards, and procedures;
- Due diligence requirements related to agents and business partners, including:
    - Documenting "risk-based due diligence," informing agents and business partners of the company's commitment to complying with anti-corruption laws and the company's policy, standards, and procedures, and seeking a reciprocal commitment;[169]
- Standard contractual provisions with agents and business partners designed to prevent violations of anti-corruption laws, including: (1) representations and undertakings related to anti-corruption compliance; (2) audit rights to ensure anti-corruption compliance; and (3) termination rights in the event of a breach of anti-corruption laws, regulations, or representations; and
- Periodic testing of the compliance code, standards, and procedures.[170]

The government also expects companies engaging in mergers and acquisitions to take a number of steps and to reflect such steps in their anti-corruption compliance programs. Companies should complete extensive pre-transaction due diligence on any mergers and acquisitions, and, when pre-closing due diligence is not possible, should conduct extensive post-closing due diligence. Integrating the acquired or merged entity into the company's existing compliance program is equally important. Companies should implement anti-corruption policies and procedures and train new employees. Companies should also evaluate the acquired entity's existing third-party relationships. In some instances, it may be advisable to conduct an FCPA-related audit after closing.[171]

Companies should take steps to ensure that their anti-corruption compliance programs are not so-called "paper programs." It is critical that employees understand anti-corruption compliance requirements. Translating policies and procedures to employees' local languages and providing training is essential.[172] Testing the efficacy of the compliance program at regular intervals through risk assessments also is advisable.

In February 2017 DOJ released a guidance document titled "Evaluation of Corporate

Compliance Programs" that formalizes these guidelines. The guidance lists eleven topics that DOJ finds relevant when evaluating a corporate compliance program, along with questions to probe the program's effectiveness. While the guidance is "neither a checklist nor a formula" for an effective compliance program, it provides helpful insight into what the government expects to see in an anti-corruption compliance program.[173] Topics include:

- Analysis and remediation of underlying misconduct;
- Commitment to compliance among senior and middle management;
- Autonomy and resources of the compliance department;
- Design, accessibility, and integration of policies and procedures;
- Risk assessment;
- Training and communications;
- Confidential reporting and investigation;
- Incentives and disciplinary measures;
- Continuous improvement, periodic testing and review;
- Third-party management; and
- Mergers and acquisitions.[174]

Q 14.41 What additional requirements have pharmaceutical companies agreed to include in their anti-corruption compliance programs when settling with the government?

Depending on the circumstances, companies may agree to implement compliance program enhancements designed to address issues that arose in the FCPA matter. Some of these enhancements may include:

- Implementing new policies and procedures concerning gifts, hospitality, and travel for government officials, including HCPs, administrators, and regulators;
- Conducting annual risk assessments of markets with government customers, including HCPs, and reviewing interactions with government officials;
- Identifying the top five "high-risk" operating companies and performing audits at least once every three years;
- Performing audits of other companies that pose a corruption risk at least once every five years, including—if possible—a review of the books and records of distributors that may present a corruption risk; and
- Updating due diligence reviews of third parties at least once every three years.[175]

Q 14.42 Do expectations for compliance programs vary depending on the jurisdiction and relevant government enforcement agency?

In recent years, there has been a growing international consensus on the essential elements of an effective compliance program.[176] This is important where, as in the United Kingdom, for example, proving that the company has an effective compliance program is a defense to certain charges.[177]

Q 14.43 How can industry codes inform anti-corruption compliance programs?

Industry codes are not intended to and do not supersede requirements under applicable laws and regulations, including the FCPA. Nonetheless, they can provide companies with much-needed guidance on the industry's view of conduct that has been the subject of FCPA enforcement actions, including guidance on interactions with and activities involving HCPs. Regional and country codes also may shed light on issues specific to a particular part of the world that could have FCPA implications. Separately, compliance with industry norms may lend credibility to the bona fide nature of expenditures on behalf of HCPs and the circumstances under which they are made.

In the pharmaceutical context, industry codes often address: permissible marketing activities and presentations to HCPs; company-sponsored medical education and speaking programs; engaging HCPs as consultants; fellowships and other educational scholarships; third-party educational conferences; the provision of gifts and educational items to HCPs; and the use of prescriber data.[178] In some cases, industry codes may impose requirements that are more restrictive than applicable laws and regulations. For example, one country's laws may permit certain types of non-educational gifts up to a limit, whereas an applicable industry code may prohibit all non-educational gifts.

Multinational pharmaceutical companies often are subject to a number of industry codes in the regions and countries in which they operate and do business. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) has collected and published relevant regional and country codes on its website (including links), and has also published a comparison of what kinds of interactions, products, and activities are covered in each code.[179] For example, section 3.3 of the comparison indicates whether a specific regional or country code addresses the provision of samples, educational items, cash, gifts, promotional aids, sponsorships, travel, hospitality, and entertainment to HCPs, as well as expenses on behalf of HCPs' guests. It also indicates whether each code establishes specific monetary limits in connection with these activities.[180] These are precisely the topics that have arisen in FCPA enforcement actions involving pharmaceutical and other life sciences companies. In light of this complex and multi-faceted environment, multinational pharmaceutical companies need to try to harmonize laws, codes, and policy positions when establishing their own anti-corruption compliance policies and procedures.

Q 14.44 How can companies mitigate FCPA risk when engaging third

parties?

As discussed in this chapter, companies cannot escape FCPA liability by taking a "head-in-the-sand" approach to the third parties they engage.[181] The government expects companies to conduct due diligence on third parties. Third-party due diligence should include an examination of: the owners—including beneficial owners—of the third parties; the prospective third parties' qualifications; whether third parties have personal, professional, or familial ties to government personnel or officials (including physicians employed or compensated by public entities); the reputation of third parties and their clientele and other business associates; and the nature and scope of any existing so-called "red flags."

Red flags include, but are not limited to:

- Unusual payment patterns or financial arrangements, including requests for cash payments, payments to third-party designees, or payments outside of the recipient's country of residency;
- Unusually high commissions;
- Large discounts that are inconsistent with market norms;
- Vaguely described services;
- Requests that payments to the third party be made in an off-shore jurisdiction;
- A lack of transparency and cooperation by the third party in terms of its general business operations;
- Indications that the third party is a shell organization incorporated in an off-shore jurisdiction;
- A lack of transparency in the third party's interactions with government officials and records;
- An apparent lack of qualifications or resources on the part of the third party to perform the services offered; and
- A foreign official insisting or expressly requesting that a third party be used.[182]

Q 14.44.1 What additional considerations are there when engaging and working with a distributor?

As discussed in Q 14.22 above, distributor conduct has been the focus of many FCPA actions in the pharmaceutical sector. Ensuring that there is transparency in distributor arrangements is critical from an FCPA risk-mitigation perspective. A company's lack of understanding with respect to its distributors' daily business operations and customer interactions may make it difficult to determine whether discounts and/or the extent of such discounts are warranted. The same is true of marketing arrangements. Many stocking distributors are responsible for marketing efforts in their territories or countries. Without

knowing how distributors market products and the marketing methods used, companies do not know whether distributors incentivize HCPs to purchase their products by offering benefits that may create exposure under the FCPA and other anti-corruption laws.

Companies should also consider whether distributors are authorized to engage third parties. For example, if distributors are authorized to engage HCP consultants, companies should confirm that there are anti-corruption compliance safeguards in place. Without such transparency, companies cannot ascertain whether payments and other benefits provided by the distributors to physicians are appropriate. A distributor's sham consulting arrangements or improper payments could create FCPA and commercial bribery exposure for a company. The same is true of sub-distributors. If a distributor is engaging sub-distributors, the company should have some insight into how they are selected and the extent of their anti-corruption compliance obligations.

Companies should confirm that they have communicated with distributors about anti-corruption compliance, in particular with respect to travel, entertainment, and gifts. Companies can face FCPA exposure for side trips and companion travel provided by their distributors. Supporting documentation submitted to the company for reimbursements, credits, and/or discounts in connection with such expenses should be accurate. Inaccurate supporting documentation can have implications for the company under the FCPA's accounting provisions.

If a distributor holds a company's product registrations or is responsible for obtaining them in a particular country, the company should make certain it has insight into the process and the distributor's interactions with government officials. These kinds of interactions are ripe for bribery, where the process is complicated and tedious and a payment could expedite or simplify the process. It also may be difficult to terminate a distributor in the event compliance is an issue because it is not always possible to transfer registrations easily and obtaining new registrations can take a significant amount of time.

Q 14.44.2 What additional considerations are there when engaging an HCP?

Like relationships with distributors, companies should ensure that there is transparency in their relationships with HCPs that may serve as consultants and provide training and medical education, or sit on advisory panels, for example. As discussed throughout this section, companies should conduct due diligence around the engagement to confirm that there is a legitimate need for the services to be provided. The process of selecting HCPs should be transparent and divorced from the sales and marketing functions. Companies should enter into written agreements with HCPs that clearly delineate the tasks for which the HCPs have been engaged and corresponding deliverables. Payments in exchange for the services rendered should be commensurate with the work performed and should be appropriate for the market in which the HCP works. Companies would be wise to conduct a fair market value assessment to support the payments made to HCP consultants. They also should assess local laws to ensure that the amounts paid to HCP consultants are permissible.

Q 14.45 How can companies mitigate the FCPA risk associated with meals, gifts, and travel?

As discussed above, having clear policies and procedures that address meals, gifts, entertainment, and travel is essential. Some companies institute monetary thresholds and frequency limits on meals and gifts for foreign officials, with advance written permission from legal or compliance personnel needed to exceed such limits. Travel presents its own unique challenges. Side trips and companion travel provided to foreign officials have featured prominently in FCPA actions over the years. Companies should take steps to confirm that travel arrangements made for foreign officials do not include side trips, the class of travel is appropriate for the duration of the trip, and travel expenses are not made on behalf of a foreign official's spouse, child, or other companion. Expenses for meals and accommodations during the foreign official's travel should be controlled and per diems should be avoided. The company should maintain appropriate supporting documentation for such expenditures. When travel is provided in conjunction with sponsorship, the company should take steps to confirm and document the HCP's attendance at the event.

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1. Joshua C. Foster co-authored earlier versions of this chapter.
2. 15 U.S.C. §§ 77dd-1, 78dd-2, 78dd-3 (2012).
3. 15 U.S.C. § 78m..
4. Lanny A. Breuer, Assistant Attorney General, U.S. Dep't of Justice, Prepared Keynote ess to The Tenth Annual Pharmaceutical Regulatory and Compliance Congress and Best ices Forum (Nov. 12, 2009) [hereinafter Breuer Keynote Address], at 2, .ehcca.com/presentations/pharmacongress10/breuer_2.pdf.
5. For example, at the "SEC Speaks" conference on February 19, 2016, the former SEC A Unit Chief, Kara Brockmeyer, indicated that the SEC's focus is "back to the pharma stry after a break for a period of years."
6. Sandra Moser, Acting Chief, Fraud Section, U.S. Dep't of Justice, Prepared Remarks at merican Conference Institute's 8 Global Forum on Anti-Corruption in High-Risk Markets 25, 2017), https://globalinvestigationsreview.com/article/jac/1145629/sandra-mosers-rks-at-the-acis-8th-global-forum-on-anti-corruption-in-high-risk-markets..
7. 15 U.S.C. § 78dd-1.
8. *See* Complaint, SEC v. Eli Lilly & Co., No. 12-cv-02045, at 3 (D.D.C. Dec. 20, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-273.pdf..
9. 15 U.S.C. § 78dd-2.
10. Non-Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Micrus Corp. and Micrus S.A. (Feb. 28, 2005) (a private medical device company ed into a non-prosecution agreement and agreed to a $450,000 civil penalty for alleged ions of the FCPA), www.justice.gov/criminal/fraud/fcpa/cases/micrus-corp/02-28-crus-agree.pdf..
11. 15 U.S.C. § 78dd-3.
12. *See, e.g.*, Information, United States v. Syncor Taiwan, Inc., No. 02-cr-1244, at 1–2

. Cal. Dec. 5, 2002), www.justice.gov/criminal/fraud/fcpa/cases/syncor-taiwan/12-05-ıcor-taiwan-info.pdf.

13. United States v. Patel, No. 09-cr-0335 (D.D.C. June 6, 2011) (making ruling from ı that sending package from the United Kingdom to the United States was an insufficient for jurisdiction under 15 U.S.C. § 78dd-3); *but see* Information, United States v. JGC ., No. 11-cr-260, at 18–19 (S.D. Tex. Apr. 6, 2011) (noting non-issuer, non-domestic ɛrn's use of correspondent bank accounts but pursuing jurisdiction under theory of ɔiring with and aiding and abetting domestic concern), .justice.gov/criminal/fraud/fcpa/cases/jgc-corp/04-6-11jgc-corp-info.pdf..

14. 15 U.S.C. § 78m.

15. *See* U.S. DEP'T OF JUSTICE AND SEC, A RESOURCE GUIDE TO THE U.S. EIGN CORRUPT PRACTICES ACT, 43 (Nov. 14, 2012) [hereinafter FCPA GUIDE], , www.justice.gov/sites/default/files/criminal-fraud/legacy/2015/01/16/guide.pdf.

16. *See, e.g.*, Complaint, SEC v. Nature's Sunshine Prods., Inc., No. 09-cv-0672, at 12-13 . Utah July 31, 2009) (charging COO and CFO with control person liability based on s and records violations and false filings with the SEC despite lack of personal knowledge or vement in conduct), www.sec.gov/litigation/complaints/2009/comp21162.pdf; *see also* 15 C. § 78t(a) ("Every person who, directly or indirectly, controls any person liable under any sion of this chapter or of any rule or regulation thereunder shall also be liable jointly and ally with and to the same extent as such controlled person to any person to whom such olled person is liable . . . .")..

17. *See* 15 U.S.C. §§ 77dd-1, 78dd-2, 78dd-3.

18. *Id.*.

19. Breuer Keynote Address, *supra* note 3, at 2..

20. 15 U.S.C. §§ 77dd-1, 78dd-2, 78dd-3.

21. *See* 15 U.S.C. §§ 78dd-1(c)(1), 78dd-2(c)(1), 78dd-3(c)(1).

22. *See* 15 U.S.C. §§ 78dd-1(c)(2), 78dd-2(c)(2), 78dd-3(c)(2).

23. *See* U.S. Dep't of Justice, FCPA Op. Release 07-01 (July 24, 2007), .justice.gov/criminal/fraud/fcpa/opinion/2007/0701.pdf..

24. *See* U.S. Dep't of Justice, FCPA Op. Release 07-02 (Sept. 11, 2007), .justice.gov/criminal/fraud/fcpa/opinion/2007/0702.pdf.

25. *See* U.S. Dep't of Justice, FCPA Op. Release 11-01 (June 30, 2011), .justice.gov/criminal/fraud/fcpa/opinion/2011/11-01.pdf..

26. *See* 15 U.S.C. §§ 78dd-1(b), 78dd-2(b), 78dd-3(b).

27. *See* FCPA GUIDE, *supra* note 14, at 25.

28. *See generally* U.K. Bribery Act, 2010, c. 23 (U.K.), .legislation.gov.uk/ukpga/2010/23/pdfs/ukpga_20100023_en.pdf.

29. 15 U.S.C. § 78m; FCPA GUIDE, *supra* note 14, at 39-41.

30. 15 U.S.C. §§ 78m(b)(5), 78ff(a); *see, e.g.*, Information, United States v. Siemens ngesellschaft, No. 08-cr-367 (D.D.C. Dec. 12, 2008), .justice.gov/criminal/fraud/fcpa/cases/siemens/12-12-08siemensakt-info.pdf..

31. 15 U.S.C. §§ 78dd-2(g)(1)(A), 78dd-3(e)(1)(A), 78ff(c)(1)(A).

32. 15 U.S.C. § 78ff(a).

33. *See* 15 U.S.C. §§ 78dd-2(g)(2)(A), 78dd-3(e)(2)(A), 78ff(c)(2)(A); 18 U.S.C. § 3571(d); *so* FCPA GUIDE, *supra* note 14, at 68.

34. 15 U.S.C. § 78ff(a).

35. 18 U.S.C. § 3571(d)..

36. Press Release, U.S. Dep't of Justice, Siemens AG and Three Subsidiaries Plead Guilty to gn Corrupt Practices Act Violations and Agree to Pay $450 Million in Combined Criminal (Dec. 15, 2008), www.justice.gov/opa/pr/2008/December/08-crm-1105.html; Press se, SEC, SEC Charges Siemens AG for Engaging in Worldwide Bribery (Dec. 15, 2008), .sec.gov/news/press/2008/2008-294.htm.

37. Press Release, SEC, SEC Charges Engineer and Former Employer with Bribe Scheme in a (Mar. 3, 2016), www.sec.gov/litigation/admin/2016/34-77288-s.pdf; Press Release, t of Justice, Teva Pharmaceutical Industries Ltd. Agrees to Pay More than $283 Million to lve Foreign Corrupt Practices Act Charges (Dec. 22, 2016), www.justice.gov/opa/pr/teva-naceutical-industries-ltd-agrees-pay-more-283-million-resolve-foreign-corrupt..

38. *See* Gary G. Grindler, Then-Acting Deputy Attorney General, U.S. Dep't of Justice, tional Guidance on the Use of Monitors in Deferred Prosecution Agreements and Non-cution Agreements with Corporations (May 25, 2010), www.justice.gov/dag/dag-memo-nce-monitors.pdf; Craig S. Morford, Then-Acting Deputy Attorney General, U.S. Dep't of e, Memorandum to the Heads of Department Components and United States Attorneys lection and Use of Monitors in Deferred Prosecution Agreements and Non-Prosecution ements with Corporations (Mar. 7, 2008), www.justice.gov/dag/morford-monitorsmemo-03072008.pdf; FCPA GUIDE, *supra* note 14, at 71.

39. *See* FCPA GUIDE, *supra* note 13, at 72.

40. *See id.*.

41. *See, e.g.*, Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., l Section and Teva Pharmaceutical Industries, Inc., at 11–13 (Dec. 22, 2016); Deferred cution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud Section and Smith ephew, Inc., at 6–7 (Feb. 1, 2012), .justice.gov/archive/usao/nj/Press/files/pdffiles/Older/Deferred%20pros%20agreementSNfi df; Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and AGA Medical Corp., at 8–9 (June 3, 2008), .justice.gov/criminal/fraud/fcpa/cases/agamedcorp/06-03-08aga-agree.pdf. The government extend the duration of corporate monitorships.

42. *See, e.g.*, Press Release, U.S. Dep't of Justice, Pfizer H.C.P. Corp. Agrees to Pay $15 on Penalty to Resolve Foreign Bribery Investigation (Aug. 7, 2012), .justice.gov/opa/pr/2012/August/12-crm-980.html..

43. *See* FCPA GUIDE, *supra* note 14, at 69–71..

44. 18 U.S.C. § 1952 (emphasis added); *see* Perrin v. United States, 444 U.S. 37, 41 (1979).

45. 18 U.S.C. § 1952(b)(i)(2).

46. *See, e.g.*, Information, United States v. Nico, No. 04-cr-092 (N.D. Ala. Mar. 2, 2004), .justice.gov/criminal/fraud/fcpa/cases/nico/03-02-04nico-info.pdf..

47. *See generally* FCPA GUIDE, *supra* note 14, at 48–49..

48. *See, e.g.*, Complaint, SEC v. Pfizer, Inc., No. 12-cv-01303, at 8 (D.D.C. Aug. 7, 2012) ribing the alleged wire transfer to a Croatian official's account to assist with product rations), www.sec.gov/litigation/complaints/2012/comp-pr2012-152-pfizer.pdf.

49. *See* Complaint, SEC v. Syncor Int'l Corp., No. 02-cv-02421, at 2–3 (D.D.C. Dec. 10,), www.sec.gov/litigation/complaints/comp17887.htm; *see also* Information, United States ncor Taiwan, Inc., No. 02-cr-1244, at 2-5 (C.D. Cal. Dec. 5, 2002), .justice.gov/criminal/fraud/fcpa/cases/syncor-taiwan/12-05-02syncor-taiwan-info.pdf..

50. Non-Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Micrus Corp. and Micrus S.A., app. A at 1 (Feb. 28, 2005), .justice.gov/criminal/fraud/fcpa/cases/micrus-corp/02-28-05micrus-agree.pdf.

51. *See* Complaint, SEC v. Syncor Int'l Corp., No. 02-cv-02421, at 2–3 (D.D.C. Dec. 10,), www.sec.gov/litigation/complaints/comp17887.htm..

52. *See In re* Orthofix Int'l N.V., Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 5 (Jan. 18, 2017), www.sec.gov/litigation/admin/2017/34-79828.pdf; mation, United States v. DePuy, Inc., No. 11-cr-099, at 6 (D.D.C. Apr. 6, 2011), .justice.gov/criminal/fraud/fcpa/cases/depuy-inc/04-08-11depuy-info.pdf; *In re* Mead son Nutrition Co., Order Instituting Cease-and-Desist Proceedings, Cease and Desist r (July 28, 2015), www.sec.gov/litigation/admin/2015/34-75532.pdf..

53. *See, e.g.*, *In re* GlaxoSmithKline plc, Order Instituting Cease-and-Desist Proceedings, e and Desist Order, at 3 (Sept. 30, 2016), www.sec.gov/litigation/admin/2016/34-5.pdf; Complaint, SEC v. Tyco Int'l Ltd., No. 12-cv-01583 (D.D.C. Sept. 24, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-196.pdf.

54. *See, e.g.*, *In re* Novartis AG, Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 4 (Mar. 23, 2016), www.sec.gov/litigation/admin/2016/34-77431-s.pdf ing a Novartis subsidiary sponsored twenty Chinese HCPs to attend a conference in ago where they took part in sightseeing and recreational activities, including an excursion to ara Falls, and paid for their spouses' travel); Complaint, SEC v. Lucent Techs. Inc., No. 07-301 (D.D.C. Dec. 21, 2007) (alleging Lucent improperly paid for "sightseeing, tainment, and leisure activities" incurred by Chinese officials visiting tourist destinations in United States, including Hawaii, Las Vegas, the Grand Canyon, Niagara Falls, Disney d, Universal Studios, and New York), .sec.gov/litigation/complaints/2007/comp20414.pdf; Non-Prosecution Agreement between Dep't of Justice, Criminal Div., Fraud Section and Lucent Technologies Inc. (Nov. 14,), www.justice.gov/criminal/fraud/fcpa/cases/lucent-tech/11-14-07lucent-agree.pdf.

55. Complaint, SEC v. Pfizer, Inc., No. 12-cv-01303, at 14-17 (D.D.C. Aug. 7, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-152-pfizer.pdf..

56. Complaint, SEC v. Wyeth, LLC, No. 12-cv-01304, at 6 (D.D.C. Aug. 7, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-152-wyeth.pdf..

57. Information, United States v. Pfizer H.C.P. Corp., No. 12-cr-00169, at 9 (D.D.C. Aug. 12), www.justice.gov/criminal/fraud/fcpa/cases/pfizer/2012-08-07-pfizer-info.pdf..

58. Complaint, SEC v. Orthofix Int'l N.V., No. 12-cr-150, at 4 (E.D. Tex. July 10, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-133.pdf..

59. *See In re* SciClone Pharm., Inc., Order Instituting Cease-and-Desist Proceedings, Cease Desist Order, at 3–4 (Feb. 4, 2016), www.sec.gov/litigation/admin/2016/34-77058.pdf.

60. SEC, *In re* Stryker Corp., Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 4 (Oct. 24, 2013), https://www.sec.gov/litigation/admin/2013/34-70751.pdf..

61. Complaint, SEC v. Tyco Int'l Ltd., No. 12-cv-01583, at 11-12 (D.D.C. Sept. 24,), www.sec.gov/litigation/complaints/2012/comp-pr2012-196.pdf; Complaint, SEC v. son & Johnson, No. 11-cv-00686, at 12 (D.D.C. Apr. 8, 2011), .sec.gov/litigation/complaints/2011/comp21922.pdf..

62. Complaint, SEC v. Eli Lilly and Co., No. 12-cv-02045, at 8 (D.D.C. Dec. 20, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-273.pdf.

63. *Id.* at 7..

64. *Id.*.

65. *Id.*.

66. *Id.*.

67. *Id.*.

68. Complaint, SEC v. Orthofix Int'l N.V., No. 4:12-cr-150, at 4 (E.D. Tex. July 10,), www.sec.gov/litigation/complaints/2012/comp-pr2012-133.pdf; *see also* Deferred cution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud Section and son & Johnson, at 25 (Jan. 14, 2011), www.justice.gov/sites/default/files/criminal-/legacy/2011/04/27/04-08-11depuy-dpa.pdf..

69. Complaint, SEC v. Orthofix Int'l N.V., No. 4:12-cr-150, at 4 (E.D. Tex. July 10,), www.sec.gov/litigation/complaints/2012/comp-pr2012-133.pdf..

70. Complaint, SEC v. Pfizer, Inc., No. 12-cv-01303, at 7 (D.D.C. Aug. 7, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-152-pfizer.pdf..

71. Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Olympus Latin America, Inc., at A-3 (Mar. 1, 2016), www.justice.gov/criminal-/file/831256/download.

72. Non-Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Micrus Corp. and Micrus S.A., app. A at 3 (Feb. 28, 2005), .justice.gov/criminal/fraud/fcpa/cases/micrus-corp/02-28-05micrus-agree.pdf.

73. *In re* GlaxoSmithKline plc, Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 3 (Sept. 30, 2016), www.sec.gov/litigation/admin/2016/34-79005.pdf..

74. Information, United States v. Pfizer H.C.P. Corp., No. 12-cr-00169, at 7–8 (D.D.C. 7, 2012), www.justice.gov/criminal/fraud/fcpa/cases/pfizer/2012-08-07-pfizer-info.pdf.

75. *See In re* SciClone Pharm., Inc., Order Instituting Cease-and-Desist Proceedings, Cease Desist Order, at 3–4 (Feb. 4, 2016), www.sec.gov/litigation/admin/2016/34-77058.pdf ging SciClone sponsored Chinese HCPs to attend conferences in the United States and

ı that also included significant sightseeing such as trips to Las Vegas, the Grand Canyon, eyland, and Mt. Fuji)..

76. *See* Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., l Section and Johnson & Johnson, at 23 (Jan. 14, 2011), .justice.gov/sites/default/files/criminal-fraud/legacy/2011/04/27/04-08-11depuy-dpa.pdf..

77. *See* Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., l Section and Pfizer H.C.P. Corp., (Aug. 7, 2012), .justice.gov/criminal/fraud/fcpa/cases/pfizer/2012-08-07-pfizer-dpa.pdf..

78. Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Johnson & Johnson, at 22–24 (Jan. 14, 2011), .justice.gov/sites/default/files/criminal-fraud/legacy/2011/04/27/04-08-11depuy-dpa.pdf.

79. *In re* Novartis AG, Order Instituting Cease-and-Desist Proceedings, Cease and Desist r, at 4–5 (Mar. 23, 2016), www.sec.gov/litigation/admin/2016/34-77431.pdf..

80. Non-Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Mircus Corp. and Micrus S.A., app. A at 2, 4 (Feb. 28, 2005), .justice.gov/criminal/fraud/fcpa/cases/micrus-corp/02-28-05micrus-agree.pdf.

81. *Id.* at 2..

82. *In re* AstraZeneca PLC, Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 3 (Aug. 30, 2016), www.sec.gov/litigation/admin/2016/34-78730.pdf.

83. *In re* GlaxoSmithKline plc, Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 3 (Sept. 30, 2016), www.sec.gov/litigation/admin/2016/34-79005.pdf..

84. Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Olympus Latin America, Inc. (Mar. 1, 2016), www.justice.gov/criminal-/file/831256/download..

85. *In re* Nu Skin Enters., Inc., Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 3-4 (Sept. 20, 2016), www.sec.gov/litigation/admin/2016/34-78884.pdf..

86. Complaint, SEC v. Eli Lilly and Co., No. 12-cv-02045, at 1-2 (D.D.C. Dec. 20, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-273.pdf; *see also* Complaint, SEC v. ing-Plough Corp., No. 04-cv-945, at 3-4 (D.D.C. June 9, 2004), .sec.gov/litigation/complaints/comp18740.pdf.

87. Complaint, SEC v. Eli Lilly and Co., No. 12-cv-02045, at 4 (D.D.C. Dec. 20, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-273.pdf..

88. *See* FCPA GUIDE, *supra* note 14, at 86–87 (explaining the opinion procedure release ss).

89. *See* U.S. Dep't of Justice, FCPA Op. Release 09-01 (Aug. 3, 2009), .justice.gov/criminal/fraud/fcpa/opinion/2009/0901.pdf.

90. *See id.*.

91. *See In re* Stryker Corp., Order Instituting Cease-and-Desist Proceedings, Cease and t Order (Oct. 24, 2013), www.sec.gov/litigation/admin/2013/34-70751.pdf; Complaint, v. Tyco Int'l Ltd., No. 12-cv-01583 (D.D.C. Sept. 24, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-196.pdf; Information, United States v.

ıy, Inc., No. 11-cr-099 (D.D.C. Apr. 6, 2011), .justice.gov/criminal/fraud/fcpa/cases/depuy-inc/04-08-11depuy-info.pdf.

92. The Department of Justice has broadly interpreted the knowledge requirement of the A and the obligations it imposes. *See* FCPA GUIDE, *supra* note 14, at 14.

93. *See* 15 U.S.C. §§ 78dd-l(f)(2), 78dd-2(h)(3), 78dd-3(f)(3); H.R. CONF. REP. NO. 576, at 916, 919-21, *reprinted in* 1988 U.S.C.C.A.N. (102 Stat. 1415) 1949 (explaining the FCPA does not excuse the "head-in-the-sand" approach and management cannot "take e from the Act's prohibitions by their unwarranted obliviousness to any action (or ion), language or other 'signaling device' that should reasonably alert them of the 'high ıbility' of an FCPA violation").

94. Complaint, SEC v. Eli Lilly and Co., No. 12-cv-02045, at 2 (D.D.C. Dec. 20, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-273.pdf.

95. Complaint, SEC v. Orthofix Int'l N.V., No. 12-cr-150, at 4 (E.D. Tex. July 10, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-133.pdf..

96. 15 U.S.C. § 78(m)(b)(2); *see also In re* Bristol Myers Squibb Co., Order Instituting e-and-Desist Proceedings, Cease and Desist Order (Oct. 5, 2015), .sec.gov/litigation/admin/2015/34-76073.pdf (stating the company failed to maintain ıate controls over joint venture).

97. 15 U.S.C. § 78(m)(b)(6)..

98. Complaint, SEC v. Nature's Sunshine Prods., Inc., No. 09-cv-0672, at 2 (C.D. Utah 31, 2009), www.sec.gov/litigation/complaints/2009/comp21162.pdf..

99. *In re* Immucor, Inc., Order Instituting Cease-and-Desist Proceedings, Cease and Desist r, at 2 (Sept. 27, 2007), www.sec.gov/litigation/admin/2007/34-56558.pdf.

100. *Id.* at 2–3..

101. *In re* Nordion (Can.) Inc., Order Instituting Cease-and-Desist Proceedings, Cease and ıt Order, at 3–4 (Mar. 3, 2016), www.sec.gov/litigation/admin/2016/34-77290.pdf.

102. Information, United States v. Teva Pharm. Indus. Ltd., No. 16-20968, at 16-17 (S.D. Dec. 22, 2016), www.justice.gov/criminal-fraud/file/920431/download; *see also* mation, United States v. Pfizer H.C.P. Corp., No. 12-cr-00169, at 8 (D.D.C. Aug. 7,), www.justice.gov/criminal/fraud/fcpa/cases/pfizer/2012-08-07-pfizer-info.pdf (alleging Pfizer made corrupt payments to a registration official in Croatia to assist with the ration of Pfizer's products).

103. Complaint, SEC v. Siemens Aktiengesellschaft, No. 08-cv-02167 (D.D.C. Dec. 18,), www.sec.gov/litigation/complaints/2008/comp20829.pdf..

104. *See* Information, United States v. Smith & Nephew, Inc., No. 12-cr-00030 (D.D.C. 24, 2012), www.justice.gov/criminal/fraud/fcpa/cases/smith-nephew/2012-02-06-s-n-mation.pdf; Complaint, SEC v. Johnson & Johnson, No. 11-cv-00686, at 12 (D.D.C. Apr. 11), www.sec.gov/litigation/complaints/2011/comp21922.pdf.

105. Complaint, SEC v. Smith & Nephew plc, No. 12-cv-00187 (D.D.C. Feb. 6, 2012), .sec.gov/litigation/complaints/2012/comp22252.pdf; Deferred Prosecution Agreement een U.S. Dep't of Justice, Criminal Div., Fraud Section and Smith & Nephew, Inc. (Feb.

12), www.justice.gov/criminal/fraud/fcpa/cases/smith-nephew/2012-02-01-s-n-dpa.pdf.

106. Complaint, SEC v. Smith & Nephew plc, No. 12-cv-00187, at 3–7 (D.D.C. Feb. 6,), www.sec.gov/litigation/complaints/2012/comp22252.pdf.

107. *Id.* at 4..

108. Non-Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and BK Medical ApS, at A-2 (June 21, 2016), .justice.gov/opa/file/868771/download..

109. Complaint, SEC v. Eli Lilly and Co., No. 12-cv-02045, at 9 (D.D.C. Dec. 20, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-273.pdf..

110. Complaint, SEC v. Pfizer, Inc., No. 12-cv-01303, at 12–13 (D.D.C. Aug. 7, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-152-pfizer.pdf..

111. Information, United States v. AGA Med. Corp., No. 08-cr-172, at 5 (D. Minn. June 3,), www.justice.gov/criminal/fraud/fcpa/cases/agamedcorp/06-03-08aga-info.pdf..

112. *Id.* at 7..

113. Complaint, SEC v. Pfizer, Inc., No. 12-cv-01303, at 13–19..

114. Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud on and Johnson & Johnson, at 17 (Jan. 14, 2011), .justice.gov/sites/default/files/criminal-fraud/legacy/2011/04/27/04-08-11depuy-dpa.pdf.

115. *Id.*

116. *In re* Alere, Inc., Order Instituting Cease-and-Desist Proceedings, Cease and Desist r, at 12 (Sept. 28, 2017), www.sec.gov/litigation/admin/2017/33-10417.pdf..

117. Complaint, SEC v. Wyeth, LLC, No. 12-cv-01304, at 5 (D.D.C. Aug. 7, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-152-wyeth.pdf.

118. *Id.* at 6–8..

119. *See In re* GlaxoSmithKline plc, Order Instituting Cease-and-Desist Proceedings, Cease Desist Order, at 3 (Sept. 30, 2016), www.sec.gov/litigation/admin/2016/34-79005.pdf.

120. *In re* AstraZeneca PLC, Order Instituting Cease-and-Desist Proceedings, Cease and t Order, at 3 (Aug. 30, 2016), www.sec.gov/litigation/admin/2016/34-78730.pdf (alleging employees generated cash for improper payments by working with a third-party travel or who submitted false or inflated invoices)..

121. Information, United States v. Carman, No. 04-J-0093-S, at 3 (N.D. Ala. Mar. 2, 2004), .justice.gov/criminal/fraud/fcpa/cases/carman/03-02-04carman-info.pdf..

122. *See* National Health and Family Planning Commission, Administrative Measures on pting Donations for Public Welfare by Healthcare Entities [title translated from original ese], (Oct. 20, 2015)..

123. *See* 15 U.S.C. §§ 78dd-1(f)(1), 78dd-2(h)(2), 78dd-3(f)(2).

124. *See, e.g.*, Complaint, SEC v. Johnson & Johnson, No. 11-cv-00686 (D.D.C. Apr. 8,), www.sec.gov/litigation/complaints/2011/comp21922.pdf.

125. While interactions with HCPs employed by or affiliated with private institutes may be de of the FCPA's scope, other U.S. laws may be used to target improper interactions with te-sector HCPs. U.S. enforcement authorities increasingly are using the Travel Act, for

ple, as a way to prosecute international commercial bribery. *See* 18 U.S.C. § 1952. In ce, the Travel Act allows prosecutors to extend the reach of a given state's commercial ry statute beyond U.S. borders. *See* Q 14.10.

126. Breuer Keynote Address, *supra* note 3, at 2..

127. *See, e.g.*, Deferred Prosecution Agreement between U.S. Dep't of Justice, Criminal Div., l Section and Smith & Nephew, Inc., at 6–7 (Feb. 15, 2012), .justice.gov/criminal/fraud/fcpa/cases/smith-nephew/2012-02-01-s-n-dpa.pdf; Deferred :cution Agreement between U.S. Dep't of Justice, Criminal Div., Fraud Section and son & Johnson (Jan. 14, 2011), www.justice.gov/sites/default/files/criminal-/legacy/2011/04/27/04-08-11depuy-dpa.pdf.

128. Breuer Keynote Address, *supra* note 3..

129. *See* Plea Agreement, United States v. DPC (Tianjin) Co. Ltd., No. 05-CR-482 (C.D. May 20, 2005), www.justice.gov/criminal/fraud/fcpa/cases/dpc-tianjin/05-19-05dpc-n-plea-agree.pdf; *In re* Diagnostic Products Corp., Order Instituting Cease-and-Desist :edings (May 20, 2005), www.sec.gov/litigation/admin/34-51724.pdf..

130. *See, e.g.*, Complaint, SEC v. Pfizer, Inc., No. 12-cv-01303 (D.D.C. Aug. 7, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-152-pfizer.pdf.

131. SEC, *In re* Koninklijke Philips Electronics N.V., Order Instituting Cease-and-Desist :edings, Cease and Desist Order (Apr. 5, 2013), www.sec.gov/litigation/admin/2013/34-7.pdf..

132. Information, United States v. Teva Pharmaceutical Industries Ltd., No. 16-20968, at 7 (Dec. 22, 2016), www.justice.gov/criminal-fraud/file/920431/download.

133. Information, United States v. Pfizer H.C.P. Corp., No. 12-cr-00169, at 20 (D.D.C. 7, 2012), www.justice.gov/criminal/fraud/fcpa/cases/pfizer/2012-08-07-pfizer-info.pdf.

134. H.R. REP. NO. 95-640, at 7, *reprinted in* 1977 U.S.C.C.A.N. 4120..

135. *See* United States v. Kay, 513 F.3d 432, 447–48 (5th Cir. 2007).

136. *See, e.g.*, Complaint, SEC v. Siemens Aktiengesellschaft, No. 08-cv-2167 (D.D.C. Dec. 008), www.sec.gov/litigation/complaints/2008/comp20829.pdf.

137. *See id.* at 21.

138. FCPA GUIDE, *supra* note 14, at 13.

139. 15 U.S.C. § 78m(b)(2)(A).

140. Complaint, SEC v. Nature's Sunshine Prods., Inc., No. 09-cv-0672, at 4 (C.D. Utah 31, 2009), www.sec.gov/litigation/complaints/2009/comp21162.pdf..

141. Information, United States v. Orthofix Int'l, N.V., No. 12-cr-150, at 8 (E.D. Tex. July 012), www.justice.gov/criminal/fraud/fcpa/cases/orthofix/2012-07-10-orthofix-info.pdf..

142. Complaint, SEC v. Pfizer, Inc., No. 12-cv-01303, at 2 (D.D.C. Aug. 7, 2012), .sec.gov/litigation/complaints/2012/comp-pr2012-152-pfizer.pdf..

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15

Collateral Consequences of Violating the Federal Food, Drug, and Cosmetic Act

Michael A. Swit

This chapter reviews the potential collateral—or indirect—legal consequences that pharmaceutical companies and their executives may face due to violating the laws administered by FDA,[1] especially those consequences spawned by criminal violations. While criminal prosecutions are not common, it is essential that companies realize some of the key negative sequelae flowing from FDA-related convictions. We will first address consequences of criminal charges[2] and convictions for companies and then for individuals.[3]

Corporations–Federal Legal Consequences–Administrative

The FDA Application Integrity Policy (AIP)

Q 15.1 What is the Application Integrity Policy (AIP)?

Formally unveiled in the summer of 1991,[4] the Application Integrity Policy, or AIP, is a policy FDA implemented to emphasize to industry that it would not review pending applications that may be affected by wrongful acts that raised significant questions on the reliability of data from an applicant. Instituted in the wake of the generic drug scandal of the late 1980s, the AIP provides that, where FDA has significant questions about the reliability of an application's data, the agency will defer substantive review of that application and possibly all other applications by the same sponsor until the questions on reliability are resolved.

Q 15.2 What triggers FDA imposing the AIP?

FDA may apply the AIP if it finds that a company has been involved in "actions subverting the FDA process" such as fraudulent applications, making untrue statements of material facts, or bribery or illegal gratuities. While the AIP typically is invoked when intentional wrongdoing has occurred, FDA left open the possibility that it might invoke the AIP where "[d]ata may be unreliable due to sloppiness and inadvertent errors."[5]

Q 15.3 What does FDA expect a firm on the AIP to do to resolve FDA concerns about the reliability of the sponsor's data to get off the AIP list?

To successfully address FDA's concerns, the agency expects the firm to implement a corrective action plan that, at minimum, meets these key requirements:

- Cooperate fully with FDA and other federal investigations;
- Identify all wrongdoers and remove them from positions of authority;
- Conduct an internal review using outside expert consultants to uncover all other instances of wrongdoing; and
- Prepare and execute a written corrective action plan to assure safety, effectiveness, and quality of products, signed by the firm's CEO, that includes:
    - Procedures and controls to preclude similar wrongdoing in the future; and
    - An ethics program

In addition, if fraud is found in an application, the agency will expect the company to withdraw the application, recall any products marketed under the application, and resubmit

and secure approval of a new application with untainted data before the product can be reintroduced into commerce.

Q 15.4 How often has the AIP been imposed on a company and for how long?

The AIP is perhaps FDA's rarest enforcement remedy and most difficult for a company to overcome successfully. Since being implemented, FDA has imposed the AIP on nineteen companies, seven of which have been removed from the list by (presumably) satisfying the demands of the AIP. Of the twelve companies still under the AIP, FDA believes that five are out of business and many of those on the list have been on the AIP list for over fifteen years.[6] The two most recent additions, Hill Dermaceuticals, Inc., and Ranbaxy Laboratories, Ltd., have been on the list for six and a half and nine years, respectively.

Generic Drug Enforcement Act of 1992 and Corporations

Q 15.5 What is the Generic Drug Enforcement Act of 1992?

The generic drug scandal of the late 1980s profoundly impacted not only FDA, but also Congress, which responded in part by passing the Generic Drug Enforcement Act of 1992 (GDEA).[7] Under the GDEA, Congress conferred on FDA[8] the power to impose an array of sanctions on companies and individuals found to have committed various offenses relating to both generic and even innovative drugs. The sanctions available under the GDEA include debarment, temporary denial of approval, suspension, civil penalties, and withdrawal of approval of an abbreviated new drug application (ANDA).[9]

Q 15.6 What is corporate debarment under the GDEA?

Debarment, when imposed by FDA, prevents the debarred corporation from submitting or helping to submit an ANDA. Debarment is mandatory[10] or permissive[11]—that is, discretionary by FDA.

Q 15.6.1 When is corporate debarment mandatory?

Mandatory debarment, when FDA is required to debar a corporation, partnership, or association (hereinafter "corporation"), is dictated by the GDEA when FDA finds that a corporation was convicted, after May 13, 1992 (GDEA's enactment date), of a federal felony "relating to the development or approval, including the process for development or approval, of any" ANDA. It applies solely to felonies relating to ANDAs and not to other types of drug applications such as those under section 505(b)(1) or 505(b)(2) of the FDCA or to a biologics licensing application (BLA) under the PHSA. However, debarment may be possible for activities relating to such applications under permissive debarment (discussed below).

Q 15.6.2 When may FDA impose "permissive" debarment on a corporation?

FDA may, on its own initiative or in response to a petition, elect to debar a corporation from submitting or assisting with submitting an ANDA if the corporation was convicted of a federal felony before the enactment of the GDEA, or convicted, after GDEA enactment, of a federal misdemeanor or state felony, or under certain other circumstances if the conviction was for conspiracy or aiding or abetting any of the criminal offenses sustaining mandatory or permissive debarment. However, to invoke permissive debarment, (a) the conviction must relate to development or approval of an ANDA and (b) FDA also must conclude that the conduct underlying the conviction "undermines the process for regulation of drugs."

Q 15.6.3 How many times has FDA debarred a corporation under the GDEA?

To date, FDA has not debarred any corporations under the GDEA, likely because it uses the AIP process, which is simpler administratively, to secure the same basic result—a bar on submission of applications.

Suspension and Debarment of Drug Companies from Federal Government Contracting

Q 15.7 Why would a drug company be concerned about suspension or debarment of its ability to contract with the federal government?

In 2016, prescription drug spending in the United States totaled $328.6 billion.[12] Given that federal governmental spending was 28.3% of all healthcare expenses,[13] the federal government thus spent about $93 billion on prescription drugs, making Uncle Sam a prime customer for drug companies. Therefore, losing access to federal purchasers can significantly impact overall sales for the suspended/debarred drug firm.

Q 15.8 What is a suspension?

Suspension is an interim measure that can be taken by a government agency when it determines that immediate action is necessary to protect the government's interest in having vendors that are "responsible." With limited exceptions, suspensions will bar a company from entering new contracts with the government during the suspension and, if formal debarment is proposed, until the debarment proceeding is resolved. Suspensions are supposed to be temporary in nature while the government investigates the underlying circumstances that have led to the suspension decision.[14] If legal proceedings have not been initiated relative to the circumstances leading to the suspension within one year, the suspension is terminated unless an assistant U.S. attorney requests its extension.[15] And, unless specifically limited by the contracting officer imposing the suspension, the

suspension applies throughout the federal government.

Q 15.9 What are grounds for suspension of a government contractor?

There are nine basic grounds[16] for suspension, including:

1. Committing fraud or a criminal offense relative to obtaining or performing a public contract or subcontract;
2. Violating federal or state antitrust law;
3. Committing embezzlement, theft, forgery, bribery, falsification, or destruction of records, making false statements, tax evasion, violating federal criminal tax laws, or receiving stolen property;
4. Drug-free workplace violations;
5. Labeling a product as "Made in America" when it was not;
6. Committing an unfair trade practice as defined in the regulation;
7. Owing more than $3,500 in delinquent federal taxes;
8. Not disclosing to the government, within three years of final payment on a contract, certain events relating to the award, performance, or closeout of the contract/subcontract, including:
    a. violations of federal criminal law involving fraud, conflict of interest, bribery, or illegal gratuities;
    b. violations of the False Claims Act; or
    c. significant overpayment(s) on the contract; and
9. Committing any other offense "indicating a lack of business integrity or honesty" that "seriously and directly affects the present responsibility" of the contractor.

The government does not necessarily have to prove the grounds listed above. Rather, under the Federal Acquisition Regulations (FAR), indictment for any of the offenses equals adequate evidence to support a suspension.[17] Suspension also can occur "for any other cause of so serious or compelling a nature that it affects the present responsibility" of the contractor.[18]

Q 15.10 How does debarment differ from suspension?

In debarment, unlike suspension, the term of the debarment will be specified and can exceed the one year to eighteen months delineated for suspensions under the FAR.

Q 15.11 What are the grounds for debarment?

The grounds for debarment resemble those for suspension, but can be imposed based on either a conviction or a civil judgment related to these five factors:[19]

1. Fraud or other criminal offense in connection with obtaining or performing a contract;
2. Federal or state antitrust violations;
3. Embezzlement, theft, forgery, bribery, falsification or destruction of records, false statements, tax evasion, federal criminal tax violations, or receiving stolen property;
4. "Made in America" violations;
5. "[A]ny other offense indicating a lack of business integrity or business honesty that seriously and directly affects the present responsibility" of the contractor or subcontractor.

In addition, even without a formal conviction or civil judgment, an agency can debar a contractor if it finds, by a preponderance of the evidence, that the contractor:[20]

1. Committed serious contract violations such as willful failure to perform a contract or a history of failure to perform;
2. Violated drug-free workplace requirements;
3. Intentionally affixed a "Made in America" label where product was not made in the United States;
4. Committed an unfair trade practice;
5. Owed delinquent federal taxes greater than $3500; or
6. Failed to notify government within three years of certain criminal or False Claims Act violations, or significant overpayments on contracts.

Q 15.12 How long can debarment last?

Under the FAR, the debarment is to last "for a period commensurate with the seriousness of the cause(s)," but generally not more than three years, except for drug free workplace violations, which can be five years.[21] And, if there was a suspension, the suspension period's length is to be factored into determining the debarment period.

Q 15.13 Is suspension or debarment punitive?

No. The FAR clearly states that suspension/debarment be imposed "only in the public interest for the Government's protection and not for purpose of punishment."[22]

Exclusion from Federal Healthcare Programs

Q 15.14 What is exclusion from healthcare programs?

Federal law provides for mandatory or permissive exclusion of individuals and entities from participating in Medicare, other federal health programs (e.g., Tricare), and state healthcare programs.[23] Exclusion effectively precludes an entity or individual from receiving any funds under the covered healthcare programs.

Q 15.15 What are the criteria for exclusion for entities?

The exclusion statute primarily provides for exclusion for offenses relating to federal healthcare programs. However, under certain circumstances, the criteria for exclusion can be triggered by criminal violations of the FDCA, including misdemeanor pleas under the Park Doctrine (see chapter 12, at Q 12.23 to Q 12.25. We will focus here on those provisions that could be triggered by FDCA violations.

Q 15.15.1 What are the criteria for mandatory exclusion for entities?

Mandatory exclusion includes several provisions that could lead to exclusion for a corporation. For pharmaceutical company convictions, the most common leading to mandatory exclusion have been:[24]

1. Conviction of a criminal offense related to delivery of an item or service subject to federal or state healthcare programs;[25] and
2. Conviction of a felony related to delivery of an item or service where the item or service was financed by a governmental agency and the conviction involved fraud, theft, embezzlement, breach of fiduciary responsibility, or other financial misconduct.[26]

Q 15.15.2 What are the criteria for permissive exclusion for entities?

There are fifteen separate grounds for exclusion under the permissive exclusion provisions.[27] Of these, several could apply to a situation involving a drug company that has been convicted of FDCA violations. These include clauses providing for permissive debarment for:

1. Fraud convictions, including
    a. misdemeanor convictions for fraud, breach of fiduciary duty, or other financial misconduct; or
    b. any conviction (felony or misdemeanor) for fraud, breach of fiduciary duty, or other financial misconduct relative to a program (other than a healthcare program) operated or financed by a federal, state, or local agency;[28]
2. Misdemeanor convictions relating to a controlled substance;[29]

3. Entities controlled by a sanctioned individual, which includes individuals that:[30]
    a. meet any of these criteria:
        i. directly or indirectly own or control 5% or more of the entity;
        ii. are an officer, director, agent, or managing employee[31] of the entity;
        iii. or did own or control 5% of the entity, but transferred ownership or control to a family or household member in anticipation of conviction, assessment, or exclusion;
    b. and has either been
        i. convicted of an offense calling for mandatory exclusion or permissive exclusion under the first three subclauses of the permissive exclusive provisions;
        ii. had a civil money penalty assessed against him/her; or
        iii. been excluded from a federal or state healthcare program.

State Manufacturing License Suspension or Revocation

Q 15.16 Can a state deny or revoke a drug firm's manufacturing license (or application for license) due to an FDCA conviction?

Yes. For example, under California law, the California Code of Regulations makes clear that the qualifications for granting an application for a drug manufacture license include:

1. Convictions relating to drugs, including drug samples, wholesale or retail drug distribution, or distribution of controlled substances;[32] and
2. Any felony conviction under federal, state, or local law related to the qualifications, functions, and duties of a licensed human prescription drug manufacturer.[33]

In California, an already-granted drug manufacturing license can be suspended or revoked for "any conviction" (misdemeanor or felony) of "any violation of federal, state, or local drug laws." In addition, any of the grounds that would have warranted denial of the original application constitute bases for suspension or revocation.[34]

Other Potential Legal Consequences for Corporations of FDCA and Related Convictions

Q 15.17 For publicly traded drug companies, what civil litigation is likely to be spawned by an indictment or conviction of FDCA violations?

Depending on the circumstances of the conviction, drug companies should be prepared for an array of different civil lawsuits, including:

1. *Securities class actions*—instituted by disgruntled public company shareholders who suffered losses due to stock price changes that can be tied to failure of the company to disclose underlying material facts that formed the basis for the criminal charges against the company. For example, in *In re Par Pharmaceutical, Inc. Securities Litigation*,[35] the court allowed a class of shareholders of Par Pharmaceutical, Inc. (Par), a NYSE-traded generic drug firm, to pursue civil remedies under the federal securities law based on allegations that the company's public statements and SEC filings failed to disclose that Par and its Quad subsidiary had made illegal payments to officials in FDA's Division of Generic Drugs that were the undisclosed reason for the success Par had shown in securing approvals of its generic drug applications. Those illegal payments later led to convictions of both Par and Quad and several former Par and Quad executives. After the litigation was initiated, other criminal wrongdoing, including filing false applications with FDA would be disclosed by Par, but those disclosures occurred, with one exception, well after the wrongdoing occurred. The company's stock had traded as high as $27.25 per share during the class period, but later dropped to as low as $3.50 per share.

2. *Shareholder derivative actions*—actions by shareholders to force a company to initiate a lawsuit where the company has failed to do so. While subject to varying requirements in different states, including frequently to make demand on the company's board to take the action that later forms the basis of the lawsuit, such litigation can arise in the wake of FDCA or similar violations. Thus, Par Pharmaceutical also faced a derivative action relating to the same facts that had triggered the securities litigation discussed above.[36]

Both the Par securities litigation discussed above and the shareholder derivative action were ultimately resolved via settlement in September 1991 by issuing new shares to affected shareholders.[37]

3. *Civil litigation by competitors*—depending on the underlying facts, an FDA-related criminal conviction may trigger a drug company's competitors to sue for damages due to various theories, including Lanham Act violations, RICO violations, and state claims. Par Pharmaceutical faced two of such lawsuits in the wake of the wrongdoing discussed above, the most well-known of which was a suit initiated by Mylan Laboratories, Inc.,[38] which ultimately was settled by Par by agreeing to issue Mylan $2 million in Par stock and $1 million in cash.[39]

Q 15.18 Can criminal convictions lead to loss of financial agreements such as mortgages and bank loans?

It is typical for commercial loans, leases, and mortgages of real property to contain clauses requiring compliance with all laws impacting a company and its business. In

addition, many transaction agreements will contain representations that no investigations or proceedings, especially criminal, are pending against a party to the agreement. A criminal investigation, indictment, or conviction, especially if not disclosed by the company subject to the criminal actions, can violate contractual requirements and justify termination of the agreements.

Q 15.19 What other adverse consequences of a legal or business nature might a drug company face when dealing with criminal violations?

The negative sequelae of a criminal probe and, ultimately, a conviction cannot be underestimated, even without focusing on the direct cost of the criminal fines that a drug company likely will sustain. Among the other adverse collateral consequences generated by criminal corporate conduct are: lost sales as customers lose confidence/trust in one's products or ability to deliver; the enormous financial expense posed by attorneys' fees and expenses, expert witness fees, document production costs, etc.; the damage to your company's reputation; and the massive disruption generated by a criminal investigation even for large companies.

Individuals—Collateral Consequences of Criminal Violations of the FDCA

Generic Drug Enforcement Act Debarment

Q 15.20 When is mandatory debarment of an individual required under the GDEA?

Mandatory debarment of an individual is required if FDA finds that an individual was convicted of a felony under federal law for conduct relating to development or approval of "any drug product" or a felony "otherwise relating to the regulation of any drug product.[40] By using "any drug product," the mandatory debarment language for individuals encompasses criminal activity relating to any type of drug, innovative or generic, and thus differs from mandatory debarment for corporations, which only relates to convictions for generic drugs.

Q 15.21 Under what circumstances is an individual subject to permissive debarment under the GDEA?

As with corporations, there are multiple grounds for individual permissive debarment, including:

1. conviction of a misdemeanor under federal law or a felony under state law for conduct relating to development or approval of any drug product or otherwise relating to the regulation of a drug product or conspiracy to do so, provided that FDA finds that the conduct leading to the conviction "undermines the process for the regulation of drugs;"[41]
2. felony conviction for:
    a. bribery, illegal gratuity payments, fraud, perjury, false statement, racketeering, blackmail, extortion, falsification or destruction of records, or interference or obstruction of an investigation or prosecution of any criminal offense; or
    b. conspiracy, or aiding and abetting, a felony under (2)(a) above;[42]
3. any "high managerial agent"[43] who worked for or as a consultant to a person (including a corporation) for whom also worked another individual at the same time and where that other individual took actions that led to a felony conviction that led to that other individual being debarred and where the high managerial agent:
    a. had actual knowledge of the actions that led to debarment, or took action to

avoid such actual knowledge, or failed to take action in order to avoid having such knowledge;

b. knew the actions of the other individual violated the law; and

c. did not report, within a reasonable time, the actions of the other individual to HHS or a law enforcement officer or "failed to take other appropriate action that would have ensured the process for the regulation of drugs was not undermined; and

d. FDA finds that the conduct leading to the other individual's conviction undermines the process for regulating drugs.

Q 15.22 How long can individual debarment last?

The length of debarment varies depending on the basis for debarment. If an individual is subject to mandatory debarment, the debarment is permanent.[44] Permissive debarment, when imposed on an individual, may not exceed five years, but FDA can decide that debarment periods may run consecutively if a person is debarred for multiple offenses.[45], [46]

Individuals—Exclusion from Federal Healthcare Programs

Q 15.23 What are the criteria for exclusion of individuals from federal healthcare programs?

As with entities, individuals are subject to both mandatory and permissive exclusion under 42 U.S.C. § 1320a-7, and the grounds for both types of exclusion are essentially the same for both entities and individuals, with some exceptions not relevant to understanding how an FDCA violation might trigger exclusion.

Q 15.24 Can an individual who pleads guilty under the Park Doctrine as a responsible corporate official, but denies intentional or knowing violations, be excluded under 42 U.S.C. § 1320a-7?

This issue was addressed in *Friedman v. Sebelius*, in which three former senior executives of Purdue Frederick who had pled guilty under the Park Doctrine to misdemeanor misbranding of OxyContin, challenged their exclusions under the permissive exclusion provisions of section 1320a-7(b)(1)(A) based on those guilty pleas. The executives asserted that, because they had not been involved in the wrongdoing, but pled guilty under the Park Doctrine, they could not have had the scienter required for fraud. The district court had rejected this argument, and, on appeal, the D.C. Circuit concurred, holding that the exclusion statute authorizes the Secretary to exclude from participation in federal healthcare programs an individual convicted of a misdemeanor if the conduct underlying that conviction is factually related to fraud, even if the individuals did not actively participate in the fraud.[47]

In the wake of *Friedman*, senior executives at FDA-regulated firms now face a dilemma

should they face a Park Doctrine guilty plea. While the misdemeanor plea under *Park* may avoid the time, expense, and risk of a felony conviction (which is often the government's leverage) and involve no overt admission of active criminal conduct, the new uncertainty of whether such a plea may lead to healthcare program exclusion may render illusory the advantages of pleading under *Park*.

Clinical Investigator Disqualification

Q 15.25 Can FDCA criminal charges also occur in conjunction with disqualification of clinical investigators?

Over the years, FDA has disqualified or otherwise restricted the rights of 227 clinical investigators to receive investigational products, the overwhelming majority of which were proceedings initiated by the agency's Center for Drug Evaluation & Research (CDER).[48] A number of these have been associated with criminal wrongdoing. For example, FDA has permanently debarred Dr. Maria Carmen Palazzo under the GDEA and also permanently disqualified her as a clinical investigator. A review of the 2003 Notice of Initiation of Disqualification Proceeding and Opportunity to Explain (NIDPOE)[49] sent to Dr. Palazzo alleges regulatory violations that are substantially similar to those which later formed the basis for her criminal convictions that supported her debarment under the GDEA.[50]

Dr. Palazzo is not the only FDA-disqualified investigator that also has been debarred under the GDEA. Fifteen other clinical investigators appear on both lists. In those situations, however, the clinical disqualification process usually came before the filing of criminal charges, perhaps reflecting the fact that a finding of disqualification does not need to be supported by the standard of proof required for criminal charges of a showing beyond reasonable doubt.

Imprisonment and Fines for Crimes

Q 15.26 What are the potential fines and prison/jail sentences for individuals for an FDCA violation?

Penalties for solely violating the FDCA include a fine of $1,000 and/or imprisonment for not more than one year (for a misdemeanor). If a repeat violation or done with intent to defraud or mislead, penalties include imprisonment up to three years and/or a fine of up to $10,000.[51] In practice, it is common for Justice Department attorneys to prosecute FDCA violations in conjunction with other federal crimes such as conspiracy,[52] mail[53] or wire fraud,[54] or false statements[55] that often carry more stringent fines and prison terms.

Right to Vote

Q 15.27 Can an individual lose their right to vote if convicted of a FDCA violation?

Possibly, especially if the conviction is for a felony. Under the Fourteenth Amendment to the U.S. Constitution, the right to vote, which is controlled by state law, may be restricted for "participation in rebellion, or other crime." Thus, states retain wide latitude to restrict the voting rights of convicted felons and all but two states[56] have instituted a variety of restrictions, ranging from losing the right to vote during incarceration to not being able to vote unless the right is restored by pardon.[57]

Eligibility to Run for Public Office

Q 15.28 Can a convicted felon run for public office?

At the federal level, there are no constitutional or statutory restrictions on a convicted felon's ability to run for president, the Senate, or the House of Representatives. However, many such restrictions exist at the state level. For example, in Texas, absent a pardon or a judicial release, a convicted felon may not run for public office.[58]

Deportation

Q 15.29 Can a non-U.S. citizen be deported if convicted of an FDCA violation?

Conviction of a crime at the federal or state level indeed may lead to deportation for non-U.S. citizens. For example, under federal immigration law, deportation may occur if a person is convicted of an "aggravated felony" as defined in 8 U.S.C. § 1101(43). Deportation also may occur if a conviction is for a crime of violence (COV) or, under certain circumstances, is a crime involving moral turpitude (CIMT) and a sentence of one year or longer may be imposed.[59]

Q 15.29.1 Does the offense have to be a felony?

Not necessarily. The term "aggravated felony" is a misnomer. For example, under 8 U.S.C. § 1101(a)(4)(M), it is an aggravated felony that can lead to deportation if a person commits an offense that "involves fraud or deceit in which the loss to the victim or victims exceeds $10,000." There is no requirement that this offense be a felony and could involve a misdemeanor violation of the FDCA. Similarly, the provisions for deportation relating to controlled substances covers any alien convicted of violating "any law or regulation . . . relating to a controlled substance."[60] Again, this could involve even a misdemeanor FDCA violation such as that encompassed in the individual executives' pleas in the Purdue Frederick case.[61]

Loss of Other Rights/Privileges

Q 15.30 What other rights or privileges can an individual lose due to a criminal conviction?

Again, depending on state law, a conviction may have other negative consequences. These include potential loss of professional licenses (e.g., attorneys, physicians, accountants), the right to bear or own firearms, to serve on a jury, and become a foster or adoptive parent.

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1. Primarily the Federal Food, Drug, and Cosmetic Act (FFDCA, 21 U.S.C. § 301) *et seq.*, lso including other statutes enforced by FDA such as the biologics licensing provisions of ublic Health Service Act (PHSA; 42 U.S.C. §§ 262–263), and other statutes.

2. As will be discussed, the public specter—or actual bringing—of criminal charges can er some of the consequences discussed in this chapter. See, for example, discussion on nsion from government contracting upon indictment for a criminal offense, *infra*, at Q

3. This chapter does not address the products liability exposure that may flow from FDA ions as that subject is addressed in chapter 10 of this Answer Book, or such other non-CA, but well known, federal criminal and civil proceedings such as those brought for ions of the False Claims Act, 31 U.S.C. § 3729 *et seq.*, or civil or criminal securities ions under federal or state law.

4. FDA Compliance Policy Guide (CPG) 120.100 Fraud, Untrue Statements of Material , Bribery, and Illegal Gratuities. Issued: July 1, 1991, ://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm0738 m, *reprinted*, with comments, *in* 56 Fed. Reg. 46,191 (Sept. 10, 1991). Current FDA mation on the AIP, including the September 10, 1991 Federal Register notice, may be sed at ://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm.

5. 56 Fed. Reg. 46,191 (Sept. 10, 1991), at cmt. 10.

6. The list of companies added to (and removed from) the AIP program did not begin to when firms were added to or removed from the list until April 2003. By inference, we can ce that those companies for which an entry does not appear under the "Revision History" of st were added before April 2003. Five of those "pre-April 2003" firms are still in business DA and are still on the list today, fifteen years later. If we combine those five firms with the irms FDA added since 2003 that are still on the list (Hill, added in October 2011, and axy, added in February 2009), the seven firms have been on the AIP list for an aggregate of ninety years, or an average of almost thirteen years each.

7. Pub. L. 102-282, 106 Stat. 149, codified at 21 U.S.C. §§ 335a, 335b, and 335c.

8. The powers under the GDEA are conferred on the Secretary of Health & Human ces (HHS), but have been delegated to FDA.

9. The debarment, temporary denial of approval, and suspension are found in 21 U.S.C. 5a; section 306 of the FDCA; civil penalties are in 21 U.S.C. § 335b; section 307 of the A; and ANDA withdrawal powers are conferred by 21 U.S.C. § 335c; section 308 of the A.

10. 21 U.S.C. § 335a(a); section 306(a) of the FDCA.

21 U.S.C. § 335a(b); section 306(b) of the FDCA.

NHE Fact Sheet, 2016, https://www.cms.gov/research-statistics-data-and-ns/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html.

Id.

48 C.F.R. 9.407-4(a).

48 C.F.R. 9.407-4(b).

48 C.F.R. 9.407-2(a)(1)–(9).

48 C.F.R. 9.407-2(b)

48 C.F.R. 9.407-2(c)

48 C.F.R. 9.406-2(a)

48 C.F.R. 9.406-2(b)

48 C.F.R. 9.406-4(a)

48 C.F.R. 9.402(b).

42 U.S.C. § 1320a-7.

We reviewed the HHS Office of Inspector General (OIG) exclusion list as of March 18, , and found thirty-three excluded companies labeled as "drug company" or that clearly were companies (e.g., Ista Pharmaceuticals is listed as "Other Business/Pharmacy"). Of the -three, eleven were subject to mandatory exclusion; the balance were excluded under the issive exclusion provisions of 42 U.S.C. § 1320a-7(b). Of the eleven, four were excluded r clause (1) and five under clause (3) of the mandatory exclusion provisions. Interestingly, ue Frederick is listed as subject to mandatory exclusion under 42 U.S.C. § 1320a-7(a)(3), ppears to have met the criteria for mandatory exclusion under 42 U.S.C. § 1320a-7(a)(4), ı provides for mandatory exclusion for an entity convicted of a felony "relating to the vful, manufacture, distribution, prescription, or dispensing of a controlled substance" as its y convictions in 2007 related to the marketing of OxyContin®, a controlled substance.

42 U.S.C. § 1320a-7(a)(1).

42 U.S.C. § 1320a-7(a)(3).

42 U.S.C. § 1320a-7(b)(1)–(15).

42 U.S.C. § 1320a-7(b)(1).

42 U.S.C. § 1320a-7(b)(3). Of the thirty-three "drug companies" found in our review of xclusion list, none were excluded on this ground.

42 U.S.C. § 1320a-7(b)(8). Eighteen of the drug companies in our review were excluded ɛing controlled by a sanctioned individual.

"Managing employee" is defined in 42 U.S.C. § 1320a-5(b) as ". . . an individual, ding a general manager, business manager, administrator, and director, who exercises ıtional or managerial control over the entity, or who directly or indirectly conducts the day-y operations of the entity."

17 C.C.R. 10377.1(a)(1).

17 C.C.R. 10377.1(a)(2).

17 C.C.R. 10377.2(a) and (b).

In re Par Pharm., Inc. Sec. Litig.,733 F. Supp. 668 (S.D.N.Y. 1990).

36. Par Pharm, Inc. Derivative Litig., 750 F. Supp. 641 (S.D.N.Y. 1990).
37. *Par to Settle with Stockholders*, J. NEWS (White Plains, N.Y.), Sept. 28, 1991, at B1.
38. *See, e.g.*, Mylan v. Akzo NV, 2 F.3d 56 (4th Cir. 1993).
39. *Par Parent to Pay Mylan $3M in Settlement*, ROCKLAND J.-NEWS, Nov. 30, 1993, at

40. 21 U.S.C. § 335a(a)(2).
41. 21 U.S.C. § 335a(b)(2)(B)(i).
42. 21 U.S.C. § 335a(b)(2)(B)(ii).
43. Defined at 21 U.S.C. § 321(cc)
44. 21 U.S.C. § 335a(c)(2)(A)(ii).
45. 21 U.S.C. § 335a(c)(2)(A)(iii).
46. FDA has debarred 146 individuals since the GDEA became law. Of these, 102 were anently debarred, and the remainder received debarments ranging from two years to ty-five years. One debarment was rescinded due to incorrect service of the required notice e intended debaree, another withdrawn because of a conviction reversal, and six permanent ments were terminated early. *See* FDA Debarment List (Drug Product Applications), ://www.fda.gov/iceci/enforcementactions/fdadebarmentlist/default.htm.
47. Friedman v. Sebelius, 686 F.3d 813, 824 (D.C. Cir. 2012).
48. *See* FDA, Clinical Investigators—Disqualification Proceedings, ://www.accessdata.fda.gov/scripts/SDA/sdNavigation.cfm? =&sortColumn=1a&sd=clinicalinvestigatorsdisqualificationproceedings&page=1&previe e=true&displayAll=true#12.
49. https://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm105778.

50. *See* FDA Proposal to Debar, Notice of Opportunity for Hearing to Maria C. Palazzo, 11, 2011, ://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm291924.htm.
51. 21 U.S.C. § 333(a).
52. 18 U.S.C. § 371.
53. 18 U.S.C. § 1341.
54. 18 U.S.C. § 1343.
55. 18 U.S.C. § 1001.
56. Maine and Vermont. See Summary of Felony Disenfranchisement Restrictions in 2016. Sentencing Project. https://www.sentencingproject.org/publications/felony-franchisement-a-primer/.
57. Criminal Disenfranchisement Laws Across the United States. Updated Oct. 6, 2016. Brennan Center for Justice. https://www.brennancenter.org/criminal-disenfranchisement-across-united-states.
58. Section 141.001 of the Texas Election Code.
59. 8 U.S.C. § 1227(a)(2)(A)(i).
60. 8 U.S.C. § 1227(a)(2)(B)(i).

See Q 15.24, *supra*.

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Prescription Drug Sampling Regulation and Enforcement

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Pharmaceutical companies frequently provide free samples of their drugs to health care providers to introduce the providers—and their patients—to the therapeutic benefits of the drugs. As Pharmaceutical Research and Manufacturers of America (PhRMA), an industry trade group, has observed, providers use drug samples for a variety of reasons, including "to get patients started on therapy right away, to optimize dosing or choice of drug before committing to a particular course of treatment, and sometimes to help patients who might not be able to afford medicines on their own."[1] These salutary effects of sampling for providers and patients accompany an evident benefit for pharmaceutical companies: because free samples give providers and patients an opportunity to try drugs, samples can result in increased use of drugs that are therapeutically beneficial and cost-effective. As a result, sampling has long comprised a significant portion of pharmaceutical companies' marketing budgets.

The prevalence of drug sampling has resulted in a significant set of laws, regulations, and guidance documents that govern the practice in the United States. Chief among these laws is the Prescription Drug Marketing Act of 1987 (PDMA), which governs the storage, handling, documentation, and distribution of prescription drug samples in the United States. As this chapter explains, where pharmaceutical companies have, on occasion, strayed outside the legal bounds set by the PDMA, U.S. regulators (and private plaintiffs) have been quick to employ other laws, including the federal Anti-Kickback Statute (AKS) and the federal False Claims Act, to police sampling practices. Enforcement and litigation in this area can lead to steep criminal and civil consequences. For this reason, pharmaceutical companies that provide samples for promotional purposes must ensure they have a strong grasp of the relevant legal restrictions.

This chapter begins by briefly summarizing drug sampling practices and the benefits this promotional practice can have for providers and patients. Next, the chapter discusses the various laws and regulations that expressly govern

drug sampling—and other statutes that may be implicated by certain sampling practices. This chapter then addresses the role of the U.S. Food and Drug Administration (FDA), the U.S. Department of Justice (DOJ), and other regulators in enforcement of these statutes. Finally, this chapter covers drug sampling enforcement and litigation, highlighting notable enforcement actions and surveying the relatively sparse jurisprudence that relates to sampling practices. One further note: in keeping with the PDMA's scope, this chapter focuses on *prescription* drug sampling, but key principles discussed herein apply similarly to over-the-counter drugs.

An Overview of Prescription Drug Sampling

Q 16.1 What is prescription drug sampling and why is it so common?

Sampling is a common promotional practice in which pharmaceutical companies disburse free samples of their drugs to health care providers, who, in turn, provide them to their patients. Statistics regarding nationwide sampling practices are not generally available. But the few published studies reflect that the value of samples provided to U.S. health care providers and patients is immense. A 2005 study in the *New England Journal of Medicine*, for example, quantified the total value of free samples provided by pharmaceutical companies to health care providers as approximately $18 billion and found that 20% of all Americans used drug samples.[2] A 2007 study in the same publication found that 78% of physicians received drug samples from pharmaceutical companies.[3] Perhaps not surprisingly, then, a 2008 study reported that nearly 50% of Medicare beneficiaries used samples each year.[4] A more recent report from the U.S. Government Accountability Office estimates that pharmaceutical companies spent approximately $8 billion on free samples in 2014, which comprised roughly 11% of the $71 billion the industry spent on marketing worldwide.[5]

As noted above, sampling allows providers to expedite the treatment process (by enabling patients to begin on a course of treatment before filling a prescription). Further, sampling enables providers to evaluate new medications, to match prescriptions to a particular patient's needs, and to calibrate dosing decisions.[6] Published research, including survey results, on sampling indicate that patients value being able to start therapy immediately without a visit to a pharmacy and that health care providers value the ability to provide more nuanced counseling regarding medications.[7]

Depending on the quantity of samples a pharmaceutical company provides, sampling also can offset costs of a medication for patients. Indeed, physicians report provision of free samples as one of their most frequently used strategies for reducing patients' out-of-pocket costs.[8]

The benefits to pharmaceutical companies of prescription drug sampling are clear. By sampling, companies may increase usage of their drugs as providers and patients alike become comfortable with the therapeutic profile of those products. Drug samples, in effect, offer the benefit of a free trial period during which, the manufacturers hope, the provider or patient will conclude that the drug suits the patient's needs.

Prescription Drug Sampling: The Legal and Regulatory Landscape

Q 16.2 What laws are implicated by prescription drug sampling?

The PDMA, as modified by the Prescription Drug Amendments of 1992 and the FDA Modernization Act of 1997, implemented a framework for appropriate prescription drug sampling practices. As detailed below, the PDMA and its implementing regulations impact each step of the sampling process. Violations of the PDMA can give rise to civil and criminal liability.[9] Thus, pharmaceutical companies seeking to adhere to U.S. restrictions on sampling must look first and foremost to the PDMA.

Like the PDMA, the Drug Supply Chain Security Act of 2013 (DSCSA) was intended to prevent the distribution of counterfeit, contaminated, or illegitimate drugs in the United States.[10] In significant part, the DSCSA lays the groundwork for an integrated electronic system to trace particular prescription drugs in the United States, as they flow through certain "transactions" involving key participants in the supply chain (e.g., manufacturers, repackagers, logistics providers, wholesalers, dispensers). Notably, however, the DSCSA exempts from the definition of "transaction" "the distribution of product samples by a manufacturer or a licensed wholesale distributor in accordance with" the PDMA.[11] Thus, by adhering to the PDMA, pharmaceutical companies can limit exposure under the DSCSA as well.

The Physician Payment Sunshine Act provisions of the Affordable Care Act also address sampling. Like the DSCSA, the Sunshine Act excludes from the statutory reporting requirements relating to pharmaceutical companies' transfers of value to health care providers. In particular, section 1320a-7h of the Sunshine Act states that "product samples that are not intended to be sold and are intended for patient use" are not subject to the Act's reporting requirements.[12]

Prescription drug sampling also may implicate multiple other federal laws, including:

- the AKS, 42 U.S.C. § 1320a-7b;
- the civil monetary penalties statute, 42 U.S.C. § 1320a-7a;
- the False Claims Act, 31 U.S.C. § 3729 *et seq.*; and
- the U.S. Foreign Corrupt Practices Act (FCPA).[13]

These laws do not address sampling specifically. Rather, conduct that runs afoul of the PDMA (or would if it took place domestically) could conceivably violate these other laws as well (e.g., in situations where a pharmaceutical company provides samples to a health care provider intending that the provider will sell or bill for the samples).[14] The interplay between the PDMA, the AKS, and the False Claims Act is addressed further in Q 16.8 below.

Additionally, depending upon the jurisdiction in which the activities take place, prescription drug sampling may give rise to liability under state analogues to the PDMA, AKS, and the False Claims Act or trigger obligations under state pharmaceutical marketing and disclosure laws. For example, under Vermont law, a pharmaceutical company that provides samples to enumerated health care providers in Vermont must disclose both free samples of prescription drugs and, if the company has other exempted expenditures to report, free samples of over-the-counter drugs.[15] By contrast, Massachusetts's pharmaceutical marketing law exempts from disclosure requirements the provision of "prescription drugs to a covered recipient solely and exclusively for use by patients."[16]

Q 16.3 Why did Congress enact the PDMA?

The PDMA was enacted to restore confidence in the prescription drug supply chain. According to Congress, Americans at the time confronted a "distribution system for prescription drugs [that was] insufficient to prevent the introduction and eventual retail sale of substandard, ineffective, or even counterfeit drugs." Among other concerns, Congress found that the "existing system of providing drug samples to physicians through manufacturer's representatives has been abused for decades and has resulted in the sale to consumers of misbranded, expired, and adulterated pharmaceuticals."[17]

In signing the bill into law in April 1988, President Ronald Reagan observed that the intent was to "reduce potential public health risks that may result from the distribution of mislabeled, subpotent, counterfeit, or adulterated prescription drugs in the secondary source market, the so-called 'diversion market.'"[18]

To these ends, the PDMA amended several sections of the Federal Food, Drug, and Cosmetic Act (FDCA) to regulate pharmaceutical sampling and several other aspects of drug distribution in the United States.[19] As FDA has explained, the PDMA:

1. Banned the sale, purchase, or trade of (or offer to sell, purchase, or trade) drug samples and drug coupons;
2. Restricted reimportation of prescription drugs to the manufacturer of the drug product or for emergency medical care;
3. Established requirements for drug sample distribution and the storage and handling of drug samples;
4. Required wholesale distributors of prescription drugs to be state licensed and required FDA to establish minimum requirements for state licensing schemes;
5. Established requirements for wholesale distribution of prescription drugs by unauthorized distributors;
6. Prohibited, with certain exceptions, the sale, purchase, or trade (or offer to sell, purchase, or trade) of prescription drugs that were purchased by hospitals or health care entities, or donated or supplied at a reduced price to charities; and

7. Established criminal and civil penalties for PDMA violations.[20]

This chapter focuses on the PDMA's ban on the sale, purchase or trade of drug samples, as well as the structure it implemented for storing, handling, and distributing drug samples.

Q 16.4 What does the PDMA require with respect to drug sampling?

Under the PDMA, "[n]o person may sell, purchase, or trade or offer to sell, purchase, or trade any drug sample" or coupon (or counterfeit a coupon).[21] Congress defined a "drug sample" as "a unit of a drug . . . which is not intended to be sold and is intended to promote the sale of the drug."[22] A "coupon" is a "form which may be redeemed, at no cost or at a reduced cost, for a drug which is prescribed" by a health care provider.[23]

The PDMA prescribes how manufacturers or authorized distributors of a drug may distribute drug samples (setting aside the provision of drug samples by "practitioner[s] licensed to prescribe such drug," "health care professional[s] acting at the direction of and under the supervision of such a practitioner," and pharmacies or other entities acting at the direction of such a practitioner).[24] By statute, pharmaceutical companies and distributors may "distribute drug samples by mail or common carrier" to licensed practitioners (or to pharmacies or other entities) at the direction of a licensed practitioner if the drug sample or samples are distributed: (1) in "response to a written request . . . made on a form" with certain statutorily specified information, *and* (2) under a "system which requires the recipient . . . to execute a written receipt for the drug sample upon its delivery and the return of the receipt to the manufacturer or authorized distributor."[25] The written request must include:

- The practitioner's name, address, professional designation, and signature;
- The "identity of the drug sample requested and the quantity requested";
- The drug manufacturer's name; and
- The date of the request.[26]

Companies that distribute samples by mail or common carrier must maintain the request forms and a "record of distributions of drug samples which identifies the drugs distributed and the recipients of the distributions" for three years.[27] These records must "be made available by the" company "to Federal and State officials engaged in the regulation of drugs and in the enforcement of laws applicable to drugs."[28]

Companies also may sample through other means, including by having sales representatives distribute the samples. But the PDMA imposes several requirements such as:

- Samples may be distributed to licensed practitioners (or pharmacies or health care entities at the direction of such a distributor) in response to a written request on a form containing the information set forth above (e.g., the practitioner's signature, the pharmaceutical company's name);
- Samples must be stored "under conditions that will maintain their stability,

integrity, and effectiveness and will assure that the drug samples will be free of contamination, deterioration, and adulteration"; and

- Companies that sample must maintain certain documentation for three years, conduct an annual "complete and accurate inventory of all drug samples" in their representatives' possession, and notify FDA of "any significant loss of drug samples and any known theft of drug samples" (as well as of any convictions of representatives for selling, purchasing, or trading samples (or offering to do so) under the PDMA or analogous state laws).[29]

Regulations promulgated pursuant to the PDMA set forth additional requirements for drug sample distributors. For example, the regulations require pharmaceutical companies that distribute samples to "establish, maintain, and adhere to written policies and procedures" for administering their drug sampling programs.[30] Further, the regulations prohibit companies from distributing samples in response to "open-ended or standing requests," but permits companies to distribute samples in response to a written request to provide a specific number of samples over a period of six months or fewer ("with the actual delivery dates for parts of the order" set subsequently by oral or electronic communication).[31] The regulations also expand on the PDMA's logistical requirements. For example, whereas the PDMA obligates pharmaceutical companies to include, in the written request forms, the "identity of the drug sample . . . and the quantity," the regulations specify that the request must specify the "strength of the drug sample."[32] Further, the regulations expand on the annual inventory requirement, covering the steps of the required sample reconciliation process,[33] and companies' statutory obligations to investigate falsified sample requests or records, report losses or theft of samples, and notify FDA of convictions of sales representatives.[34]

Violating the PDMA triggers criminal consequences, although the statute also provides that it does not "subject an officer or executive of a drug manufacturer or distributor to criminal liability solely because of a sale, purchase, trade, or offer to sell, purchase, or trade . . . by other employees of the manufacturer or distributor."[35]

Q 16.5 Who regulates prescription drug sampling?

The FDCA, of which the PDMA is a part, grants FDA the authority to regulate prescription drugs.[36] FDA has promulgated regulations pursuant to its authority under the PDMA regarding sample distribution, requests for samples, sample storage and handling, sample donation, and investigation of diversion and falsification of sample requests and records.[37] If FDA receives a report concerning prescription drug sample theft, loss, falsification, or diversion, it refers the complaint to the Center for Drug Evaluation and Research (CDER) Division of Supply Chain Integrity (DSCI).[38] The DSCI also conducts routine inspections of manufacturers that have drug sampling programs to ensure compliance with the PDMA.[39]

Whether routine or initiated by complaint or report, DSCI determines whether to refer

investigations to FDA's Office of Criminal Investigations (OCI) headquarters for evaluation.[40] FDA's PDMA guidance document suggests that certain criminal activity or possible fraud should be reported directly to the OCI.[41]

As described in Chapter 12, OCI partners with DOJ to enforce criminal provisions of the FDCA. DOJ also may pursue purportedly improper sampling practices under the False Claims Act and other health care fraud and abuse laws.[42] The results of several noteworthy DOJ enforcement actions relating to sampling practices are summarized in Q 16.9 below.

When PDMA investigations indicate possible Medicare, Medicaid, or Social Security fraud, DSCI also initiates contact and coordinates with the local offices of the Department of Health and Human Services (HHS), Office of the Inspector General (OIG).[43]

Lastly, state regulators also enforce sampling restrictions contained in state analogues to the PDMA.

PDMA and Sampling Enforcement and Litigation

Q 16.6 What guidance have federal regulators provided regarding compliance with laws governing prescription drug sampling?

Several federal regulators have issued guidance documents to assist individuals and companies in understanding and complying with the PDMA and other laws related to sampling. These documents generally acknowledge the common practice of providing promotional pharmaceutical samples, while at the same time warning of legal consequences that may result from improper distribution of or billing for samples.

Given its key role in regulating prescription drug sampling, FDA has issued guidance documents addressing various PDMA requirements, but only two pertain directly to drug sampling. In its Compliance Program Guidance Manual, FDA provided general information for "individuals, drug manufacturers, distributors, and other parties that may be involved in prescription drug sample theft, loss, falsification, or diversion" and set forth instructions for FDA personnel who conduct PDMA-related investigations or evaluate "compliance with recordkeeping and monitoring systems required under the PDMA."[44] As FDA explained, the DSCI is the "designated . . . focal point for all potential, emerging, and ongoing routine and directed investigations of prescription drug samples."[45] Additionally, FDA listed coverage areas for potential inspections of drug sampling programs, including "[r]ecords of employees terminated by the firm for lack of compliance with PDMA samples and recordkeeping procedures" and "copies of the firm's recordkeeping standard operating procedures (SOPs)."[46]

Similarly, in a short March 2006 guidance document, FDA provided interim guidance for free clinics that receive donated prescription drug samples (while the agency considered fixes to the applicable regulations in response to concerns raised by clinics).[47] FDA acknowledged that some had raised concerns that the sampling regulations' recordkeeping requirements (e.g., 21 C.F.R. § 203.39) unduly burdened small and underfunded free clinics.[48] In response, FDA announced that it intended to exercise enforcement discretion with regard to such requirements and would not object "if a clinic fails to comply with § 203.39(b), (d), (e), (f), and (g)."[49] Those regulations address the delivery of donated drug samples, the disposal of samples, recipient donation records, subsequent sample drug recordkeeping, and sample drug inventory reports respectively.[50]

As for the remaining PDMA-related guidance documents, each touches on restrictions relating to wholesalers and the statute's "pedigree" requirements (i.e., statements regarding a drug's origin). In November 2006, for instance, FDA issued a guidance document with a series of questions and answers for industry focusing on the PDMA provisions that impose requirements on wholesalers.[51] Three other guidance documents likewise pertain exclusively to the PDMA's pedigree requirements found in 21 U.S.C. § 353(e)(1)(A) and

21 C.F.R. § 203.50(a) and, in particular, how FDA would enforce those requirements after a district court preliminarily enjoined the latter regulation in the mid-2000s.[52]

Whereas FDA's guidance to date has focused primarily on the logistics of a sampling program, HHS OIG addressed the interplay between sampling and key U.S. health care fraud and abuse statutes in its April 2003 Compliance Program Guidance for Pharmaceutical Manufacturers.[53] There, OIG advised pharmaceutical companies that provide free samples to "closely follow" all provisions of the PDMA and to consider taking the following additional measures: (1) training sales representatives to inform sample recipients that samples may not be sold or billed; (2) "clearly and conspicuously" labeling individual samples as units that are not for sale; and (3) including a "clear and conspicuous" notice on any samples or related documentation that "samples are subject to PDMA and may not be sold."[54]

OIG also warned companies that "[r]ecent government enforcement activity has focused on instances in which drug samples were provided to physicians who, in turn, sold them to the patient or billed them to the federal health care programs on behalf of the patient."[55] As OIG explained, if a sample is traded, sold, or billed to a federal health care program in violation of the PDMA, that sample may "have monetary value to the recipient (e.g., a physician)," thereby potentially triggering potential liability under the AKS, the False Claims Act, and other anti-inducement or anti-fraud statutes.[56] By contrast, OIG recognized, if a sample is not traded, sold, or billed for, its monetary value is "vitiate[d]."[57]

OIG advisory opinions offer further insight into OIG's view on the proper use of drug samples and ways to mitigate the risks associated with sampling. In Advisory Opinion 08-04, for example, OIG invoked the Compliance Guidance in analyzing a proposed free trial prescription program for Hemophilia A patients.[58] OIG focused on the program's requirement that physicians and the program administrator "sign statements acknowledging that the [m]edication is complimentary . . . [and] provided at no cost, and *neither may be resold nor billed to* third-party *payers*"; that safeguard, according to OIG, helped distinguish the proposed program "from problematic programs that offer free goods or other remuneration to prescribers as a means to 'seed' or introduce new products into the marketplace."[59] Likewise, in Advisory Opinion No. 06-08, OIG evaluated the legal risks associated with a free clinic's practice of providing free drugs under patient assistance programs (PAPs) sponsored by pharmaceutical companies.[60] It concluded that, given the programs' charitable mission and structure, such a program faced "minimal risks" of either impermissible payments from the PAP sponsors or impermissible inducements to federal health care program beneficiaries.[61]

The Centers for Medicare and Medicaid Services (CMS), too, has addressed sampling, including in the agency's Medicare Claims Processing Manual.[62] That Manual expressly states that providers are prohibited from billing Medicare for these free items.[63] Implemented in 2007, the Manual explains that "item[s] (such as a device or drug) . . . offered [to providers] by a manufacturer/supplier free of charge" are considered "no cost items" and that providers should therefore refrain from seeking any reimbursement for

them "as noted in Section 1862(a)(2) of the Social Security Act," which excludes from coverage items for which the recipient "has no legal obligation to pay, and [for] which no other person . . . has a legal obligation to provide or pay."[64]

A final rule promulgated by CMS in 2013 likewise offers manufacturers clarity regarding the interaction between the PDMA and other health care fraud and abuse laws. In particular, the rule addresses whether providing free samples to physicians triggers the Sunshine Act's requirement that manufacturers report transfers of value to health care professionals.[65] As noted above, the Sunshine Act, on its face, excludes samples provided for patient use from the statutory reporting requirements. But CMS continued on to explain that it "do[es] not believe the applicable manufacturer should be responsible for tracking what actually happens to samples."[66] Rather, "as long as the manufacturer and covered recipient agree in writing that the products will be provided to patients, which is commonplace in the industry, the provision of samples can be excluded."[67] As described above, the Sunshine Act only requires reporting of transfers of value to health care professionals, and this rule makes clear that CMS does not view samples as providing financial benefit or "value" to physicians because they are not sold.

CMS also periodically provides less formal guidance for industry participants and health care providers regarding fraud and abuse topics. In a November 2017 CMS "roadmap" for avoiding Medicare fraud and abuses, CMS offered its perspective on sampling in the context of Medicare billing.[68] There, CMS cautioned health care providers that "[t]he Federal Government prosecutes physicians for billing Medicare for free samples" and that, to avoid such an outcome, [providers] accepting free samples should institute "reliable systems . . . to safely store the samples and ensure samples remain separate from your commercial stock."[69] Nevertheless, the CMS roadmap noted that "[m]any drug and biologic companies provide physicians with free samples that they may give to patients free of charge"; CMS further stressed that "[i]t is legal to give these samples to your patients for free, but it is illegal to sell them."[70]

Q 16.7 What guidance have industry groups and non-profit organizations provided regarding compliance with laws governing prescription drug sampling?

In addition to public regulators, private organizations also have issued guidance to pharmaceutical companies, physicians, and other health care providers about sampling practices.

In 2013, for example, the Pew Charitable Trusts issued best practices recommendations for the conflict of interest policies of academic medical institutions.[71] Among other recommendations, Pew suggested that such institutions bar their clinical faculty members and staff from accepting and using free samples absent "compelling circumstances to do so."[72] The organization posited that free samples are marketing tools by pharmaceutical companies that some argue do not benefit the patients most in need of low-cost drugs.[73] Some other private organizations, including hospitals and clinics, also have questioned the

practice or explicitly banned it altogether in recent years.[74]

By contrast, in its Code on Interactions with Healthcare Professionals, PhRMA counseled a less-restrictive approach to sampling, simply noting that while "[i]t is appropriate to provide product samples for patient use[,]" companies must be sure to do so "in accordance with the Prescription Drug Marketing Act."[75]

Q 16.8 How have regulators enforced the laws governing prescription drug sampling?

Historically, DOJ has actively pursued enforcement actions under the False Claims Act and the AKS against pharmaceutical companies and health care providers in connection with inappropriate sampling practices.

In 2001, for example, TAP Pharmaceutical Products, Inc. (TAP), a pharmaceutical company, agreed to pay $875 million to the government to settle criminal and civil charges stemming in part from the company's sampling practices.[76] According to DOJ, TAP "caused . . . billings to hundreds of elderly Medicare program beneficiaries and to the Medicare program directly" for thousands of free samples of the company's prostate cancer drug, Lupron, in violation of the PDMA.[77] DOJ alleged that the company knew that physicians were securing government reimbursement amounting to hundreds of dollars per dose for the Lupron samples—and, in some instances, aided the physicians in seeking that reimbursement. TAP pled guilty to conspiring to violate the PDMA and paid a $290 million criminal fine, which was, at the time, the highest fine ever in a health care fraud matter. TAP paid an additional approximately $560 million to the government to resolve allegations that its drug pricing and sales and marketing activities violated the False Claims Act. Notably, DOJ also prosecuted multiple TAP employees and physicians for their involvement in the improper sales, marketing, and billing practices.[78] Three TAP sales representatives and four physicians pled guilty or were successfully prosecuted earlier in the investigation.[79]

Two years after the TAP resolution, the government reached another large settlement with a pharmaceutical company based again, in part, on allegations of improper uses of free samples in violation of the False Claims Act and PDMA. On June 20, 2003, DOJ announced that AstraZeneca Pharmaceuticals LP ("AstraZeneca"), had pled guilty to charges including conspiracy to violate the PDMA by causing the submission of claims for payment for samples of the prostate cancer drug Zoladex that AstraZeneca provided to urologists for free.[80] DOJ alleged that employees of AstraZeneca gave thousands of free samples of Zoladex to physicians as kickbacks in order to induce physicians to purchase Zoladex and with the expectation that physicians would prescribe and administer the free samples and bill those samples to patients and federal health insurance programs.[81] As part of its guilty plea, AstraZeneca agreed to pay $355 million to resolve these and other allegations involving violations of the False Claims Act and the PDMA.[82]

In recent years, the government has continued to pursue AKS and False Claims Act theories against pharmaceutical companies, as well as individuals who allegedly sold or

billed for samples. In 2012, for instance, two U.S. subsidiaries of Sanofi S.A. agreed to pay $109 million to resolve allegations that they violated the AKS and the False Claims Act by providing free samples of Hyalgan, a knee injection drug.[83] DOJ asserted that the free samples also impacted the average sales price for Hyalgan and thereby led the Sanofi subsidiaries to submit purportedly false ASP reports that were used to set Medicare reimbursement rates for the drug. According to DOJ, sales representatives of the subsidiaries promised to provide certain physicians with samples in return for purchases of the drug.

Further, in late 2017, a Minnesota-based dermatological practice and its founder agreed to pay the government $850,000 to resolve numerous allegations, including that the practice and its founder illegally billed Medicare after providing patients with free samples of a phototherapy drug.[84]

Q 16.9 How have the federal courts handled claims invoking the PDMA?

Case law on the PDMA—and sampling issues more generally—is sparse. In recent years, however, a few courts have begun to address the interplay between the PDMA and other health care fraud and abuse statutes.

In *United States v. Edelstein*,[85] DOJ pursued civil claims against pharmacists who had pled guilty to knowingly selling prescription drug samples in violation of the PDMA.[86] The government alleged that the defendants defrauded Medicaid when they sold drug samples to pharmacy customers and that the defendants caused false and fraudulent claims for full payment of the prescription drugs to be submitted to Medicaid in violation of the False Claims Act. The government moved for summary judgment against the defendants, arguing that the pharmacists who had pled guilty to violating the PDMA were estopped from denying liability as to the government's fraud claims. But the district court rejected that argument, reasoning that the defendant pharmacists had not pled guilty to a charge of fraud or false statements—only to knowingly selling prescription drug samples in violation of the PDMA.[87] The court explained that the PDMA does not require the government to show fraud or false statements—essential elements under the False Claims Act.[88]

In *United States ex rel. Wood v. Allergan Inc.*,[89] the U.S. District Court for the Southern District of New York evaluated whether prescription drug sampling could constitute "remuneration" under the AKS. The relator alleged that Allergan provided free drug samples to induce physicians to prescribe Allergan drugs to the physicians' cataract patients, including Medicare and Medicaid beneficiaries.[90] Allergan moved to dismiss the relator's complaint, contending (among other arguments) that the PDMA specifically authorizes pharmaceutical companies to provide samples for promotional purposes.[91] The court did not directly address the apparent conflict between the PDMA and the relator's AKS theory, instead relying on the relator's allegations that absent the provision of free samples, physicians may have had to purchase some amount of the drugs at issue to use in their practices. According to the court, the samples could be "remuneration" insofar as they "subsidized . . . [the physicians'] costs."[92]

Plaintiffs in other cases have included allegations that pharmaceutical companies provided kickbacks in the form of free samples, but the courts have not addressed the interplay between the AKS and PDMA in those actions.[93] For example, in *Plumbers' Local Union No. 690 Health Plan v. Sanofi*,[94] the relators alleged that Sanofi helped physicians illicitly bill Medicare for free samples that Sanofi had provided to those physicians. But the court granted Sanofi's motion to dismiss under Rules 8 and 9(b), concluding that the relators' mere allegations that drug samples had been provided were not sufficient. Because the relators failed to "explain the who, what, when, where and how of this scheme," the court dismissed the suit.[95]

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13. Sampling could trigger liability under the FCPA if, for example, a pharmaceutical any corruptly provided samples to foreign officials (e.g., physicians at public overseas) *for benefit* (rather than for the benefit of patients) in order induce or retain business (e.g., the cians' prescriptions). 15 U.S.C. § 78dd-1-3.

14. In this context, samples are distinct from "free goods," which companies also provide to customers as a negotiated price concession (e.g., a deal allowing the customer to buy ten and receive one free). Although both samples and free goods are distributed by naceutical companies to others at no cost, companies typically provide samples for the ns discussed in this chapter—namely, as a means to start patients on new therapies or to de patients with drugs they might otherwise struggle to afford. Free goods, on the other , were once commonly included in pharmaceutical companies' purchase agreements with esalers and other entities. Like prescription drug samples, free goods can implicate the AKS. ıer, the practice of providing free goods also can raise price-reporting concerns because only goods" that are "not contingent upon any purchase requirement" are excluded from age manufacturer price" and "best price" calculations. *See* 42 C.F.R. § 447.504(c)(24); *see* 2 C.F.R. § 447.505(c). Pharmaceutical companies should keep in mind, however, that the nment or relators' counsel may argue that recipients of drug samples are in close enough on to the purchasers of drugs that sampling implicates price-reporting laws and regulations.

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17

The 21st Century Cures Act: Overview and Impact on Product Development and the U.S. Food & Drug Administration

Daniel A. Kracov and Pari Mody

Introduction

Q 17.1 What was the 21st Century Cures Act Initiative?

The 21st Century Cures Initiative was a bipartisan and bicameral effort, led by the House Committee on Energy & Commerce and the Senate Committee on Health, Education, Labor, and Pensions, to accelerate the pace of the discovery, development, and delivery of new treatments and cures. The 21st Century Cures Initiative culminated in passage of the 21st Century Cures Act (the "Cures Act").

Q 17.2 When was the 21st Century Cures Act enacted?

Former President Barack Obama signed the Cures Act into law on December 13, 2016.[1] Both chambers of Congress passed the Cures Act with strong bipartisan support. The House of Representatives passed the legislation by a vote of 392-26 on November 30, 2016, and the Senate approved the bill on December 7, 2016 by a 94-5 vote.

Overview of Significant Cures Act Provisions Impacting FDA

Research Funding

Q 17.3 What does the Cures Act do to support research and the discovery of new therapies?

Section 1001 of the Cures Act provides $4.8 billion, over ten years, to support research funded by the National Institutes of Health (NIH). This includes dedicated funding for the:

- Precision Medicine Initiative, which aims to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease;
- Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which aims to improve our understanding of the human brain;
- Beau Biden Cancer Moonshot, for purposes including the development of cancer vaccines, more sensitive diagnostic tests for cancer, immunotherapy, and the development of combination therapies; and
- Regenerative medicine using adult stem cells, including autologous stem cells.

In addition to research funding, the Cures Act encourages the Secretary to take steps to implement the Precision Medicine Initiative,[2] support young and emerging scientists,[3] and streamline NIH administrative processes.[4]

Pharmaceutical Development and Review

Q 17.4 How does the 21st Century Cures Act support the Patient-Focused Drug Development Initiative?

Patient-Focused Drug Development (PFDD) was launched in 2012, under the fifth reauthorization of the Prescription Drug User Fee Act, to systematically gather patients' perspectives on their conditions and available therapies to treat their conditions. Since that date, FDA has held over twenty public meetings, each focused on a different disease area, including autism, Parkinson's disease, and breast cancer.[5]

The Cures Act advances the PFDD by requiring the Secretary of Health and Human Services (HHS) to disclose how the agency is collecting and using patient experience data in drug development. Specific requirements under the law include:

- Drug and Biologic Approval. Section 3001 requires the Secretary to make a brief, public statement following FDA approval of a drug or biologic regarding the "patient experience data"[6] and related information that was submitted and

reviewed as part of the product application. FDA began implementing this requirement for applications submitted after June 12, 2017.[7]

- Guidance. Section 3002 requires the Secretary to develop a plan to issue draft and final versions of guidance documents, over a period of five years, regarding the collection of patient experience data and the use of such data and related information in drug development. FDA issued the Plan for Issuance of Patient-Focused Drug Development Guidance in May 2017.[8]
- Streamlining Patient Input. Section 3003 exempts the collection of certain patient experience data from the requirements under the Paperwork Reduction Act of 1995.
- Public Reports. Section 3004 requires FDA to issue a series of public reports assessing the use of patient experience data in regulatory decision-making.

Q 17.5 How does the 21st Century Cures Act support the qualification of drug development tools?

Section 3011 requires the Secretary to establish a process for the qualification of drug development tools for use in supporting or obtaining FDA approval for, or investigational use of, a drug or biologic. Drug development tools are defined broadly to include biomarkers, clinical outcomes assessments, or any other measure that the Secretary determines "aids drug development and regulatory review for purposes of this section."[9]

Drug development tools that are determined to be qualified by the Secretary may be used by any person within the context for which they have been qualified. This includes supporting or obtaining approval or licensure of a drug or biologic product, or supporting the investigational use of a drug or biologic product.

The Secretary is required to issue guidance on the implementation and regulatory framework of the drug development tool qualification process, as well as to engage in a "collaborative public process" to establish a taxonomy for the classification of biomarkers (and other related scientific concepts) for use in drug development. The Secretary is also required to convene a public meeting, before December 13, 2018, and issue a report before December 13, 2021, regarding the qualification process.

Q 17.6 How does the Cures Act support the development of drugs and biologics for rare diseases?

Section 3012 allows sponsors of a drug or biologic application for a "genetically targeted drug" or a "variant protein targeted drug" to leverage data and information previously developed and submitted by the same sponsor (or another sponsor with a contractual right of reference to such data and information) in another product application. The purpose of this section is to "facilitate the development, review, and approval of genetically targeted drugs and variant protein targeted drugs to address an unmet medical need in one or more patient subgroups, including subgroups of patients with different mutations of a gene, with

respect to rare diseases or conditions that are serious or life-threatening," and to "maximize the use of scientific tools or methods, including surrogate endpoints and other biomarkers, for such purposes."[10]

Additionally, section 3015 of the Cures Act expands the scope of the Orphan Drug Grant Program, providing that grants may be used for "prospectively planned and designed observational studies and other analyses conducted to assist in the understanding of the natural history of a rare disease or condition and in the development of a therapy."

The Cures Act also reauthorized the pediatric rare disease priority voucher program until 2020.[11]

Q 17.7 How does the Cures Act support continuous manufacturing?

Traditionally, pharmaceuticals have been produced using "batch manufacturing," which involves hold times for quality testing between multiple, discrete steps. During the hold times, the materials may be shipped to different facilities, potentially adding substantial time to production. In contrast, pharmaceuticals made using "continuous manufacturing" are moved nonstop through an assembly line of integrated components in a single facility, which reduces both the production time and the likelihood for human error.[12]

Section 3016 supports the use of continuous manufacturing, by authorizing the Secretary to issue grants to institutions of higher education and nonprofit organizations for the purpose of studying and recommending improvements to the process of continuous manufacturing for drugs and biologics. During fiscal year 2017, FDA granted an award to the University of Connecticut to develop and build a continuous manufacturing platform, as well as to create a library based on Graphical User Interfaces.[13]

Q 17.8 What does the Cures Act do to modernize trial design and evidence development?

Section 3021 of the Cures Act requires the Secretary to convene a public meeting and to issue guidance, for the purpose of assisting sponsors in incorporating complex adaptive and other novel trials designs into proposed clinical protocols and applications for new drugs and biologics.

The public meeting on "Promoting the Use of Complex Innovative Designs in Clinical Trials" was held on March 20, 2018. [14]

Q 17.9 How does the Cures Act advance the use of real world evidence to support regulatory decision-making?

Real world evidence is defined as "data regarding the usage, or potential benefits or risks, of a drug derived from sources other than randomized clinical trials."[15] Such evidence includes data related to healthcare delivery and its outcomes, which may be derived from electronic health records, claims and billing data, product and disease registries, patient-related activities in outpatient or home settings, or health monitoring devices.

Section 3022 of the Cures Act requires the Secretary to establish a program to evaluate the potential use of real world evidence to help support the approval of a new indication for an already approved drug, and to help support or satisfy post-approval study requirements. The Secretary is required to first publish a draft framework, in consultation with a diverse set of stakeholders. The real world evidence program must be implemented by December 13, 2018.

Q 17.10 How does the Cures Act streamline the clinical data that product sponsors must submit to support the approval of a new indication of an already approved drug?

For indications that the Secretary determines are "appropriate for summary review," section 3031 authorizes the Secretary to rely upon a summary of clinical data that demonstrates the safety and effectiveness of a drug to support the approval of a new indication for an already approved drug or biologic. A supplemental application is eligible for summary review, only if there is existing data available and acceptable to the Secretary demonstrating the safety of the product, and the data used to develop the qualified data summaries are submitted to the Secretary as part of the supplemental application.

Q 17.11 What is Expanded Access, and how is it addressed in the Cures Act?

FDA's Expanded Access program, also known as "compassionate use," in certain circumstances allows for the use of an investigational medical product on an individual patient basis, or for a small set of patients, outside of a broader clinical trial protocol.

While the Cures Act does not amend the standards or criteria for the Expanded Use program, section 3032 of the Cures Act requires manufacturers or distributors of investigational drugs "for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions" to make their policy for evaluating Expanded Access requests publicly available on their website. The policy must include contact information for the manufacturer or distributor, procedures for making such requests, general criteria for evaluating the requests, anticipated length of time that the manufacturer or distributor will need to acknowledge receipt of the request, and a reference to the clinical trial record containing information about the expanded access for such drug.

Q 17.12 How does the Cures Act advance regenerative medicine therapies?

The Cures Act includes several provisions that support the approval of regenerative medicine therapies. Regenerative Medicine therapies include "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products," except for those regulated solely under section 361 of the Public Health Service Act [Regulations to Control Communicable Diseases] and part 1271 of title 21 of the Code of Federal Regulations [Human Cells, Tissues, and Cellular and Tissue-Based Products].[16]

Most significantly, section 3033 required the Secretary to establish an accelerated

approval pathway for regenerative medicine advanced therapies (RMAT), which are "intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition," and for which "preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs" for such disease or condition. The Secretary must determine whether a RMAT meets the criteria for accelerated approval within sixty days after receipt of a request. Applications for accelerated approval may also be eligible for priority review. As of October 31, 2017, FDA had granted eleven RMAT designations.[17]

The Cures Act also requires the Secretary to:

- Issue draft and final guidance, clarifying how the Secretary will evaluate medical devices used in the recovery, isolation or delivery of regenerative advanced therapies.[18] FDA issued draft guidance on the Evaluation of Devices Used with Regenerative Medicine Advanced Therapies in November 2017;[19]
- Submit annual reports to Congress on the number and type of applications for regenerative advanced therapies filed, approved, licensed, withdrawn, or denied, and how such applications were granted accelerated approval or priority review. The first report to Congress was due February 28, 2018, and the subsequent reports are due before March 1 of each calendar year thereafter; [20] and
- In consultation with the National Institute of Standards and Technology (NIST) and stakeholders, develop standards and consensus definition of terms for the development, evaluation, and review of regenerative medicine therapies and regenerative advanced therapies.[21]

Q 17.13 How does the Cures Act support the development of antimicrobial therapies?

Section 3042 creates a new limited population pathway for antibacterial or antifungal drugs that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs. Under this new pathway, FDA's safety and efficacy determination would only reflect the "benefit-risk profile of such drug in the intended limited population, taking into account the severity, rarity, or prevalence of the infection the drug is intended to treat and the availability or lack of alternative treatment in such limited population." FDA, however, would require drugs approved under this pathway to disclose prominently on labeling and promotional materials that the drug is indicated for use in a limited and specific population of patients.

Apart from the development of new antimicrobial therapies, the Cures Act also includes provisions supporting antimicrobial resistance monitoring,[22] and clarifying the Secretary's authority to efficiently update susceptibility test interpretive criteria[23] for antimicrobial drugs when necessary for public health.[24]

Medical Device Development and Review

Q 17.14 What is the Breakthrough Device pathway?

Section 3051 of the Cures Act established a new expedited pathway for "breakthrough devices," which are devices intended to provide for "more effective treatment or diagnosis of life-threatening or irreversibly debilitating human diseases or conditions." Under the Breakthrough Devices program, devices may be eligible for priority review if either: (a) they represent a "breakthrough technology;" (b) there are no approved or cleared alternatives; (c) they offer significant advantages over the alternatives; or (d) the availability of the device is in the "best interest of patients." Sponsors are required to request designation as a breakthrough device before submitting the device application, and the Secretary must respond within sixty calendar days of receipt.

On October 25, 2017, FDA issued draft guidance, describing the policies that the Agency intends to use to implement the Breakthrough Device Program.[25]

Q 17.15 What is the Humanitarian Device exemption, and how did the Cures Act expand the exemption?

The Humanitarian Device Exemption Program was created under the Safe Devices Medical Act of 1980, to create a new regulatory pathway for medical devices intended for diseases or conditions that affect rare populations.[26] Under this exemption, devices are exempt from the effectiveness requirements, under sections 514 and 515 of the Federal Food, Drug, and Cosmetic Act, and are subject to certain profit and use restrictions.

Section 3052 of the Cures Act provided FDA with the authority to apply the humanitarian device exemption to devices that treat diseases and conditions that affect up to 8,000 individuals in the United States. The prior cap was 4,000 individuals.

Q 17.16 How does the Cures Act advance least burdensome review of medical devices?

Since 1997, FDA has been required to consider the "least burdensome means" of evaluating medical devices for marketing.[27] Section 3058 requires FDA to take affirmative steps to ensure that the Agency is following this directive. This includes requiring FDA employees to receive training on the least burdensome requirements and auditing to track the implementation of the requirements. Additionally, this section clarifies that when FDA requests additional information from an applicant, then the Agency "must consider the least burdensome appropriate means necessary to demonstrate a reasonable assurance of device safety and effectiveness."

FDA updated its guidance on the least burdensome review of medical devices in December 2017.[28]

Q 17.17 Which types of medical software are regulated as medical devices?

Section 3060 of the Cures Act clarifies which types of medical software are regulated as medical devices. The law excludes from being regulated as a medical device several types of

"software functions," including software for administrative support of a healthcare facility, for maintaining and encouraging a healthy lifestyle, and certain types of electronic patient records. Conversely, the Cures Act states that medical software shall be regulated as a device if the Secretary finds that use of the software function "would be reasonably likely to have serious adverse health consequences" and if the Secretary identifies such software functions in a final order.

FDA has since issued several guidance documents clarifying the scope of medical software regulation, including:

- Draft Guidance for Industry and Food and Drug Administration Staff: Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act.[29]
- Draft Guidance for Industry and Food and Drug Administration Staff: Clinical and Patient Decision Support Software.[30]
- Guidance for Industry and Food and Drug Administration Staff: Medical Device Accessories—Describing Accessories and Classification Pathways.[31]

Other Provisions

Q 17.18 What are combination products, and does the Cures Act impact the process under which such products are reviewed?

Combination products are therapeutic and diagnostic products that combine two or more FDA-regulated components (that is, drugs, devices, and/or biological products).[32] Because combination products involve components that would traditionally be regulated under different FDA authorities, these products blur the conventional lines of separation between FDA's medical product centers—the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).

Section 3038 requires the Secretary to assign a primary Agency center to lead the premarket review of a combination product, based on the "primary mode of action" of the combination product. If a sponsor disagrees with the Secretary's determination of the primary mode of action, the sponsor will have an opportunity to request a substantive rationale and to propose additional studies. Sponsors also will have an opportunity to request a meeting with the Agency to address the standards and requirements for market approval or clearance, other issues relevant to such combination product, and to identify subjects for future discussion.

The Cures Act also requires the Secretary to issue guidance on the structured process of managing pre-submission interactions with sponsors developing combination products, best practices for ensuring that feedback in the pre-submission interactions represents the Agency's best advice, and information on meetings between the sponsor and FDA.

Q 17.19 How does the Cures Act advance the development and availability of Medical Countermeasures?

Medical Countermeasures (MCMs) are FDA-regulated products that may be used in the event of a potential public health emergency stemming from a terrorist attack with chemical, biological or radiological/nuclear (CBRN) material, a naturally occurring emerging disease, or a natural disaster.[33] MCMs may include vaccines, blood products, antimicrobial or antiviral drugs, diagnostic tests to identify threat agents, or personal protective equipment.

Subtitle H of title III of the Cures Act clarifies the Secretary of HHS's role in developing and procuring MCMs. Notably, section 3086 establishes a transferable, priority review voucher to encourage the development of treatments for agents that present national security threats. Under this voucher, the Secretary is required to review and take action on the product application within six months of receipt. This MCM priority voucher program sunsets after October 1, 2023.

Additionally, the Cures Act modifies FDA's Emergency Use Authorization (EUA) authority, under which the Agency may allow unapproved medical products or unapproved uses of approved medical products to be used, in an emergency, to diagnose, treat, or prevent serious or life-threatening diseases or threats caused by CBRN threat agents when there are no adequate, approved, and available alternatives.[34] Section 3088 of the Cures Act clarifies that FDA's EUA authority applies to certain unapproved animal drugs and unapproved uses of approved animal drugs.

Q 17.20 How does the Cures Act support the coordination between FDA's product review centers?

Section 3073 of the Cures Act directs the Secretary to establish one or more "Intercenter Institutes" focused around a major disease area or areas. The goal of these institutes is to help coordinate and streamline activities in major disease areas between the drug, biologics, and device centers, and to improve the regulation of combination products.

The first Intercenter Institute, the Oncology Center of Excellence, was launched on January 19, 2017.[35] In its first year, the Oncology Center of Excellence approved sixteen new drug and biologic applications, including the first two cell-based gene therapies. The Center also approved thirty supplemental drug and biologic applications, two biosimilar applications, and cleared or approved several in vitro diagnostics.[36]

Q 17.21 Does the Cures Act address the dissemination of healthcare economic information?

Section 3037 of the Cures Act amended section 114 of the Food and Drug Administration Modernization Act (FDAMA), to clarify and facilitate the dissemination of healthcare economic information (HCEI). This section:

- Broadened the definition of HCEI to expand the types of HCEI materials and

analyses firms could prepare and use with payors or formulary committees to include "any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug." The expanded definition would explicitly allow HCEI to be "comparative to the use of another drug, to another health care intervention, or to no intervention."

- Extended the dissemination of HCEI explicitly to payors generally, as well as formulary committees or other similar entities with knowledge and expertise in the area of healthcare economic analysis and the selection of drugs for coverage or reimbursement.
- Clarifies that HCEI must only "relate" to an FDA-approved indication of a drug, rather than be "directly" related to such approved indication. However, this section explicitly does not protect HCEI that "relates only" to an unapproved indication.
- Requires manufacturers to, where applicable, affix to HCEI materials and communications "a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug."

Q 17.22 Other than the medical innovation provisions, what other policies are in the Cures Act?

The Cures Act is an extensive law, which at its core includes policies to advance the discovery, development, and delivery of new cures and therapies. Although the bill in its entirety is titled the "21st Century Cures Act," the Cures Act, in fact, is only the first of the bill's three divisions:

- Division A: 21st Century Cures
- Division B: Helping Families in Mental Health Crisis
- Division C: Increasing Choice, Access, and Quality in Health Care for Americans

As is often the case with significant pieces of legislation, the Cures Act served as a "legislative vehicle" for many other policies, which fall within the healthcare committees of jurisdiction, to become law. In addition to the provisions impacting FDA and product development, the Cures Act also includes several sections on human research subjects and patient privacy,[37] mental health and substance use disorder,[38] and Medicare and Medicaid reforms.[39] Several of these other sections were included as "pay-fors" to help offset the cost to the federal government that resulted from enacting the law.[40]

Current Status and Implementation

Q 17.23 Has FDA started implementing the Cures Act?

Yes. On July 7, 2017, FDA made public its 21st Century Cures Act Work Plan,[41] which provides detail on how the Agency will allocate funds to implement the new statutory authorities granted to the Agency. As previously described in this chapter, title III of the Cures Act provided FDA with several new authorities aimed at enhancing and accelerating FDA's processes for reviewing and approving new drugs, biologics, and medical devices. The law also authorized $500 million over ten years to an FDA Innovation Account to help the Agency carry out these new authorities.[42]

Q 17.24 How can I track the status of FDA's implementation of the Cures Act?

The Agency has posted a chart of FDA-related requirements and deliverables under the Cures Act on its website.[43] This document is organized by Cures Act section, and lists the statutory deadline, the FDA component responsible for implementing the requirement, and the date that each requirement is completed. The chart is intended to serve as a tracking tool to help the public follow FDA's progress in implementing the Cures Act.

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1. 21st Century Cures Act Pub. L. No. 114-255 (2016) ["Cures Act"], ://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.

2. Subtitle B of title II encourages the Secretary of Health and Human Services (HHS) to out the Precision Medicine Initiative, including the All of Us Research Program, which to gather long-term data from at least one million human subjects. As such, the Cures Act des several privacy protections, including establishing a certificate of confidentiality for ally funded research, exempting certain individually identifiable biomedical information disclosure under the Freedom of Information Act, and authorizing the NIH to establish lrails for sharing data that involves human subjects.

3. Subtitle C of title II supports young and emerging scientists, including by coordinating olicies and programs within the Institutes that are focused on promoting and providing rtunities for new researchers and earlier research independence, as well as establishing ate loan repayment programs for intramural and extramural researchers.

4. Subtitle D of title II includes several provisions that streamline NIH administration and ase regulatory burdens on grantees, including requiring NIH to develop a Strategic Plan at every six years, requiring the Secretary and Director of NIH to review current policies and ement measures to reduce administrative burdens on researchers, and requiring the NIH to collaboration between clinical research projects funded by national research institutes and rs that collect similar data.

5. FDA, The Voice of the Patient: A Series of Reports from FDA's Patient-Focused Drug lopment Initiative, ://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm.

6. Cures Act § 3001 defines "Patient experience data" as "data that—

> are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and
>
> are intended to provide information about patients' experiences with a disease or condition, including—
>
> (A) the impact of such disease or condition, or a related therapy, on patients' lives; and
>
> (B) patient preferences with respect to treatment of such disease or condition."

7. FDA, 21st Century Cures Act Deliverables, ://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstoth CAct/21stCenturyCuresAct/ucm562475.htm.

8. FDA, Plan for Issuance of Patient-Focused Drug Development Guidance (May 2017), ://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.

9. *See* Cures Act, § 3011 [Qualification of Drug Development Tools].

10. *See* Cures Act, § 3012 [Targeted Drugs for Rare Diseases].

11. *See* Cures Act, § 3013 [Reauthorization of Program to Encourage Treatments for Rare ıtric Diseases].

12. FDA, Modernizing the Way Drugs Are Made: A Transition to Continuous ıfacturing, https://www.fda.gov/Drugs/NewsEvents/ucm557448.htm.

13. Testimony of Scott Gottlieb, House Energy and Commerce Subcommittee on Health ing on Implementing the 21st Century Cures Act: An Update from FDA and NIH, p. 10 . 30, 2017), http://docs.house.gov/meetings/IF/IF14/20171130/106667/HHRG-115- -Wstate-GottliebS-20171130.pdf.

14. Public Meeting on "Promoting the Use of Complex Innovative Designs in Clinical s" (Mar. 20, 2018), https://www.fda.gov/downloads/Drugs/NewsEvents/UCM601630.pdf.

15. *See* Cures Act, § 3022 [Real World Evidence].

16. *See* Cures Act, § 3033 [Accelerated Approval for Regenerative Advanced Therapies].

17. Testimony of Scott Gottlieb, *supra* note 13.

18. *See* Cures Act, § 3034 [Guidance Regarding Devices Used in the Recovery, Isolation, or ery of Regenerative Advanced Therapies].

19. FDA, Draft Guidance for Industry: Evaluation of Devices Used With Regenerative cine Advanced Therapies (Nov. 2017), ://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInfor ɔn/Guidances/CellularandGeneTherapy/UCM585417.pdf.

20. *See* Cures Act, § 3035 [Report on Regenerative Advanced Therapies].

21. *See* Cures Act, § 3036 [Standards for Regenerative Medicine and Regenerative Advanced apies].

22. *See* Cures Act, § 3041 [Antimicrobial Resistance Monitoring].

23. Defined to mean: (1) one or more specific numerical values which characterize the ptibility of bacteria or other microorganisms to the drug tested; and (2) related orizations of such susceptibility, including categorization of the drug as susceptible, nediate, resistant, or such other term as the Secretary determines appropriate.

24. *See* Cures Act, § 3044 [Susceptibility Test Interpretive Criteria for Microorganisms; nicrobial Susceptibility Testing Devices].

25. FDA, Breakthrough Devices Program: Draft Guidance for Industry and Food and Drug inistration Staff (Oct. 25, 2017), ://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDoc nts/UCM581664.pdf.

26. 21 U.S.C. § 360j(m).

27. *See* Pub. L. No. 105-115 (1997), codified as amended at 21 U.S.C. § 360c(a)(3)(D)(ii) e Secretary shall consider, in consultation with the applicant, the least burdensome opriate means of evaluating device effectiveness that would have a reasonable likelihood of ing in approval.").

28. FDA, Draft Guidance for Industry and Food and Drug Administration Staff: The Least ensome Provisions: Concept and Principles (Dec. 15, 2017), ://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-locuments/document/ucm588914.pdf.

29. FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Changes to ing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act . 8, 2017), https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-locuments/document/ucm587820.pdf.

30. FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Clinical Patient Decision Support Software (Dec. 8, 2017), ://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDoc nts/UCM587819.pdf.

31. FDA, Guidance for Industry and Food and Drug Administration Staff: Medical Device ssories—Describing Accessories and Classification Pathways (Dec. 30, 2017), ://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDoc nts/UCM429672.pdf.

32. FDA, About Combination Products, ://www.fda.gov/CombinationProducts/AboutCombinationProducts/default.htm.

33. FDA, What Are Medical Countermeasures?, ://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AbouMi/ucm431268.htm.

34. 21 U.S.C. § 360bbb-3.

35. Press Release, FDA, Statement from FDA Commissioner Robert Califf, M.D., ›uncing FDA Oncology Center of Excellence Launch (Jan. 19, 2017), ://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm537564.htm.

36. The One Year Anniversary of the Oncology Center of Excellence (Jan. 19, 2018), ://blogs.fda.gov/fdavoice/index.php/tag/oncology-center-of-excellence/.

37. Several sections of the Cures Act impact human subject and patient privacy. These de:

Sec. 2012. Privacy Protection for Human Research Subjects.

Sec. 2013. Protection of Identifiable and Sensitive Information.

Sec. 2014. Data Sharing.

Sec. 2063. Accessing, Sharing, and Using Health Data for Research Purposes.

Sec. 4006. Empowering Patients and Improving Access to their Electronic Health mation.

Division B, Title XI. Compassionate Communication on HIPAA.

38. *See* Cures Act, Division B [Helping Families in Mental Health Crisis].

39. *See* Cures Act, Division C [Increasing Choice, Access, and Quality in Health Care for :icans].

40. The Cures Act offsets are under title V of Division A of the law. The offsets include:

Sec. 5001. Savings in the Medicare Improvement Fund.

Sec. 5002. Medicaid reimbursement to States for durable medical equipment.

Sec. 5003. Penalties for violations of grants, contracts, and other agreements.

Sec. 5004. Reducing overpayments of infusion drugs.

Sec. 5005. Increasing oversight of termination of Medicaid providers.

Sec. 5006. Requiring publication of fee-for-service provider directory.

Sec. 5007. Fairness in Medicaid supplemental needs trusts.

Sec. 5008. Eliminating Federal financial participation with respect to expendituresunder caid for agents used for cosmetic purposes or hair growth.

Sec. 5009. Amendment to the Prevention and Public Health Fund.

Sec. 5010. Strategic Petroleum Reserve drawdown.

Sec. 5011. Rescission of portion of ACA territory funding.

Sec. 5012. Medicare coverage of home infusion therapy.

41. FDA, Food & Drug Administration Work Plan and Funding and Proposed Funding ations of FDA Innovation Account (June 6, 2017), ://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmen ıtstotheFDCAct/21stCenturyCuresAct/UCM562852.pdf.

42. *See* Cures Act, § 1002 [FDA Innovation Projects].

43. 21st Century Cures Act Deliverables, *supra* note 7.

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