January 2017

Memorandum

Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products

Glossary

This document discusses manufacturer communications regarding unapproved uses of approved or cleared human drugs and medical devices, including biological products, and animal drugs in nonfood producing animals. As described in Appendix A, there are some distinctions in the review processes for these different types of medical products that ultimately permit firms to market the products. In discussing these products together, this document uses several general terms,[1] which are as follows:

Approved/cleared medical product; approval/clearance	Approved/cleared medical product refers to a medical product intended for human use that may be legally introduced into interstate commerce for at least one use under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act as a result of having satisfied applicable premarket review requirements. It also refers to an approved animal or human drug that can legally be used in an extralabel use manner in animals, pursuant to sections 512(a)(4) or (5) of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 530. It also refers to devices that are exempt from premarket notification. Approval/clearance refers to the satisfaction of the applicable premarket review requirements.
Approved/cleared use	This term refers to an intended use in the labeling approved by FDA, an intended use included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that falls within an exemption from clearance under section 510 of the Federal Food, Drug, and Cosmetic Act.
Device	This term refers to a medical device intended for human use, including a device that is licensed as a biological product.
Drug	This term refers to a human drug, including a drug that is licensed as a biological product, and an animal drug that may legally be used in an extra-label manner in animals, pursuant to sections 512(a)(4) or (5) of the Federal Food, Drug, and Cosmetic, and 21 C.F.R. § 530.
FDA or Agency	This acronym or term refers to the Food and Drug Administration.
FDA Authorities	This term refers to the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, as well as implementing regulations.
Firms	This term refers to medical product manufacturers, packers, and distributors and all their representatives, including both corporate entities and natural individuals.
Health care providers	This term refers to individuals such as physicians, veterinarians, dentists, physician assistants, nurse practitioners, or registered nurses who are licensed or otherwise authorized by the state to administer or use medical products.
Medical products	This term refers to both drugs and devices.

[1] The descriptions in this table and in the Summary of Statutory and Regulatory Authority below are not intended to reflect a complete and detailed recitation of the relevant legal authority. Appendix A contains a more complete discussion of the relevant statutory provisions and implementing regulations.

Premarket review	This term refers to FDA's review of scientific evidence regarding a medical product to evaluate whether it satisfies requirements for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act that enable a medical product to be legally introduced into interstate commerce for a specified intended use. For devices, the term encompasses FDA's classification of a device type (including *de novo* classification) as well as review of premarket approval applications (PMA) and premarket notifications (510(k)).
Unapproved use	This term refers to an intended use that is not included in the labeling approved by FDA, an intended use that is not included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that does not fall within an exemption from clearance under section 510 of the Federal Food, Drug, and Cosmetic Act.

I. INTRODUCTION

The Agency is engaged in a reexamination of its rules and policies relating to firm communications regarding unapproved uses of approved/cleared medical products, with the goal of determining how best to integrate the significant and sometimes competing public health and safety interests served by FDA's regulatory approach related to unapproved uses of medical products with ongoing developments in science and technology, medicine, health care delivery, and constitutional law. To that end, FDA held a two-day public hearing on November 9-10, 2016, to obtain input on these issues, and created a docket for the submission of written comments. FDA is grateful to all of the speakers at the hearing for their thoughtful presentations.

At the public hearing, a number of speakers presented legal views regarding the application of First Amendment principles to firm communications regarding unapproved uses of approved/cleared medical products. Some expressed the view that FDA had not sufficiently discussed the First Amendment in the notice of the public hearing. FDA is now placing this Memorandum in the docket for the public hearing to provide additional background and seek input on the full range of issues to consider as part of its reexamination, including First Amendment considerations. FDA is seeking comment on the public health and safety interests advanced by the FDA Authorities, many of which are discussed in this document, as well as comment on what approaches could integrate and advance these sometimes competing public health and safety interests with First Amendment jurisprudence.

II. SUMMARY OF STATUTORY AND REGULATORY AUTHORITY

The FDA Authorities prohibit the introduction (or causing the introduction) into interstate commerce of a medical product that fails to comply with applicable requirements for approval, licensing, or clearance, or is otherwise misbranded or adulterated.[2] This prohibition includes introducing (or causing the introduction) into interstate commerce a medical product that is intended for a use that has not been approved or cleared by FDA, even if that same product is approved or cleared for a different use.

Congress developed the premarket review frameworks for medical products in response to public health tragedies, realizing that: (1) safety and effectiveness need to be appropriately studied by firms and then independently evaluated for each intended use because the evidence that demonstrates effectiveness and safety for one use of a product provides no guarantee of the effectiveness or safety of additional uses; and (2) exclusive reliance on post-market remedies, such as enforcement actions for false or misleading labeling, is inadequate because it does not prevent consumers from experiencing harm from unsafe and/or ineffective treatments.

The concept of intended use is fundamental to the regulatory approach embodied in the FDA Authorities. Intended use is an element in the definitions of drug and device and thus helps

[2] *See supra* note 1.

define the scope of FDA's jurisdiction over medical products.[3] For example, charcoal is the key ingredient in common products sold as fuel, a use outside FDA's jurisdiction, but charcoal products are drugs when intended for emergency treatment of poisoning by ingestion. Thus, it is the intended use to treat poisoning that is key to distinguishing a product that might be sold to fuel a fire from a drug subject to the FDA Authorities. In addition to establishing a threshold element that makes the product subject to the drug or device provisions of the FDA Authorities, intended use may affect the appropriate premarket review pathway for a device and also is a separate element in establishing certain violations under the FDA Authorities.

For both drugs and devices, the intended use of a product can be established from its label, accompanying labeling, promotional claims, advertising, and any other relevant source.[4] As the legislative history of the Federal Food, Drug, and Cosmetic Act (FD&C Act) reflects, "[t]he manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put."[5] Accordingly, a firm's communications are relevant to establishing whether its product is subject to the FDA Authorities.

FDA's regulatory authority extends to the labeling and certain advertising of medical products, which again involve firm communications. This type of regulatory framework is not unique to FDA's regulation of medical products – numerous Federal and state agencies regulate the conduct of particular industries, including the content of their commercial communications.[6]

While there are distinctions in the review frameworks for different types of medical products,[7] as a general matter, FDA considers the benefit-risk profile of the product for each intended use during the premarket review process. In that process, FDA considers whether the established health benefits of the product for a particular use outweigh the identified risks of the product. The separate weighing of benefit and risk for each intended use is critical because evidence establishing effectiveness in one setting (e.g., for a particular disease or when a specified dosage is used) does not establish effectiveness of the same product in another setting (e.g., for a

[3] 21 U.S.C. §§ 321(g)(1)(B)-(C) and (h)(2)-(3); *see also* United States v. Caronia, 703 F.3d 149, 170-71 (2d Cir. 2012) (Livingston, J. dissenting).

[4] *See, e.g.,* United States v. Storage Spaces Designated Nos. "8" & "49", 777 F.2d 1363, 1366 (9th Cir. 1985); Action on Smoking and Health v. Harris, 655 F.2d 236, 239 (D.C. Cir. 1980). Intended use can be established not only by the firm's subjective claims of intent, but also by objective evidence, which may include a variety of direct and circumstantial evidence. 21 C.F.R. §§ 201.128 and 801.4.

[5] *See* United States v. An Article … Sudden Change, 409 F.2d 734, 739 (2d Cir. 1969) (quoting S. REP. NO. 361, 74 Cong., 1st Sess.).

[6] *See* Sorrell v. IMS Health Inc., 564 U.S. 552, 585-92 (2011) (Breyer, J., dissenting) (discussing examples of regulatory authority related to the content of communications of particular industries); *see also* Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 549-50 (2014) ("This pattern in the law - using intent as the predicate for regulation and then using speech as evidence of intent - is quite common, and not peculiar to pharmaceutical regulation. As early as 1888, the Supreme Court affirmed a state court criminal conviction for someone who manufactured an 'oleaginous substance' otherwise perfectly legal, except that he intended for it to be used as food, and thereby his manufacture of it fell under the purview of a state regulator. Similarly, a hollow piece of glass with a bowl on the end is illegal drug paraphernalia only if intended for such illicit uses. An automobile is not subject to regulation by the Federal Aviation Administration, unless it is 'intended to be used for flight in the air.'") (citations omitted).

[7] *See* Appendix A.

different disease or when a different dosage is used). Similarly, a product considered safe in one setting might not be considered safe in another setting. Despite the distinctions in the legal frameworks and associated differences in premarket review pathways and processes, underlying them all are the goals of spurring innovation based on reliable scientific evidence of effectiveness and of ensuring the safety and effectiveness of medical products for each intended use.

III. PUBLIC HEALTH INTERESTS RELATED TO FIRM COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED/CLEARED MEDICAL PRODUCTS AND MEASURES THAT ADVANCE THESE INTERESTS

Firm communications regarding unapproved uses of approved/cleared medical products implicate several substantial government interests related to health and safety. Among these are motivating the development of robust scientific data on safety and efficacy; maintaining the premarket review process for safety and efficacy of each intended use in order to prevent harm, protect against fraud, misrepresentation, and bias, and to prevent the diversion of health care resources toward ineffective treatments; ensuring required labeling is accurate and informative; protecting the integrity and reliability of promotional information regarding medical product uses; protecting human subjects receiving experimental treatments; ensuring informed consent; maintaining incentives for clinical trial participation; protecting innovation incentives, including statutory grants of exclusivity; promoting the development of products for underserved patients; supporting informed decision-making for patient treatment; and furthering scientific understanding and research. All of these interests relate to FDA's larger substantial interest in protecting and promoting public health.

The FDA Authorities, among other things, motivate the development of scientific evidence that enables the reliable, population-level determination of the safety and efficacy of medical products for each intended use; require that the evidence be developed and independently reviewed before the products are marketed to the general public for each intended use; and require that the product bears labeling that identifies each approved or cleared use of the product and provides information for using the product safely and effectively for that approved or cleared use for patients. At the same time, health care providers prescribe and use approved/cleared medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their patients. Scientific or medical information regarding unapproved uses of products may help health care providers make better decisions regarding a patient, such as where the patient has a disease for which there is no approved/cleared treatment, where the patient is part of a population that has not been studied, or where all approved/cleared treatments have been exhausted. However, the use of approved/cleared medical products for unapproved uses has also been associated with harm to patients, fraud, and waste of health care resources.

Integrating the many substantial interests, some of which are in tension with each other, in a way that best promotes public health and comports with recent First Amendment jurisprudence is a complex task. Because of the importance of these and the other interests discussed below, we are making this Memorandum available for comment to help advance the dialogue about these issues. To assist in that discussion, this section identifies many of these substantial interests.

A. How the FDA Authorities Advance Public or Individual Health Interests

1. Motivating the Development of Robust Scientific Data on Safety and Efficacy

Congress mandated that firms gather data from rigorous scientific studies for each new use of a medical product by establishing scientific evidentiary thresholds for premarket review and approval/clearance. This mandate developed over time, in large part in response to conduct by firms that led to public health tragedies and insufficiency of previous regulatory authority to prevent the harm from occurring.[8] In enacting the 1962 Kefauver-Harris Amendments to the FD&C Act (which first introduced an explicit efficacy requirement for drugs), Congress recognized that poorly conducted studies and anecdotal evidence from clinical practice do not provide adequate scientific information to conduct the drug risk/benefit assessments that are necessary to protect and promote public health.[9] Due to similar concerns about unsafe and ineffective marketed devices, Congress enacted the Medical Device Amendments of 1976, which established a comprehensive scheme for the premarket and postmarket regulation of devices.[10]

The current premarket review processes for each new use of a medical product under the FDA Authorities require firms to generate the kind of data that supports a reliable conclusion that the reported results, particularly with regard to benefits (i.e., effectiveness), are caused by the use of the drug or device, and not a result of other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. These evidentiary requirements are also designed to motivate research to spur innovation based on reliable scientific evidence and to prevent harm.[11]

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[8] For example, the Food, Drug, and Cosmetic Act of 1938, which introduced the requirement that firms demonstrate a drug product to be safe before being marketed, followed the deaths of approximately 100 people from ingesting "Elixir Sulfanilamide," in which the lethal substance diethylene glycol was used as a solvent. There were no premarketing requirements that mandated that the firm test its product's safety. Similarly, the passage of the Kefauver-Harris Amendments was precipitated in part by the distribution of thalidomide, a sleeping pill that caused birth defects when taken by pregnant women. *See* Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420 (1981). Significant problems with medical devices likewise preceded the Medical Device Amendments of 1976, including significant defects in cardiac pacemakers that led to 34 voluntary recalls involving 23,000 units, and serious side effects following implantation of intraocular lenses, including serious impairment of vision and the need to remove the eyes of some patients (H.R. REP. NO. 94-853, at 8 (1976)).

[9] *See* Cooper Labs., Inc. v. FDA, 501 F.2d 772, 778 (D.C. Cir. 1974); *see also* Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 619 (1973) ("The hearings underlying the 1962 Act [the Kefauver-Harris amendments to the FD&C Act] show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.").

[10] For congressional history regarding the need for the Medical Device Amendments of 1976, *see* S. REP. NO. 94-33, at 2-6 (1975) and H.R. REP. NO. 94-853, at 5-12 (1976).

[11] *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 347 (2007) ("[D]rug regulation has come to play" an "important structural role" of "promoting a valuable form of pharmaceutical innovation - the development of credible information about the effects of drugs."); Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 560-61 (2014) (The FD&C Act "provide[s] and protect[s] an epistemic and economic process of research and discovery, one that helps physicians make more rational decisions.") (citations omitted); Tewodros Eguale et al., *Comment & Response: In Reply to In Defense of Off-label Prescribing*, 176 JAMA INTERN MED. 861-62 (June 2016) (Premarket review under the FDA Authorities "is exactly what produces

Developing scientific information sufficient to establish safety and effectiveness for new uses of medical products remains critically important because there are harms that have been associated with the use of medical products for unapproved uses – harms to health, as well as fraud and the diversion of limited resources to ineffective treatments.[12] When rigorous studies appropriately designed to evaluate a new use have not been completed and subjected to FDA's independent scientific review, there is uncertainty about both effectiveness and safety for a particular unapproved use. In late 2015, researchers announced the results of a large study of the incidence of adverse drug events associated with unapproved uses of approved drugs. The study found the risk of adverse events was higher for unapproved uses than for approved uses, and even higher when the unapproved use was not supported by reliable scientific data.[13] And, as the examples described in Appendix B illustrate, experience has shown that even widespread acceptance of an unapproved use in the medical community is not a guarantee that the medical product is safe or effective for that use.

However, to conduct rigorous clinical research that can identify a benefit caused by a medical product (and not a result of other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation), firms must invest time and resources. Many of the incentives to sponsor such research are likely to be diminished once products have been approved/cleared for at least one use and can then be legally placed into widespread distribution. The legal requirement to generate appropriate evidence to demonstrate the safety and effectiveness of medical products for each intended use creates the impetus for firms to conduct those studies for subsequent uses of products – studies that no other actor will likely have the motivation and resources to undertake. If firms can promote general public use of unevaluated uses, there may be greater potential for wide-scale public health tragedies, wasted public and private health care dollars, and fraud.[14]

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the scientific evidence that physicians need to prescribe appropriately.").

[12] *See, e.g.*, Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN MED. 55-63 (Jan. 2016) (summarizing study across cohort of 46,000 patients, and concluding that unapproved use of prescription drugs is associated with adverse drugs events, particularly where those uses lack strong scientific evidence in the form of at least one randomized controlled trial); Chester B. Good & Walid F. Gellad, *Off-Label Drug Use and Adverse Events, Turning up the Heat on Off-Label Prescribing*, 176 JAMA INTERN MED. 63-64 (Jan. 2016) (discussing reports of harm from unapproved uses of drugs); Aaron S. Kesselheim et al., *Mandatory Disclaimers On Dietary Supplements Do Not Reliably Communicate The Intended Issues*, 34 HEALTH AFFAIRS 438-46 (2015) ("Off-label drug prescribing has led to poor efficacy or harm in many instances in recent years, such as the use of nesiritide (Natrecor) for stable congestive heart failure, paroxetine (Paxil) for depression in children, antipsychotic drugs in elderly patients with dementia, and anti-epileptic medications for certain mood disorders. In each of these cases, patients were harmed by unsafe or ineffective off-label prescription drug use, which led to litigation. Manufacturers' promotional practices were found to have encouraged these off-label uses.") (citations omitted).

[13] *See* Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population,* 176 JAMA INTERN MED. 55-63 (Jan. 2016).

[14] *See* Aaron S. Kesselheim & Michelle M. Mello, *Healthcare Decisions in the New Era of Healthcare Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1585 (2014) ("There [would] be no need for companies to design these studies to meet the FDA's standards for methodological rigor if the companies have no intention of submitting an application for approval of the new use but rather intend to use the study findings only in marketing communications. Companies [could] design studies in ways that maximize the chances of obtaining a desired result and select which studies to

2. Preventing Harm to Members of the Public; Protecting Against Fraud, Misrepresentation and Bias; and Preventing the Diversion of Limited Health Care Resources Toward Ineffective Treatments

Given the harms associated with the use of medical products, Congress determined that FDA must review the safety and effectiveness of each intended use of certain medical products before the product is marketed for that use. This requirement serves at least three distinct but interrelated government interests: preventing harm to members of the public; protecting against fraud, misrepresentation, and bias; and preventing the diversion of health care resources toward ineffective treatments. The discussion below explains how the premarket review requirement advances these interests.

a. Timing of Review to Prevent Harm. Premarket review of safety and effectiveness is a very effective way to protect the public from harm; post-market remedies are often taken only after harm has occurred, and thus such remedies do not provide an equivalent level of protection. The harms premarket review protects against include:

- Direct harms to health. Many medical products have significant adverse side effects, and therefore may be deemed safe by FDA only with respect to particular uses that involve significant countervailing benefits.
- Indirect harms to health. Medical products that are ineffective cause indirect harm, including the lost opportunity to select an effective intervention against underlying disease (or the delayed diagnosis of a disease or condition in the context of diagnostic products), which is a harm that often cannot be fully remedied after it is incurred.[15] This also leads to a waste of health care resources.

The history of drug product regulation before 1962 demonstrates that exclusive reliance on post-marketing remedies, such as enforcement actions for false or misleading labeling, was inadequate to protect the public health. Those post-market remedies were not sufficient to deter some firms from making unsubstantiated or misleading claims to encourage use of their products and therefore could not prevent the often serious harm to health caused by the use of these products. Premarket approval for each intended use was necessary to prevent some firms from obtaining approval for one use, then promoting the drug for other, unapproved uses without first demonstrating through the approval process that the drug was safe and effective for each new use.[16] Likewise, premarket review of medical devices was a key feature of the Medical Device

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emphasize in promotional communications, ignoring others that do not support their promotional message."); Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427-28 (2008) (Encouraging unapproved uses "undermines the incentives for manufacturers to perform rigorous studies — and instead subtly encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice.").

[15] *See* Declaration of Robert Temple, MD, Allergan, Inc. v. United States, 1:09-cv-01879 (D.D.C. Dec. 11, 2009).

[16] *See* S. REP. NO. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (if firms were not required to demonstrate safety and effectiveness for new uses, "[t]he expectation would be that the initial claims would tend to be quite limited," and "[t]hereafter 'the sky would be the limit' and extreme claims of any kind could be made"). As

Amendments of 1976 when Congress overhauled the post-market surveillance system put in place for devices by the 1938 FD&C Act, replacing it with a comprehensive framework that included premarket review. Among the reasons for the changes to the statute was Congress' concern about unsafe and ineffective marketed devices.[17]

When what exists is preliminary scientific data, the ultimate relevance and utility of that data is often unknown. That is, one might truthfully summarize the data generated by a preliminary study without being able to determine whether any inferences or conclusions drawn from the data would ultimately be shown to be correct.[18] If the government bears the burden to prove that a communication is false or misleading, the government may not be able to meet that burden until after the evidence is generated to establish that the product is unsafe or ineffective (and relief is likely to come too late to prevent harm to members of the public). The requirement for premarket review reflects Congress' determination that, where there is an absence of scientifically robust evidence, firms should not be free to market a product based merely on conjecture or rosy predictions, even if well-intentioned or logical.[19] Where emerging and developing scientific data are not yet sufficiently complete or robust to determine that a medical product causes the observed benefit and that the risks are outweighed by the benefit, claims of safety and effectiveness are misleading. Premarket review addresses that problem by placing the burden of uncertainty on the firm – by restricting the firm's distribution of its product for an unapproved use, the requirement obligates the firm to develop robust data that enables a reliable evaluation and determination of safety and effectiveness for new uses.

b. Protecting Against Fraud, Misrepresentation and Bias through Robust Review by an Independent Scientific Agency. FDA premarket review also assures that safety and efficacy are evaluated on a population level under rigorous scientific standards by independent, scientifically expert reviewers. The history of public health tragedies caused by medical products demonstrates that there have been some unscrupulous players in the marketplace who have made deceptive or unsubstantiated claims about medical products.[20] Even

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the Secretary of Health, Education, and Welfare told Congress, "[i]t is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse-game where a firm can fool the public until the [FDA] finally catches up with him" (The Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the Comm. on the Judiciary, 87th Cong., 2d Sess. 171 (1962)).

[17] For congressional history regarding the need for the Medical Device Amendments of 1976, *see* S. REP. NO. 94-33, at 2-6 (1975) and H.R. REP. NO. 94-853, at 5-12 (1976).

[18] *See* Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment,* 94 B.U. L. REV. 545, 560-61 (2014) ("In this realm, truth or falsity is not knowable a priori. Any knowledge of truth or falsity emerges from our economic and temporal investments").

[19] *See* S. REP. NO. 87-1744 (1962), *reprinted in* 1962 U.S.C.C.A.N. 2884, 2901-2902 ("On what logical basis can one possible [sic] argue that the initial claim for a drug, say the relief of headaches, should be supported by 'substantial evidence,' but that successive claims, for instance the cure of acne, need not be so supported? The considerations which would warrant examination and approval of the initial claim would be just as appropriate and compelling for successive claims…. [Otherwise] extreme claims of any kind could be made, subject only to the very cumbersome power of the FDA to seize a single specific shipment of the drug as misbranded. It takes months or years to go through the legal st[e]ps leading to an injunction-- for contempt of court-- against the company to prevent continuing marketing of interstate commerce. In the past 2 dozen years, FDA has invoked its seizure powers against not more than two or three prescription drugs").

[20] *See generally, e.g.*, Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299 (2003).

where a firm is not deliberately manipulating the message, independent scientific review helps ensure that conclusions about the product are adequately supported and unbiased.[21] As created and assigned by Congress, FDA conducts this review to evaluate whether a medical product is safe and effective for a particular use by comparing the demonstrated therapeutic benefit of that use against the product's risks. In its premarket reviews, FDA evaluates, among other things, safety and efficacy data gathered and/or generated by the firm to verify that the applicable standards for safety and efficacy have been met. For example, in implementing these requirements for new drug applications (NDAs), FDA requires the submission of, among other things, data and information on chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; human pharmacokinetics and bioavailability; microbiology; clinical data; and statistical evaluations of clinical data.[22] Similar requirements exist for certain devices and new animal drugs.[23] FDA generally evaluates medical devices using clinical (e.g., adequate, well-controlled investigations, partially controlled studies, studies and objective trials without matched controls) and non-clinical studies (e.g., microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests) with the device.[24] Over the past several years, FDA has also developed an enhanced approach to benefit-risk assessment in regulatory decision-making for human drug and device products that takes into account the patient perspective, including on disease severity and current available options in a therapeutic area, and on the risks and benefits that matter most to them.[25] In addition to reviewing the summarized reports of studies submitted as part of an application, FDA can review underlying data and inspect clinical trial records, which allows the Agency to examine the integrity of the data on which its review is based.[26]

For each of these and other topics relevant to a particular application, FDA assigns review teams and primary reviewers who specialize in that scientific discipline to review that portion of the application and to generate a written evaluation.[27] FDA then integrates the conclusions from

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[21] *See, e.g.*, Joel Lexchin et al., *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED. J. 1167 (2003) (reviewing 30 studies finding that "[s]ystematic bias favours products which are made by the company funding the research."); Andreas Lundh et al., *Industry Sponsorship and Research Outcome*, THE COCHRANE COLLABORATION (2013) (reviewing 48 studies showing that "[s]ponsorship of drug and device studies by the manufacturing company leads to more favorable results and conclusions than sponsorship by other sources.").

[22] *See* 21 C.F.R. § 314.50. *See also* Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW. ENG. J. MED. 1727, 1730 (2008) ("In the pharmaceutical market, determining whether a drug is safe and effective for an intended use can involve dozens of FDA scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials. In essence, the agency acts as a learned intermediary on behalf of prescribing physicians.").

[23] *See* 21 C.F.R. §§ 514.1 and 814.20.

[24] *See* Appendix A for a more complete discussion of the relevant statutory provisions and implementing regulations.

[25] See FDA, *Enhancing Benefit Risk-Assessment in Regulatory Decision-Making*, *at* http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm (last updated July 7, 2015); FDA, *CDRH Patient Engagement*, *at* http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhpatientengagement/default.htm (last updated Nov. 4, 2016).

[26] *See, e.g.*, 21 C.F.R. §§ 312.58, 312.68, 511.1, and 812.145.

[27] *See* FDA, *Guidance for Review Staff and Industry, Good Review Management Principles and Practices for PDUFA Products* (April 2005), *at*

these separate review activities to determine the appropriate outcome for the application. FDA's multi-disciplinary scientific review cannot be replicated by individual health care providers.[28]

This robust independent review protects the public health in several ways. Review by an independent scientific agency ensures that any product approval/clearance is properly evidence-based and that standards are applied consistently across a class of products intended for treatment or diagnosis of a disease or condition. This process protects the public from uses for which the benefits do not outweigh the risks, either because of the direct adverse effects caused by the medical product or because the use is ineffective, which can harm patients when the choice of an ineffective product causes them to delay or forego appropriate medical treatment, as well as by exposing them to unnecessary risks. Although some of the assurances from independent review for a particular study can be obtained by review by non-governmental entities (such as peer review coordinated by a scientific or medical journal), the standards governing FDA review provide an assurance of data completeness, scientific rigor, and a thoroughness of evaluation that are not met by the more narrow examination of the peer review process, given the limited data typically available to and reviewed by peer reviewers, the more limited number of peer reviewers (and thus more limited areas of expertise), and the scope of a journal article.[29] When review is

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf; FDA, *The 510(k) Process: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], Guidance for Industry and Food and Drug Administration Staff* (July 2014) *at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf; FDA, *Acceptance and Filing Reviews for Premarket Approval Applications (PMAs), Guidance for Industry and Food and Drug Administration Staff* (Dec. 2012), *at* http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313368.pdf; FDA, *Guidance for Industry, Administrative Applications and the Phased Review Process* (May 2015), *at* http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052532.pdf.

[28] *See* Aaron S. Kesselheim et al., *FDA Regulation of Off-Label Drug Promotion Under Attack*, 309 JAMA 445, 446 (2013) ("It is not 'paternalistic' to recognize the obstacles that prevent physicians from [sorting through marketing claims and making sound decisions on their own] when it comes to off-label prescribing. FDA approval involves numerous highly skilled scientists reviewing a great deal of data for months. It is not possible for individual prescribers to conduct the same rigorous evaluation, even if such data are available to them (which they often are not) or to expect that sales representatives' presentations will effectively meet this need."); Chester B. Good & Walid F. Gellad, *Off-Label Drug Use and Adverse Events, Turning up the Heat on Off-Label Prescribing*, 176 JAMA INTERN MED. 63-64 (Jan. 2016) ("Even in situations where an off-label indication has been studied, pharmacokinetics, drug-disease interactions, and other safety considerations are unlikely to have been studied systematically to the level required during the FDA drug approval process. Likewise, few clinicians have the time or the motivation to review evidence for those off-label indications to arrive at a balanced assessment of the risks and benefits to support the appropriate use of that drug"); Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERN. MED. 295 (Mar. 2016) ("Although physicians are a more sophisticated audience, they are not in a position to substitute for regulators. Relatively few have training in research methods. Those who do have such training lack access to comprehensive clinical trial data and rely heavily on the published literature, which is skewed toward positive results."); Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427-28 (2008) ("[O]ff-label use . . . undercuts expectations that drug safety and efficacy have been fully evaluated."). *See also* Brian S. Alper et al., *How much effort is needed to keep up with the literature relevant for primary care?*, 92 J MED LIBR ASS'N 429-37 (2004) (study on overall workload of systematically keeping up with the medical literature relevant to primary care estimated that it would require 627.5 hours per month).

[29] *Compare supra* notes 22-27 and accompanying text *with* discussion regarding the limitations of the peer review process in Kerry Dwan et al., *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome*

conducted by private entities, the review could also be influenced by industry affiliation or other biases.[30] Furthermore, the results of negative trials often are unpublished, which limits stakeholders' access to data that calls into question a medical product's safety or effectiveness for a particular use.[31]

c. Preventing Diversion of Limited Health Care Resources. Promotion regarding unapproved uses of approved/cleared medical products may lead to the diversion of limited health care resources. The expenditure of resources on unsafe or ineffective products is itself wasteful, limits the availability of these resources for safe and effective treatments, and causes financial harm to consumers, private insurers, and government health care programs. In addition, when there are adverse health consequences from the use of unsafe and/or ineffective products, the additional treatment of those consequences increases costs, causing a negative impact on patients (or, for animals, caretakers), private insurers, and government health care programs.[32]

3. Ensuring Required Labeling is Accurate and Informative

Medical product labeling is intended to provide an accurate and informative statement of the scientific data and information necessary for the safe and effective use of the product. FDA plays a pivotal role in helping to ensure that required labeling for a drug or medical device is accurate and informative. For example, the FDA process for reviewing a drug firm's or certain device firm's clinical studies leads to approved product labeling that conveys important information related to the safe and effective use of the product for its intended use, such as

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Reporting Bias—An Updated Review, 8 PLOS ONE e66844 (2013); Tom Jefferson et al., *Effects of Editorial Peer Review: A Systematic Review*, 287 JAMA 2784-86 (2002); Fiona Godlee et al., *Effect on the Quality of Peer Review of Blinding Reviewers and Asking Them to Sign Their Reports: A Randomized Controlled Trial*, 280 JAMA 237-40 (1998); Mohammadreza Hojat et al., *Impartial Judgment by the "Gatekeepers" of Science: Fallibility and Accountability in the Peer Review Process*, 8 ADVANCES IN HEALTH SCI. EDUC. 75-96 (2003); Marlies van Lent et al., *Role of Editorial and Peer Review Processes in Publication Bias: Analysis of Drug Trials Submitted to Eight Medical Journals*, 9 PLOS ONE e104846 (2014); Sara Schroter et al., *Effects of Training on Quality of Peer Review: Randomized Controlled Trial*, 328 BRIT. MED. J. 673 (2004). *Also compare supra* note 26 and accompanying text (discussing FDA's ability to review underlying data and inspect clinical trial records) *with* Charlotte J. Haug, *Peer-Review Fraud — Hacking the Scientific Publication Process*, 373 NEW ENG. J. MED. 2393-95 (2015); Alok Jha, *False positives: fraud and misconduct are threatening scientific research*, THE GUARDIAN (Sept. 13, 2012) (as amended online *at* https://www.theguardian.com/science/2012/sep/13/scientific-research-fraud-bad-practice).

[30] *See, e.g., supra* note 21.

[31] See, e.g., Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016); Kerry Dwan et al., *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias—An Updated Review*, 8 PLOS ONE e66844 (2013).

[32] Roberto Cardarelli et al., *A Cross-Sectional Evidence-Based Review of Pharmaceutical Promotional Marketing Brochures and Their Underlying Studies: Is What They Tell Us Important and True?*, 7 BMC FAM. PRACTICE 1-2 (2006) (pharmaceutical industry marketing to prescribing physician creates the potential for prescribing practices that may not benefit the patient, which contribute to escalating health care costs); Michael A. Steinman & Dean Schillinger, *Drug Detailing in Academic Medical Centers: Regulating for the Right Reasons, with the Right Evidence, at the Right Time*, 10 AM. J. BIOETHICS 21, 22 (2010) (the evidence "strongly suggests that detailing achieves its intended effect of increasing the volume of prescriptions written by physicians for the higher cost, brand-name products marketed by industry.").

indications, dosage, precautions, warnings, and contraindications. Accurate and informative labeling is an essential tool to help ensure appropriate prescribing practices and use of the product; indeed, a product is misbranded if it lacks labeling that adequately informs patients and practitioners how to use the product safely for the uses for which it is intended. When medical products are used for unapproved uses, health care providers and consumers do not have the benefit of any FDA-required labeling related to that use and designed to assure there is adequate information to support safe and effective selection and administration for that use. In the absence of accurate information on how to use a medical product safely and effectively for an unapproved use, including the lack of such important information as appropriate dosing, contraindications, or instructions for use, there is a significant potential for harm to patients.

4. Protecting the Integrity and Reliability of Promotional Information Regarding Medical Product Uses

The FDA Authorities also help protect the integrity and reliability of the promotional information in the medical marketplace, which helps health care providers and consumers make informed decisions. Before these requirements were in effect, medical products were commonly marketed for uses when there was little or no evidence of their effectiveness. For example, after the passage of the Kefauver-Harris Amendments, FDA retained the National Academy of Sciences to evaluate the effectiveness of the 16,500 uses claimed on behalf of the 4,000 drugs marketed under NDAs in 1962. Seventy percent of these claimed uses were found not to be supported by substantial evidence of effectiveness, and only 434 drugs were found effective for all their claimed uses.[33] Prior to the passage of the Kefauver-Harris Amendments, the advertising of these products was subject to the Federal Trade Commission Act, including the restrictions on false advertisements.[34] Even so, the vast majority of these drugs were marketed for ineffective and/or dangerous uses.[35] In this environment, health care providers and other audiences could not trust or rely on the promotional information in the medical marketplace, as the uses for which the products were marketed were more likely to be ineffective than effective. Such an environment also made it difficult to distinguish any useful products from the shams.[36]

More recent studies have similarly found that the majority of unapproved uses for which drugs are prescribed lack adequate evidence of effectiveness,[37] and that the risk of adverse events is

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[33] *See* Weinberger v. Hynson, Westcott and Dunning, 412 U.S. 609, 621 (1973).

[34] *See* Wheeler-Lea Act of 1938, Pub. L. No. 75-447, 52 Stat. 111 (1938), amending the Federal Trade Commission Act, 15 U.S.C. §§ 52-57.

[35] *See* Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299 (2003); *see also* Kate Greenwood, *The Ban on "Off-Label" Pharmaceutical Promotion: Constitutionally Permissible Prophylaxis Against False and Misleading Commercial Speech?*, 37 AM. J. L. & MED. 278, 291-92 (2011) (describing the history of misleading firm claims in promoting unapproved uses).

[36] *See* S. REP. NO. 87-1744 (1962), *reprinted in* 1962 U.S.C.C.A.N. 2884, 2898, 2901.

[37] *See* David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERN. MED. 1021-1026 (2006) (Using data from a nationally representative survey of office-based physicians in an attempt to systematically describe the overall magnitude of off-label prescribing in general outpatient care as a function of the strength of scientific support for those practices, the authors found that 21 percent of the 725 million total drug prescriptions in 2001 were for off-label uses and that most of these off-label uses (73 percent) lacked evidence of clinical efficacy); Surrey M. Walton et al., *Prioritizing Future Research on Off-Label Prescribing: Results of a*

higher for unapproved versus approved uses, and even higher when the unapproved use is not supported by reliable scientific data.[38] Many devices and drugs that appear promising based on early stage research have ultimately failed to show clinical benefit in later phase research, while increasing risk among patients.[39] Furthermore, results for the majority of studies of failed uses are not published in peer-reviewed journals.[40]

Research has also shown that marketing of drugs toward health care providers drives prescribing practices, including prescribing for unapproved uses, and that commonly used marketing techniques can influence prescribing decisions in a manner that is not in the patient's best interest.[41] Studies have found that health care providers overestimate their knowledge of what

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Quantitative Evaluation, 28 PHARMACOTHERAPY 1443-1452 (2008) (In examining the top 25 drugs in terms of total combined off-label uses with inadequate evidence of effectiveness for January 1, 2005 through June 30, 2007, the authors found that 29 percent of all uses for these drugs were off-label and 82 percent of these off-label uses had inadequate evidence of efficacy. If uses that were supported by uncertain evidence of efficacy were also included, 90 percent of all off-label uses had either inadequate or uncertain evidence of efficacy); Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN MED. 55-63 (Jan. 2016) (In a study conducted in Quebec, Canada examining prescriptions from 2005 through 2009, 11.8 percent of the prescriptions were for off-label uses and 80.9 percent of these off-label uses lacked strong scientific evidence).

[38] Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN MED. 55-63 (Jan. 2016); Tewodros Eguale et al., *Comment & Response: In Reply to In Defense of Off-label Prescribing*, 176 JAMA INTERN MED. 861-62 (June 2016) ("Unscientific prescribing constitutes 4 of 5 off-label uses, and this unscientific prescribing has resulted in a 54% increased risk of adverse drug events compared with on-label uses.").

[39] *See, e.g.*, Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016) (the authors found that more than half of drugs entering late-stage clinical development fail during or after pivotal clinical trials, primarily because of inadequate efficacy, safety, or both).

[40] *See, e.g.*, Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016); Kerry Dwan et al., *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias—An Updated Review*, 8 PLOS ONE e66844 (2013).

[41] *See, e.g.*, Puneet Manchanda & Elisabeth Honka, *The effects and role of direct-to-physician marketing in the pharmaceutical industry: an integrative review*, 5 YALE J HEALTH POLICY LAW ETHICS 785-822 (2005) (summarizing a number of studies establishing that detailing has a significant positive impact on physician prescription behavior, even while other studies indicate many physicians do not consider information from sales representatives to be accurate); Ian Larkin et al., *Restrictions on pharmaceutical detailing reduced off-label prescribing of anti-depressants and antipsychotics in children*, 33 HEALTH AFFAIRS 1014-23 (2014) (finding that detailing strongly affected prescribing of antidepressants and antipsychotics in children, including for unapproved uses); Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERN. MED. 295 (Mar. 2016) ("To be effective, a company's marketing must also influence the prescribing patterns of physicians. . . . [T]here is a strong and specific association between pharmaceutical marketing and physician behavior, independent of the evidence supporting the products."); Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1730 (2008) ("[M]anufacturers could potentially bury physicians and patients in an avalanche of 'information' to promote drugs, including reports of individual cases, uncontrolled or biased clinical studies, and poorly conducted observational analyses . . . chosen selectively to create an appearance of safety or efficacy that would not meet FDA standards."); Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 698 (2014) ("The information that sales representatives provide is more likely to be biased than truthful. They are trained to emphasize the benefits of their product, to suppress any negative information about their product, and to highlight negative aspects of a competitor's product. Thus, although manufacturers are in a unique position to

uses are FDA-approved for drugs and assume that many unapproved uses are supported by sound scientific evidence when they are supported by uncertain or no evidence.[42] Marketing activities and communications regarding the safety and effectiveness of a medical product for a particular use that are not properly supported by scientific evidence may thus create a false or misleading impression about the safety and efficacy of the medical product for that use, which can lead to prescribing or use decisions that harm patients.[43] Examples of some marketing activities that caused such harm are described in Appendix C.

The requirements of the FDA Authorities, including the evidence generation requirements and the prohibitions on distributing products for unapproved uses, help protect the integrity and

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provide information to the medical community, they are more likely to control the information in a manner that best advances sales"); Kate Greenwood, *The Ban on "Off-Label" Pharmaceutical Promotion: Constitutionally Permissible Prophylaxis Against False and Misleading Commercial Speech?*, 37 AM. J.L. & MED. 278, 292 (2011) (discussing evidence of misleading marketing by pharmaceutical sales representatives); Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. Rev. 1539, 1581-82 (2014) (citing published reports of pharmaceutical sales representatives admitting to spinning information to convey the positive while downplaying the negative).

[42] *See* Donna T. Chen et al., *U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey*, 18 PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 1094-1100 (2009) (study examining physicians' knowledge of the FDA-label status of commonly used prescription drugs found that a significant percentage prescribed some drugs for unapproved used in the belief that that the uses were approved when there was uncertain or no evidence supporting that use).

[43] *See, e.g.*, Jerry Avorn et al., *Forbidden and Permitted Statements about Medications – Loosening the Rules*, 373 NEW ENG. J. MED. 967, 971-72 (2015) ("Considerable research shows that marketing can drive prescribing practices, which in turn can lead to adverse patient outcomes if those decisions are not evidence-based."); Micah L. Berman, *Manipulative Marketing and the First Amendment*, 103 GEORGETOWN L.J., 497, 518, 522 (2015) ("Marketing, neuromarketing, and social psychological research have all converged on 'dual-processing models' of human thought and behavior, which posit that 'behavior is produced by both intentional, conscious, 'explicit' thought and unintentional, nonconscious, 'implicit' thought.'[citation omitted] . . . [M]arketing and psychological research . . . suggests that marketers (1) are most successful when emotional content—not information—is presented to consumers, (2) can carefully craft marketing appeals (using humor and other noninformational techniques) to increase the viewer's/reader's receptivity to the marketing message while disengaging critical faculties, and (3) can influence consumer behavior without consumers being aware of the powerful effect of advertising."); Kristen E. Austad et al., *Association of Marketing Interactions With Medical Trainees' Knowledge About Evidence-Based Prescribing: Results From a National Survey*, 174 JAMA INTERN MED. 1283, 1288-89 (2014) ("[O]ur data add to the literature showing that pharmaceutical marketing is associated with less-evidence-based prescribing choices and greater inclination to prescribe brand-name products over less expensive generic options or nondrug treatment plans that have equal or greater comparative effectiveness. . . . [T]rainees with fewer connections to industry promotional activities had greater knowledge of evidence-based prescribing . . . . Our study is another reminder of the negative effects those interactions can have on the quality and cost of patient care."); Jerry Avorn et al., *Scientific versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, 73 AM. J. OF MED. 4, 7-8 (1982) ("Although the vast majority of practitioners perceived themselves as paying little attention to drug advertisements and detail men, as compared with papers in the scientific literature, the [data] revealed quite the opposite pattern of influence in large segments of the sample. . . . [T]he predominance of nonscientific rather than scientific sources of drug information is consistent with what would be predicted from communications theory and marketing research data. Drug advertisements are simply more visually arresting and conceptually accessible than are papers in the medical literature, and physicians appear to respond to this difference."); *see also generally* Shelly Chaiken et al., *Heuristic and Systematic Information Processing within and beyond the Persuasion Context*, *in* UNINTENDED THOUGHT 212 (James E. Uleman ed., 1989); Richard E. Petty & John T. Cacioppo, *The Elaboration Likelihood Model of Persuasion*, *in* ADVANCES IN EXPERIMENTAL SOCIAL PSYCHOLOGY 123 (Academic Press, Inc. 1986).

reliability of the promotional information in the medical marketplace by helping to ensure that the uses for which medical products are marketed are ones for which they have been shown to be safe and effective, and that these products have labeling that provides appropriate directions for these uses. In this way, the FDA Authorities serve to promote the flow of truthful, non-misleading, and scientifically valid promotional information.

5. Protecting Human Subjects Receiving Experimental Treatments, Ensuring Informed Consent, and Maintaining Incentives for Clinical Trial Participation

The protection of human subjects receiving experimental treatments is an important public health goal, and Congress has required FDA to issue regulations governing the investigational use of medical products in clinical trials. As Congress directed, these regulations generally require investigators to obtain informed consent before studying a medical product for an unapproved use in human subjects.[44] The regulations also prescribe other requirements for the conduct of clinical trials. These requirements are designed to provide protections to human subjects when products are studied for unapproved uses. The same protections are not routinely provided when approved/cleared medical products are prescribed to patients for unapproved uses as part of their medical care. Several presenters at the November 9-10, 2016 public hearing who experienced adverse events associated with the unapproved use of approved or cleared medical products noted that they did not know, prior to using the product, that the use for which they were prescribed the product was unapproved. They further indicated that it would have impacted their decision to use the product if they had been told that the use for which it was being prescribed for them was not approved by FDA, and advocated providing this information to patients before a product is prescribed or administered for an unapproved use.

With regard to maintaining incentives for clinical trial participation, firms' actions to promote widespread use of approved/cleared medical products for unapproved uses may undermine the clinical trial process, and thus ultimately impede the development of robust and reliable scientific data to better support medical decision-making. Particularly if there is the prospect that they may be assigned to a placebo arm, potential participants who believe they may benefit from the use of a product that has not been approved/cleared to treat their condition may decide not to join a clinical trial designed to rigorously examine safety and effectiveness of the medical product for that investigational use. If enough potential participants make the same decision, the study may not have sufficient statistical power to determine whether any observed effect is truly due to the product and not to chance, or may not be able to go forward at all. Accordingly, sponsors would have more difficulty developing data of an adequate quality and quantity to permit review and approval of the safety and effectiveness of the medical product.[45]

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[44] *See* 21 U.S.C. §§ 355(i)(4) and 360j(g)(3)(D); 42 U.S.C. § 262(a)(2)(A); 21 C.F.R. Part 50. There are narrow exceptions to the informed consent requirements. *See* 21 U.S.C. §§ 355(i)(4) and 360j(g)(3)(D); *see also* 21 C.F.R. § § 50.23 (providing exceptions to informed consent requirements in several specified situations and upon waiver by the President of the United States to a member of the armed forces); 21 C.F.R. § 50.24 (providing for exception from informed consent requirements for "emergency research").

[45] For example, with respect to human drugs, FDA has long recognized that expanded access to unapproved products has the potential to interfere with enrollment in clinical trials. In the 1987 treatment Investigational New Drug (IND) regulations, FDA authorized a treatment IND only if "[t]he drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed" (21 C.F.R.

6. Protecting Innovation Incentives, Including Statutory Grants of Exclusivity

The FDA Authorities provide robust incentives for innovation by ensuring that drug firms have meaningful patent protection and a period of marketing exclusivity (i.e., exclusive marketing rights granted by FDA upon approval of a drug) for certain innovations and for changes to approved drugs.[46] The relevant legislation, such as the Drug Price Competition and Patent Term Restoration Act (commonly known as the Hatch-Waxman Amendments), was carefully crafted by Congress to seek to ensure that, on the one hand, brand-name pharmaceutical manufacturers whose changes to their drug products meet certain criteria would have meaningful patent protection and a period of marketing exclusivity to enable them to recover their investments in the development of new products and new uses for previously approved products, spurring innovation in pharmaceutical research and development; while, on the other hand, ensuring that once applicable patent protection and exclusivity for these new drugs has expired, consumers would benefit from the rapid availability of lower-priced generic versions of innovator products.[47] During the time that relevant patent protection or exclusivity is in effect for a new condition of use, FDA may not approve other applications for the protected use. For example, if a drug is approved for one use and is later granted a period of three-year Hatch-Waxman exclusivity for a new use, FDA may not approve a generic version of that drug for that change before the expiration of the three-year exclusivity.[48] The generic drug can only be approved and labeled for non-protected conditions of use during the three-year exclusivity term,[49] and it cannot

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§ 312.34(b)(1)(iii); 52 Fed. Reg. 19466, 19476 (May 22, 1987)). Subsequent regulations for investigational device exemptions (IDEs) similarly state that FDA will only consider a treatment IDE if, among other things, "[t]he device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed" (21 C.F.R. § 812.36(b)(3); 62 Fed. Reg. 48940, 48947 (Sept. 18, 1997)). Both FDA and firms have recognized this important concern. The current regulations on expanded access for drugs also address these issues. *See* 21 C.F.R. § 312.305(a)(3).

[46] *See* 21 U.S.C. §§ 355(j)(5)(B) and (F); 21 C.F.R. § 314.108 (new drug product exclusivity); *see also* 21 U.S.C. § 360cc and 21 C.F.R. § 316.31 (orphan drug exclusivity); 21 U.S.C. § 355a (pediatric exclusivity); 21 U.S.C. § 360b(c)(2)(F). The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) (subtitle A of Title VII of Pub. L. 111-148, 124 Stat 119 (2010)) also provides for exclusivity periods for biological products licensed under section 351(a) of the Public Health Service Act (PHS Act) (see, e.g., sections 351(k)(7) & (m) of the PHS Act (42 U.S.C. §§ 262(k)(7) & (m)); section 7002(h) of the BPCI Act).

[47] H.R. REP. NO. 98-857, pt. 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647-2648. The goal of the BPCI Act is similar, in concept, to that of the Hatch-Waxman Amendments.

[48] 21 U.S.C. § 355(j)(5)(F)(iv).

[49] Three-year exclusivity does not prevent the submission or approval of every application that references the product with the exclusivity protection. Instead, it protects against the approval of a 505(b)(2) application or abbreviated new drug application (ANDA) for the conditions of approval of the original new drug application, or for a change approved in the supplemental new drug application. 21 U.S.C. § 355(j)(5)(F)(iii) and (iv). A generic drug can be approved for less than all of the indications for which the brand drug has been approved; generic applicants may carve out from proposed labeling patent or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use. *See* H.R. REP. NO. 98-857, pt.1, at 21 ("The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved."); 21 C.F.R. § 314.92(a)(1) (a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted"). The regulations at 21 C.F.R. § 314.127(a)(7) further provide that to approve a generic drug application containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are protected by patent, or

be marketed for the protected conditions of use during the exclusivity term. If firms promote their approved drugs for unapproved uses, including for conditions of use that are protected by patents or exclusivity held by another applicant, it would undermine these incentives for innovation in the FDA Authorities.[50]

7. Promoting the Development of Products for Underserved Patients

The FDA Authorities provide a number of incentives and alternative review pathways aimed at encouraging development of safe and effective medical products for underserved patient populations. For example, there are a number of FDA programs that are intended to facilitate and expedite development and review of new medical products to address unmet medical needs in the treatment of a serious or life-threatening conditions, including fast track drug designation, breakthrough therapy/device designation, accelerated drug approval, expedited access program for certain devices, and priority review drug designation. These programs help ensure that therapies for serious conditions are approved/cleared and available to patients as soon as it can be concluded that the therapies' benefits justify their risks.[51] The FDA Office of Orphan Products Development (OOPD) also works to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. OOPD implements programs that provide incentives and an alternative review pathway for sponsors to develop products for rare diseases, including through the Orphan Drug Designation program (which can result in a period of seven year orphan-drug exclusivity upon approval), the Rare Pediatric Disease Priority Review Voucher program, the Humanitarian Use Device program, and three extramural grant programs.[52] Through these programs, OOPD has successfully enabled the development and marketing of more than 575 drugs and biological products for rare diseases since 1983 and more than 65 Humanitarian Device Exemption approvals.[53] These incentives and programs recognize the importance of the public health protections advanced by the FDA premarket review framework for underserved patient populations, and are intended to facilitate the development of approved or cleared therapies for such populations. If firms promote their approved or cleared medical products for unapproved uses, these incentives and programs could be weakened.

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by exclusivity," FDA must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."

[50] *See* Spectrum Pharms., Inc. v. Burwell, 824 F.3d 1062, 1068 (D.C. Cir. 2016) (recognizing the need for FDA misbranding enforcement action to deter manufacturer promotion of a generic drug for use approved for the sponsor but not for the generic).

[51] *See* FDA, *Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014), *at* http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf.

[52] *See* FDA, *Developing Products for Rare Diseases & Conditions*, *at* http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm (last updated Jan. 5, 2017).

[53] *Id*.

B. How Firm Communications Regarding Unapproved Uses of Approved or Cleared Medical Products Can Advance Public or Individual Health Interests

1. Supporting Informed Decision-Making for Patient Treatment

In its premarket reviews, FDA evaluates, among other things, safety and efficacy data gathered and/or generated by the firm to verify whether there are adequate tests to show safety and substantial evidence of efficacy (for drugs) or a reasonable assurance of safety and effectiveness (for devices). FDA evaluates this information and makes an approval/clearance decision based on a determination of the safe and effective use of the product in the general population(s) included in the studies submitted in the application.

However, after the initial approval/clearance, questions arise in practice relating to the use of products for particular patients. Health care providers prescribe and use medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their particular patients – whose characteristics and needs may differ from the characteristics of the population studied for the approved/cleared uses. This practice may be most common in patients with diseases for which there is no proven treatment, or in patients who have exhausted all approved/cleared treatments.[54]

As discussed in the preceding section, Congress and FDA have taken steps to incentivize and expedite the successful development of more and better treatments that will be safe and effective for underserved patient populations. Notwithstanding these efforts, several presenters at the November 9-10, 2016 public hearing maintained that there is still a need for information about unapproved uses of approved or cleared products for these special populations. Thus, while the FDA Authorities have incentivized the successful development of many important treatments for underserved patient populations, the reality remains at any point in time that for some patients, approved/cleared therapies are not available or have failed. In such instances, both health care providers and patients may be interested in information about unapproved uses of products, and payers and similar entities have also expressed interest in information that is potentially relevant to coverage decisions which affect patient care.

2. Furthering Scientific Understanding and Research

In addition, reliable scientific information regarding unapproved uses may help further scientific research, such as through hypothesis generation, and increasing scientific understanding in new

[54] *See* John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y L. & ETHICS 299, 304 (2010) ("[T]here is little doubt that in oncology and pediatrics off-label prescribing is exceedingly common. . . . [I]n some therapeutic areas off-label uses are the customary, preferred treatments."); Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) ("Physicians' freedom to prescribe drugs off-label carries important advantages. It permits innovation in clinical practice, particularly when approved treatments have failed. . . . And it can provide the only available treatments for 'orphan' conditions."); Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1730 (2008) ("In certain patient groups, such as children and patients with rare diseases, off-label use may reflect the standard of care.").

and developing areas.[55] Making the data and information public may also encourage the collection of outcomes through surveillance and reporting, stimulate appropriate additional evidence generation, and identify unapproved uses that are likely to present an unreasonable risk to patients. Sharing information may also allow for collaborative efforts to develop new treatments or improve existing ones.

In September 2016, the Department of Health and Human Services (HHS) issued a final rule[56] that clarifies and expands requirements for the submission of certain objective results information from clinical trials to a publicly available website – ClinicalTrials.gov – pursuant to section 402(j) of the Public Health Service Act.[57] Neither the statute nor the rule authorize any promotion of unapproved uses of approved or cleared medical products. The rule recognizes several research-related benefits from the disclosure of this objective results data including: facilitating assessments of the quality and appropriateness of trial reporting; aiding in the identification of knowledge gaps for trials of all types of products; helping investigators avoid repeating trials on medical products that have been found to be unsafe or unsuccessful; helping determine where information might be missing from the literature (e.g., missing trials, missing outcome measures); and honoring the contribution of the clinical trial volunteers by creating a public record of the trial and its results.

* * *

FDA believes there is widespread agreement that no government interests are served by firm communications that do not fairly present reliable scientific information. A firm communication that conveys scientific information that is not truthful, complete, or balanced or that lacks scientific validity has at least the potential to mislead the audience and does not contribute meaningfully to the marketplace of ideas.[58] Similarly, firm communications that are designed to

[55] *See* Jeffrey K. Francer & Natalie A. Turner, *Responsible Clinical Trial Data Sharing: Medical Advancement, Patient Privacy, and Incentives to Invest in Research*, 8 J. HEALTH & LIFE SCI. L. 63 (2014) ("Responsible data sharing agreements between biopharmaceutical companies and qualified researchers for clinical trial data and information at different stages of the drug development process may help improve public health, increase innovative drug development, and enhance patient safety through data pooling and analysis."); Joseph S. Ross & Harlan M. Krumholz, *Ushering in a New Era of Open Science Through Data Sharing*, 309 JAMA 1355 (2013) ("Sharing maximizes the value of collected data and promotes follow-up studies of secondary research questions using existing data."); Michelle M. Mello et al., *Preparing for Responsible Sharing of Clinical Trial Data*, 369 NEW ENG. J. MED. 1651 (2013) ("Independent researchers may use aggregated participant-level data to explore questions of public health significance that have not been addressed in individual trials. Pooling of these data may increase the precision of estimates of treatment efficacy, detect safety problems unobservable in smaller samples, allow exploration of subgroup effects, and permit analysis of how therapeutic effects vary in different geographic settings because of such factors as population genetics and health care delivery systems."); John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y L. & ETHICS 299, 332-33 (2010) (publication of study results "serves to advance the science and . . . enable the medical community to better understand the safety and efficacy profile of the drug").

[56] Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64982 (Sept. 21, 2016) (to be codified at 42 C.F.R. pt. 11).

[57] 42 U.S.C. § 282(j).

[58] *See, e.g.*, Joshua M. Sharfstein & Alta Charo, *The Promotion of Medical Products in the 21st Century – Off-label Marketing and First Amendment Concerns*, 314 JAMA 1795-96 (2015) ("[T]he marketplace of ideas and physician discretion does not work well without accurate information from well-designed studies."); Spencer Phillips Hey &

cause the audience to reach safety or efficacy conclusions independent of or not supported by the available data are misleading, have the potential to harm patients, and lead to a waste of health care resources.[59]

Furthermore, the ability to adequately assess benefit and risk for an unapproved use is dramatically impacted by the objective and transparent presentation of data and information. Transparency with respect to the data and information can help ensure scientific validity by promoting scrutiny, evaluation, and public discussion of the data and information by health care entities and other interested and informed stakeholders.[60] FDA recognizes that technological and business changes are increasingly affecting medical decision-making and prescribing. There are an increasing number of entities in the health care system with a stake in evaluating evidence to assess the rational and systematic use of medical products. For example, many physicians who prescribe medicines or use devices for patient care are employed by large group practices or integrated health systems. Consolidation of practices and hospitals into integrated systems has increased the use of system measurements of quality, with an emphasis on measurement of appropriate use of medical products, including increasing use of analytics to determine access to carefully monitored formularies. Insurance carriers, health care systems, and similar entities also monitor use of medical products, restrict access based on assessments of value, and employ performance measures to monitor appropriate use and outcomes. Transparency through open access to the supportive data underlying firms' communications with these groups and with other

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Aaron S. Kesselheim, *An Uninformative Truth: The Logic of Amarin's Off-Label Promotion*, 13 PLOS MED. e1001978 (2016) ("'[T]ruthfulness' is not a sufficiently restrictive criterion for regulating promotional speech as concerns off-label medications. A better and clearer standard would demand that promotional claims must be informative, in the sense that they actually have empirical truth content, which is the assurance that FDA review and validation provides."); Joanna K. Sax, *Protecting Scientific Integrity: The Commercial Speech Doctrine Applied to Industry Publications*, 37 AM. J.L. & MED. 203, 204, 221 (2011) (stating that tactics by firms to flood the literature with positive information about their products while suppressing negative information may mislead health care providers into using harmful or inferior products); Jerry Avorn et al., *Forbidden and Permitted Statements about Medications — Loosening the Rules*, 373 NEW ENG. J. MED. 967 (2015) ("[F]or both claims of efficacy and statements about side effects, the results of individual studies can be incomplete or misleading while not being outright fraudulent; publication in a peer-reviewed journal does not in itself protect against this. Poorly designed or conducted clinical trials or observational studies can readily overstate benefits or minimize risks; unorthodox or inept statistical analyses can create the impression of efficacy or of safety even when more rigorous assessments would come to a different conclusion.").

[59] *See, e.g., supra* notes 41-43.

[60] *See* Joseph S. Ross & Harlan M. Krumholz, *Ushering in a New Era of Open Science Through Data Sharing*, 309 JAMA 1355-56 (2013) ("If science is to be progressive and self-correcting, then data, not just summary conclusions, must be open to independent scrutiny. . . . There have been too many prominent examples in which independent analyses of trial data, often made available through litigation but sometimes through public release by the National Institutes of Health, revealed important insights about medical products' relative balances of benefit and harm that were neither identified nor reported by those who generated the data. Examples include well-known medications such as digoxin, rofecoxib, rosiglitazone, and oseltamivir."); Jeffrey K. Francer & Natalie A. Turner, *Responsible Clinical Trial Data Sharing: Medical Advancement, Patient Privacy, and Incentives to Invest in Research*, 8 J. HEALTH & LIFE SCI. L. 63 (2014) ("Enhanced clinical trial data sharing may improve the integrity of clinical trials by exposing inappropriate analytical methods and selective use of data, encouraging an accurate portrayal of a drug's risk-benefit profile, and protecting against publication bias and inaccurate reporting."); Michelle M. Mello et al., *Preparing for Responsible Sharing of Clinical Trial Data*, 369 NEW ENG. J. MED. 1651 (2013) ("[C]oncern about the completeness, timeliness, and accuracy of sponsor-reported summary results" have led independent researchers to demand access to the underlying data.).

interested and informed stakeholders is critical in attempting to safeguard the integrity of the information in the communications.

IV. ENSURING A POLICY APPROACH THAT INTEGRATES THE MULTIPLE PUBLIC HEALTH INTERESTS TO MAXIMIZE PUBLIC GOOD AND REFLECTS APPROPRIATE CONSIDERATION OF THE FIRST AMENDMENT

As shown above, there can be, in certain instances, a tension between the public health interests directly advanced by the premarket review requirements and other aspects of the FDA Authorities and other important interests—particularly with regard to patient treatment decisions. As important and successful as the FDA Authorities have been, and continue to be, in incentivizing the successful development of more and better treatments that are safe and effective for more patients with different diseases, the reality remains at any point in time that for some patients, approved/cleared therapies are not available or have failed. While the goal of promoting robust research and development of new products to meet these underserved patients remains important to the public health, the latitude for health care providers to prescribe or use approved/cleared medical products for unapproved uses for their patients functions as a critical safety valve. Cognizant of this, FDA, in implementing the FDA Authorities, has sought to strike a careful balance, supporting medical decision-making for patients in the absence of better options, but doing so without undermining the measures designed to incentivize the development and approval/clearance of medical products that would reduce the need to rely on unapproved use, in light of its risks.

FDA's current implementation approach does not proscribe all firm communications about unapproved uses of approved or cleared medical products. FDA has issued guidance documents to describe some of the circumstances when it would not consider a manufacturer's distribution of reprints, clinical practice guidelines, or reference texts regarding unapproved uses of approved/cleared medical products to be evidence of intended use and/or false or misleading.[61] FDA has also issued a draft guidance on responding to unsolicited requests, which states that "FDA has long taken the position that firms can respond to unsolicited requests for information about FDA-regulated medical products by providing truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to the specific request, even if responding to the request requires a firm to provide information on unapproved or uncleared indications or conditions of use."[62] FDA has also described how industry may support scientific or educational activities (such as Continuing Medical Education programs) without being subject

[61] FDA, *Revised Draft Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (Feb. 2014), *at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf; FDA, *Good Reprint Practices for Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, Guidance for Industry* (Jan. 2009), *at* http://www fda.gov/oc/op/goodreprint.html.

[62] FDA, *Draft Guidance for Industry, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (Dec. 2011), *at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf.

to FDA regulation.[63] In addition, it has long been FDA policy not to consider a firm's presentation of truthful and non-misleading scientific information about unapproved uses at medical or scientific conferences to be evidence of intended use when the presentation is made in non-promotional settings and not accompanied by promotional materials. In a similar vein, HHS recently promulgated a rule that clarifies and expands requirements for the submission of certain objective results information from clinical trials to a publicly available website: ClinicalTrials.gov.[64] Most recently, in January 2017 FDA issued two additional draft guidance documents. One draft guidance addresses firms' communications of data and information not contained in their products' approved or required labeling but that are consistent with the FDA-approved or -required labeling and clarifies that such communications alone are not considered evidence of a new intended use.[65] The other draft guidance addresses firms' communications with payors and similar entities and provides recommendations on firms' communications to payors of health care economic information that relates to a drug's approved indication, as well as recommendations regarding firms' communications to payors about investigational drugs and devices not yet approved/cleared for any use.[66]

At our November 9-10, 2016, public meeting, a number of speakers addressed First Amendment considerations. Some asserted that FDA's current implementation approach appropriately addresses the applicable First Amendment issues. Others asserted that, after *United States v. Caronia*,[67] when an approved or cleared medical product is marketed for an unapproved use, FDA is constrained to regulating such communication only if it is false or misleading. To further this discussion, this section describes the different ways that courts and commentators have addressed the intersection of the FDA Authorities and the First Amendment. To the extent that commenters propose alternatives to FDA's current approach (whether discussed below or not), we hope that this discussion will inform your comments; it would be very helpful if you would also provide an analysis of how any proposed alternatives would advance the public health objectives the FDA Authorities are designed to promote as compared to FDA's current implementation approach and other potential alternative approaches discussed in this section.

A. Evidence of "Intended Use"

Courts have held that the government's reliance on speech as evidence of intended use under the FD&C Act does not infringe the right of free speech under the First Amendment[68] based on

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[63] FDA, *Guidance for Industry, Industry-Supported Scientific and Educational Activities* (Dec. 1997), *at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125602.pdf.

[64] Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64982 (Sept. 21, 2016) (to be codified at 42 C.F.R. pt. 11).

[65] FDA, *Draft Guidance for Industry, Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers*, (Jan. 2017), *at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[66] FDA, *Draft Guidance for Industry, Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers*, (Jan. 2017), *at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[67] 703 F.3d 149 (2d Cir. 2012).

[68] *See* Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004); United States v. Cole, 84 F. Supp. 3d 1159, 1166 (D. Or. 2015) (The FD&C Act "does not prohibit disease claims as such; it prohibits the sale of products with a particular intent, and disease claims are merely probative evidence of that intent. See 21 U.S.C. § 321(g)(1)(B); 21

Supreme Court precedent establishing that "[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent."[69] The D.C. Circuit applied that precedent in the context of the FD&C Act and held that "th[e] use of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is constitutionally valid" and hence "it is constitutionally permissible for the FDA to use speech [by the manufacturer] . . . to infer intent for purposes of determining that [the manufacturer's] proposed sale . . . would constitute the forbidden sale of an unapproved drug."[70]

Under these rulings, the FDA Authorities do not directly prohibit or restrict speech by a firm about unapproved new uses of the firm's medical products. Instead, the FDA Authorities regulate the introduction of unapproved, adulterated, or misbranded medical products into interstate commerce and the speech of firms may be relevant to establishing an element of a violation of those provisions. Courts have found that FDA can rely on a broad range of evidence, including a firm's speech, to establish intended use as a medical product and as an element of a prohibited act under the FD&C Act.[71] Although the district court in *Amarin Pharma, Inc. v. FDA* held that the *Caronia* decision foreclosed reliance (in the Second Circuit) on the use of speech as evidence of intended use in the context of an FDA enforcement action where the misbranding was based solely on truthful, non-misleading speech regarding the unapproved use of an approved drug,[72] the Second Circuit later confirmed that "*Caronia* left open the government's ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug's FDA-approved label."[73]

C.F.R. § 201.128. The First Amendment 'does not prohibit the evidentiary use of speech . . . to prove motive or intent.' *Wisconsin v. Mitchell*, 508 U.S. 476, 489 . . . (1993). When Defendants incorporate a customer testimonial into advertising material, they endorse and adopt the disease claims made in the testimonial; therefore, the testimonial is evidence of their intent that the product be used to treat disease."); United States v. Regenerative Sciences, LLC, 878 F. Supp. 2d 248 (D.D.C. 2012) (finding product is a drug under FD&C Act based on statements on company website), *aff'd*, 741 F.3d 1314 (D.C. Cir. 2014); United States v. Livdahl, 459 F. Supp. 2d 1255, 1268 (S.D. Fla. 2005) (allegation that defendant promoted product as a cheap alternative to Botox in workshops, booths, and emails was constitutionally permissible as the indictment sought to punish the defendant "not for his speech, but for the underlying crime evidenced by that speech"); United States v. Lane Labs-USA, Inc., 324 F. Supp. 2d 547, 578 (D.N.J. 2004) ("[F]ollowing Whitaker, the Government's restriction of certain labeling, as well as the dissemination of third-party literature, does not violate free speech principles."); *see also* United States v. Article of Drug Designated B-Complex Cholinos Capsules, 362 F.2d 923, 927 (3d Cir. 1966) (statements made by a lecturer employed by a party may be considered evidence of intended use without violating the First Amendment); United States v. General Nutrition, Inc., 638 F. Supp. 556, 562 (W.D.N.Y. 1986) ("[I]t is not speech per se which invokes prosecution." Instead, the government "contends that in certain circumstances such commentary may become part of the labeling of the product and serve, in a sense, as evidence of a violation of the Act," and that is constitutionally permissible).

[69] Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993).

[70] Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004).

[71] *See, e.g.*, United States v. Storage Spaces Designated Nos. 8 & 49, 777 F.2d 1363, 1366 (9th Cir. 1985); Action on Smoking and Health v. Harris, 655 F.2d 236, 239 (D.C. Cir. 1980); Nat'l Nutritional Foods Ass'n v. Mathews, 557 F.2d 325, 334 (2d Cir. 1977). FDA's regulations reflect this line of cases. *See* 21 C.F.R. §§ 201.128 and 801.4.

[72] 119 F. Supp. 3d 196 (S.D.N.Y. Aug. 7, 2015).

[73] United States ex rel. Polansky v. Pfizer, Inc., 822 F.3d 613 n.2 (2d Cir. 2016).

B. Commercial Speech under *Central Hudson*

Under the *Central Hudson* framework, the government may prohibit commercial speech that is false, inherently misleading, or actually misleading, and commercial speech related to illegal activity.[74] If the commercial speech is truthful or potentially misleading, the government may nonetheless impose restrictions on that speech if the restrictions advance a "substantial" government interest and are no "more extensive than is necessary to serve that interest."[75]

Communications that are not supported by objective and scientifically valid evidence are misleading, have the potential to harm patients, and lead to a waste of health care resources. *Central Hudson* permits the prohibition of such false or inherently misleading communications outright. However, even with respect to communications that are not false or inherently misleading, under the test set forth in *Central Hudson*, restrictions on speech are permitted if they advance substantial government interests in ways that are not more extensive than is necessary to serve those interests. The government's multi-faceted interests in the public health are substantial and, as described in more detail above, the relevant FDA Authorities directly advance many of those interests.[76] Nevertheless, as discussed, some of the interests are in tension with each other. Accordingly, analyses of how particular approaches advance the public health interests in this space must address the complex interactions among various interests.

There are several points worth noting regarding the *Central Hudson* evaluation conducted by the Second Circuit panel majority in *United States v. Caronia*. First, the panel majority limited its analysis to addressing the constitutionality of a specific "construction of the FDCA's misbranding provisions to prohibit and criminalize off-label promotion" (see 703 F.3d 149, 161-64, 166-69 (2d Cir. 2012)), rather than evaluating FDA's implementation approach. Second, the panel majority did not consider multiple components of public health interests advanced by the FDA Authorities and FDA's implementation approach.[77] Finally, the results of the Canadian

[74] *See* Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557 (1980); In re R.M.J., 455 U.S. 191, 203 (1982).

[75] Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 566 (1980); 1-800-411-Pain Referral Serv., LLC v. Otto, 744 F.3d 1045, 1055-56 (8th Cir. 2014) (pursuant to *Sorrell v. IMS Health Inc*., 564 U.S. 552 (2011), courts should assess the constitutionality of commercial speech restrictions under *Central Hudson*). This standard does not require the government to employ "the least restrictive means" of regulation or to achieve a perfect fit between means and ends. Bd. of Trustees v. Fox, 492 U.S. 469, 480 (1989). Instead, it is sufficient that the government achieve a "reasonable" fit by adopting regulations "'in proportion to the interest served.'" *Id*. (quoting In re R.M.J., 455 U.S. at 203). The requirement of narrow tailoring is satisfied "so long as the . . . regulation promotes a substantial government interest that would be achieved less effectively absent the regulation." United States v. Albertini, 472 U.S. 675, 689 (1985).

[76] *See* Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERN. MED. 295, 296 (Mar. 2016) ("Commercial speech serves an 'informational function' and can be regulated to ensure that the public has access to accurate information. The FDA serves exactly this end. The agency aims not to censor company speech, but to foster the development of accurate and reliable information, and channel that information into settings where it can be rigorously evaluated.").

[77] These components include motivating the development of reliable scientific evidence that enables the evaluation of the safety and effectiveness of each intended use of a medical product; requiring that the evidence be developed and independently reviewed before the products are marketed to the general public for each intended use to prevent harm, protect against fraud, misrepresentation and bias, and prevent the diversion of health care resources toward ineffective treatments; and requiring that labeling accompany the product that identifies each approved or cleared

study showing an association between unapproved uses and adverse drug events, reported in Tewodros Eguale et al., Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population, 176 JAMA INTERN MED. 55-63 (Jan. 2016), were released more than three years after the *Caronia* decision. Accordingly, the *Caronia* court, in conducting its *Central Hudson* evaluation, did not have the benefit of considering the significant findings of this study.

C. Content- and Speaker-Based Restrictions

Some have argued that the applicable FDA Authorities are content- and speaker-based restrictions on speech and therefore, under *Sorrell v. IMS Health Inc.*,[78] heightened scrutiny should be applied. The *Sorrell* court stated, however, that "content-based restrictions on protected expression are sometimes permissible, and that principle applies to commercial speech."[79] However, even if the premarket review provisions of the FDA Authorities are characterized as resulting in content- and speaker-based limitations on speech, courts and commentators have recognized that they are appropriate in these circumstances.

First, when speech is used as evidence to discern intent, a focus on the speech alone will often appear to be speaker- and content-based, but it has not been found to be unconstitutional. For example, in the area of employment discrimination, whether a particular employment action that is otherwise legal is in fact prohibited can depend on whether it was motivated by a prohibited intention. To apply this in any given case, where speech is involved, the trier of fact will necessarily examine the statements of persons who act on behalf of the employer who made the decision and look at the content of those statements to see whether they indicate prohibited intention.[80] The same principle applies to determining whether a particular act constituted a hate crime – the identity of the speaker and the content of his speech are essential parts of the examination. So too here – whether speech is relevant evidence of a particular intended use will necessarily depend, in part, on the speaker and the content.[81]

Second and alternatively, even if these restrictions on firm activity were viewed as commercial speech restrictions, they are necessarily both speaker- and content-based as part of reasonable

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use of the product and provide information for using it safely and effectively for that approved or cleared use. Because the various steps of the *Central Hudson* analysis are connected, the interests at stake necessarily affect the rest of the *Central Hudson* analysis.

[78] 564 U.S. 552 (2011).

[79] 564 U.S. at 579. *See also, e.g.,* CTIA -- The Wireless Ass'n v. Berkeley, 139 F. Supp. 3d 1048, 1061 n.9 (N.D. Cal. 2015) ("Ironically, the classification of speech between commercial and noncommercial is itself a content-based distinction. Yet it cannot seriously be contended that such classification itself runs afoul of the First Amendment.").

[80] *See, e.g.*, Price Waterhouse v. Hopkins, 490 U.S. 228, 251-52 (1989) (plurality opinion) (finding that, where statute prohibited failure to grant partnership only if that decision was motivated by sexual discrimination, necessary evidence of discrimination could be established based on comments of voting partners).

[81] *See, e.g.*, Christopher Robertson & Aaron S. Kesselheim, *Regulating Off-Label Promotion — A Critical Test*, 375 NEW ENG. J. MED. 2313-15 (Dec. 2016) ("The FDCA's intent requirement is like innumerable other laws that require juries to determine whether a party had a certain intent when undertaking certain acts. It may be perfectly legal to buy a gun or drive across state lines, but if a defendant's own speech reveals he or she did so as part of a conspiracy to sell cocaine or a murder-for-hire plot, that speech is routinely used to prove the illegal intent.").

[81] Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993).

government regulation of particular industries in the interest of greater public good.[82] The law imposes duties and requirements on firms because those firms create the risks and have the knowledge or the ability to acquire knowledge relevant to product risk.[83] The relevant provisions of the FDA Authorities are directed to the entities which effectuate product distribution and are best positioned to conduct the research and gather information necessary for premarket review. When emerging and developing scientific data are not yet sufficiently complete or robust to determine safety and efficacy for an unapproved use, reliance on incomplete information could lead (and has led) to adverse results. Premarket review under the FDA Authorities places the burden of uncertainty on the firm by restricting the firm's distribution of its product for that unapproved use, thereby limiting the firm's ability to expose patients to the risks associated with the use – an approach that furthers the substantial government interest in preventing harm to the public health.[84]

It makes sense for these restrictions to apply only to firms, who have an economic motivation related to product distribution, and not to independent health care providers and researchers.[85] A broader approach – that, for example, restricted all communication about unapproved uses by both firms and others – would impact more speech and would be less tailored to advancing the various government interests. Thus, focusing on firms who actually control the distribution of the products is an appropriate way to tailor the impact on communications so that it is not more expansive than necessary.

[82] *See* Sorrell v. IMS Health Inc., 564 U.S. 552, 582-92 (2011) (Breyer, J., dissenting); United States v. Caronia, 703 F.3d 149, 180-81 (2d Cir. 2012) (Livingston, J., dissenting). *See also* Caronia, 703 F.3d at 178-179 (Livingston, J., dissenting) (the FDA Authorities do not selectively apply to a certain class of speakers; they apply to all medical product firms, i.e., the industry that has to participate in the premarket review process for that process to function in a manner that protects the public health.).

[83] *See* Christopher Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment,* 94 B.U. L. REV. 545, 551 (2014).

[84] *See, e.g.*, Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment,* 94 B.U. L. REV. 545, 560-61 (2014) ("In this realm, truth or falsity is not knowable a priori. Any knowledge of truth or falsity emerges from our economic and temporal investments, by those who have incentives to make those investments, in legal and institutional contexts that define those incentives. . . . In this sense, the [FD&C Act] does not exist to police the truth. Instead, the [FD&C Act] exists to provide and protect an epistemic and economic process of research and discovery, one that helps physicians make more rational decisions.") (citations omitted).

[85] *See, e.g.*, Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 550-51 (2014) ("It is notable that the [FD&C Act] does not regulate promotion of off-label uses by independent scientists, physicians, advocacy groups, or even laypersons. Such independent information may be more reliable than the self-interested sales pitch of a pharmaceutical representative. More importantly for the law, such independent speakers have no statutory obligations with regard to labeling or distribution of drugs. Thus, their intent that the drug be used off-label is irrelevant. The [FD&C Act] does not regulate mere speech; instead, it regulates the introduction of misbranded drugs into interstate commerce, and it is the intent of the company manufacturing and selling the drug that determines whether the drug is misbranded.") (citations omitted).

D. Alternative Approaches

FDA has examined alternative approaches suggested, for example, by the court in *United States v. Caronia,*[86] as well as by commentators. Although many of these proposed approaches address one or more of the interests identified above, FDA is concerned that none of them appear to integrate the complex mix of numerous, and sometimes competing, interests at play and thus do not best advance those multiple interests. FDA seeks comment on its review of these alternatives. FDA also seeks comments on other alternatives, as well as comment on how they would advance the multiple interests at play.

- *Prohibiting altogether the use and/or prescribing of an approved/cleared medical product for an unapproved new use.* An outright prohibition on the use of approved/cleared medical products for unapproved uses has been proposed as an alternative because the restriction does not bear directly on speech. This approach would be extremely effective in protecting the government interests in motivating scientifically robust research into unapproved uses and ensuring that new uses of approved/cleared medical products are proven to be safe and effective before they are used to treat patients. However, this prohibition does not take into account the public health interests behind allowing health care providers and patients to work to determine the best treatment options for each patient in specific circumstances.[87] Viewing FDA's approach as constitutionally prohibited because this alternative – prohibiting unapproved uses altogether – would impose less restriction on speech relies on a narrow view as to the substantial government interests at stake. This alternative could ultimately injure the audience that is supposed to benefit from the speech.

- *Barring approval of generics and other affected products until all periods of exclusivity on the reference product have expired.* Similarly, with respect to the incentives for innovation provided by the FDA Authorities, such as periods of marketing exclusivity for certain innovations, orphan drugs, and for changes to approved drugs, it has been suggested that, instead of restricting speech of generic (or other affected) manufacturers by preventing them from, for example, promoting their products for exclusivity-protected conditions of use during an innovator product's period of marketing exclusivity, the FD&C Act could instead be amended to fully bar approval of generic drugs (or other affected products) during any period of exclusivity, including their approval for non-protected conditions of use.[88] Such an alternative would be contrary to the goal of Congress in enacting the relevant legislation that provides for these periods of exclusivity, which sought to ensure that, on the one hand, brand-name drug manufacturers would have meaningful patent protection and a period of marketing exclusivity to enable them to recover their investments in the development of new drugs, while, on the other hand, ensuring that once applicable patent protection and exclusivity for these new drugs has

[86] 703 F.3d at 167-68 (2d Cir. 2012).

[87] *See* United States v. Caronia, 703 F.3d 149, 180 (2d Cir. 2012) (Livingston, J. dissenting) ("[A] ban on off-label prescriptions would . . . constitute an unprecedented intrusion into the practice of medicine, and would result in perhaps an even greater restriction on speech."). At the public hearing on November 9-10, 2016, several presenters described populations and conditions for which there are few or no approved/cleared medical products. *See also supra* note 54.

[88] Stephanie M. Greene and Lars Noah, *Debate: Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. ONLINE 239, 264 (2014).

expired, consumers would benefit from the rapid availability of lower-priced versions of innovator drugs. Under the regime created by Congress, a generic drug can be approved for fewer than all of the indications for which the brand drug has been approved; generic applicants may carve out from proposed labeling patent or exclusivity-protected conditions of use (including conditions of use protected by three-year Hatch-Waxman exclusivity, orphan exclusivity, or pediatric exclusivity) and obtain approval for the remaining non-protected conditions of use.[89] Delaying generic entry, including for non-protected conditions of use, is a more restrictive approach than is taken under the current FDA Authorities, and would fail to achieve the goal of ensuring that consumers benefit from lower-priced versions of products once relevant patent or exclusivity protection expires for particular intended uses.

- *Creating ceilings or caps on the number of prescriptions for an unapproved use*. This proposed approach is similar to the total prohibition on unapproved use above, except that it would allow some amount of prescribing before a ceiling or cap was reached. Once the prohibition was operative, it would present the same problem of limiting health care provider discretion in determining treatments geared toward the needs of each patient. However, before that ceiling was reached, firms could encourage the use of a product for an unapproved use with none of the safeguards of FDA review – just as if there were no requirement of premarket review for a second intended use. Thus, a cut-off of this type does not align with any discernable government interest and would adversely affect the public health. It is also unclear how the ceiling or cap would be determined, and by what public health rationale. If the unapproved use is thought to be potentially harmful for patients, how would one ascertain and justify the number of patients who can be exposed to the unapproved use? And if the unapproved use is thought to be potentially positive, how would one justify denying all other patients access to the product for the unapproved use after the cap is reached? In addition, this approach would be impractical to administer and enforce because, in many cases, it may be difficult to determine for what specific use a health care provider prescribes a product.[90] Prescriptions written by health care providers do not ordinarily reflect whether a medical product was prescribed for an approved or unapproved use. With certain limited exceptions (for example, in the case of products with significant risks or very high costs where authorization is required prior to dispensing or use), the reason for which a product was prescribed is not available in the data provided to the Government in claims for reimbursement under Medicare or Medicaid.

- *Limiting Medicare and Medicaid reimbursement to approved uses*. This approach – having the government limit its Medicare and Medicaid reimbursement to approved uses – would again limit health care provider discretion in determining treatments geared toward the needs of patients under Medicare and Medicaid. There would be no governmental interest in virtually eliminating the prescribing of unapproved uses for one subset of the population but having it continue for the remainder of the population (i.e., non-Medicare or -Medicaid patients). And, as in the previous approach, this approach would be impractical to administer and enforce.

[89] H.R. REP. NO. 98-857, pt.1, at 21.

[90] *See* United States v. Caronia, 703 F.3d 149, 179-80 (2d Cir. 2012) (Livingston, J. dissenting) ("A ceiling on off-label prescriptions would require collecting data from countless numbers of doctors and patients and, given the medical uncertainties involved, could needlessly (and simultaneously) result in the denial of some effective treatments and the overprescription of ineffective and even dangerous ones.").

- *Prohibiting specific unapproved uses that are exceptionally concerning or developing tiers based on level of safety concerns with greater regulatory controls for the relatively higher risk products*. These approaches would tie the regulatory controls to the degree of safety concerns about the medical product. It bears noting at the outset that without adequate evidence of benefit and risk for the unapproved intended use and some form of premarket review, it is unclear how such a system would operate. Under the first alternative, the government would prohibit specific unapproved uses for medical products that were exceptionally concerning from a safety perspective. The second alternative would similarly tie the applicable regulatory control to the level of safety concern, with stronger controls applied to more dangerous products. Both approaches would be inadequate by themselves to protect the public safety because the required safety assessment depends on the generation of data regarding product dangers before any controls can be applied (and both approaches also ignore the fact that the acceptability of product risks can only be properly evaluated in the context of robust data about the efficacy of the product for the unapproved use so that a determination of whether the benefits of the product for the intended use outweigh its risks can be made). With respect to the less exceptional or lower tier medical products, both approaches would undermine the incentives to engage in premarket review and conduct the necessary research to demonstrate safety and effectiveness, and the incentives for innovation provided by the statutory exclusivity periods discussed above.

- *Requiring firms to list all potential indications for a product in the initial premarket application.* Another proposal is to require manufacturers to list all potential uses in the first application to enable health care providers, the government, and patients to track a medical product's development. However, it is not possible to divine all potential uses of a medical product from an initial study; data and information develop over time through scientific study before and after product approval, as well as product use. If a firm's listing of one or more potential indications, submitted at the same time as the data supporting the primary indication, were the only requirement necessary before firms were allowed to market their product for the claimed indications, this would undermine several government interests listed above, including incentivizing robust research by firms, requiring premarket safety and effectiveness review for each use, developing appropriate instructions for use, and protecting the integrity and reliability of promotional information regarding medical product uses.[91] This alternative would also impact the incentives for innovation provided by the statutory exclusivity periods. This alternative raises additional issues for devices where a firm could seek and receive 510(k) clearance for a device based on one intended use, but then market the product for other intended uses for which FDA has specifically determined that premarket approval is necessary to provide a reasonable assurance of safety and effectiveness.

[91] *See* Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1595 (2014) ("Requiring companies to go on record as to other potential uses of their drug does nothing to eliminate the incentive problem that is created when they are not required to seek FDA approval for those uses in order to promote them without restriction. Nor does it give physicians useful information with which to evaluate off-label uses or promotional communications about off-label uses, or create any mechanisms to protect patients from unsafe prescribing.").

Potential variations on this proposed approach also raise questions. For example, if firms were required to obtain approval/clearance at one time for all intended uses, the initial application might be significantly delayed while new indications were explored. If a firm were unable to seek approval/clearance later for uses that were not identified at the time of an initial application, there would be no incentive to continue scientific exploration that could lead to the development and approval/clearance of new medical treatments. Thus, this approach would negatively impact the public health. For example, Imbruvica (ibrutinib) was approved to treat Mantle Cell Lymphoma in 2013, then for Chronic Lymphocytic Leukemia in 2014. In 2015, it was approved through the breakthrough therapy designation to treat Waldenstrom's Macroglobulinemia, a rare form of cancer. It is the only product currently approved to treat that disease. Similarly, Rapamune (sirolimus) was initially approved in 1999 as an immunosuppressive agent to help prevent organ rejection. In 2015, it became the first drug to receive approval to treat lymphangioleiomyomatosis (LAM), a rare, progressive lung disease that primarily affects women of childbearing age.

- *Allowing firms to actively promote an unapproved use as long as they disclose that the use is unapproved and include other appropriate warnings.* This proposed approach would allow firms to undertake active efforts to promote and encourage adoption of the unapproved use as long as they disclose that the use is unapproved and include other appropriate warnings. Warnings and disclosures can help provide material information necessary to assist in understanding data and their value. However, studies show there are limitations to disclosures in terms of the recipients' perception and understanding.[92] There is also an inherent contradiction in firms on the one hand promoting a product for an unapproved use while on the other hand disclosing that the product is not approved/cleared for that use (and that the available evidence has not established safety and efficacy for the unapproved use), which further calls into question whether disclosures would be sufficient to prevent harm or deception.[93] Furthermore, warnings and disclosures do not protect all of the public health interests advanced by premarket review because this approach would permit firms to bypass the premarket review process for new

[92] *See* Aaron S. Kesselheim et al., *Mandatory Disclaimers On Dietary Supplements Do Not Reliably Communicate The Intended Issues*, 34 HEALTH AFFAIRS 438, 445 (2015) ("Our review of the literature indicates that appending disclaimers to 'free speech' claims for uses of medications that have not passed scientific muster has not demonstrated sufficient effectiveness to warrant the use of disclaimers on a large scale in the marketing of health care products. We found ample evidence that such disclaimers are often misunderstood or ignored by consumers and had no effect on consumers' ability to understand messages about health care products and critically evaluate potentially unsupported statements about effectiveness or safety. Thus, the prospect of replacing FDA restrictions on permissible statements for prescription drugs with largely ineffective disclaimers risks returning the pharmaceutical market to a previous era when such inappropriate marketing claims proliferated, to the likely detriment of the public health."); Aaron S. Kesselheim, *Off-label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 250-51 (2011) (describing inadequacies of disclosures); Christopher Robertson, *The Money Blind: How to Stop Industry Bias in Biomedical Science, Without Violating the First Amendment*, 37 AM. J. L. & MED. 358, 366-69 (2011); Aaron Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1731 (2008).

[93] *See, e.g.*, Federal Trade Commission, *FTC Policy Statement on Deception*, (Oct. 14, 1983), at https://www.ftc.gov/public-statements/1983/10/ftc-policy-statement-deception; In the Matter of Warner-Lambert Co., 86 F.T.C. 1398, 1414 (1975), *aff'd* Warner-Lambert Co. v. F.T.C., 562 F.2d 749 (D.C. Cir. 1977), *cert denied*, 435 U.S. 950 (1978) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds).

intended uses once FDA approves/clears the product for just one use.[94] Again, in the context of devices, this alternative raises additional issues, as it would allow firms to use the 510(k) pathway for devices based on one intended use and then market the device for different intended uses for which FDA has specifically determined that premarket approval is necessary to provide a reasonable assurance of safety and effectiveness. It would therefore undermine the government interests listed above, including incentivizing robust research by firms, requiring premarket safety and effectiveness review for each use, developing appropriate instructions for use, and protecting the integrity and reliability of promotional information regarding medical product uses. And, if firms do not conduct the research necessary to demonstrate the safety and effectiveness of their products for each intended use, it is unlikely that any other party will have the motivation and resources to undertake it. If disclosures were the only limitation on a firms' ability to distribute a medical product for an unapproved use, we are concerned that it would result in a return to an environment where audiences are faced with a large volume of advertising and promotional labeling claims based on conjecture or extrapolation from limited data, most of which is later found to be false or misleading, but not before misinformation is widely circulated and patients are harmed.[95] This approach would also undermine the incentives for innovation provided by the statutory exclusivity periods.

- *Educating health care providers and patients to differentiate false and misleading promotion from truthful and non-misleading information.* Although FDA does have several

[94] *See* United States v. Caronia, 703 F.3d 149, 179 (2d Cir. 2012) (Livingston, J., dissenting) ("A disclaimer system or required listing of intended uses would provide manufacturers much less incentive to submit their drugs for FDA approval, and in turn encourage promotion based on data much less reliable than the clinical investigations required under 21 U.S.C. § 355(d).").

[95] *See* S. REP. NO. 87-1744 (1962), *reprinted in* 1962 U.S.C.C.A.N. 2884, 2898, 2901 ("[P]hysicians are regularly inundated with a great mass of advertising and promotional material, much of which is misleading and some actually false. . . ." "Leading physicians testified that it is impossible to keep currently informed of the state of medical knowledge to be found scattered in hundreds of medical journals. . . . Moreover, they stressed that the marketing of a safe but ineffective drug may well be positively injurious to public health. . . . The problem is compounded by the fact that usually a considerable period elapses between the time when a highly-advertised new drug is put on the market and when knowledge becomes widely disseminated among the medical profession that its performance falls seriously short of its claims"). As we reexamine our approach and consider the First Amendment jurisprudence, FDA believes it is critical to avoid a result that "injures the very audience that is supposed to benefit from free speech." United States v. Caputo, 517 F.3d 935, 940 (7th Cir. 2008). FDA seeks to protect against harm to the health and well-being of patients who are not necessarily party to the communications in question. *See* Constance E. Bagley et al., *Snake Oil Salesmen or Purveyors of Knowledge: Off-Label Promotions and the Commercial Speech Doctrine*, 23 CORNELL J.L. & PUB. POL'Y 337, 364 (2013) (noting the conceptual distinction between regulating commercial speech "s*olely* for the sake of withholding information" and regulating it to prevent the societal harm resulting from the information's effect on behavior); Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1592 (2014) ("[I]n seeking to curb the excesses of off-label promotion of medical products to physicians, the FDA seeks to protect not the recipients of the promotion, but their patients. When physicians decide to prescribe a drug for an unapproved use based on a biased presentation of the evidence concerning that use, they put a third party at risk of physical harm. Congress has tasked the FDA with the responsibility to protect the public from unsafe and ineffective drugs. It is not paternalism for the agency to discharge its responsibility in this way.") (citation omitted).

educational resources in this area,[96] it is unrealistic to suggest that this type of program can be conducted on the scale necessary to effectively combat the adverse impact of the many different ways promotion can be false or misleading.[97] Even assuming that a large-scale government-sponsored education program was feasible, this approach removes the burden from the seller of the product and puts it on health care providers and patients. Like the preceding proposal, this alternative would allow firms to bypass the premarket review process by marketing or promoting a product for an unapproved use and thereby undermine the substantial government interests in incentivizing robust scientific research, requiring premarket review, developing required labeling that provides appropriate information for safe and effective use, and protecting the integrity and reliability of promotional information regarding medical product uses. This approach would replace the FDA's thorough and rigorous scientific review process with a review of promotional materials by health care providers and patients. Health care providers and patients cannot be expected to acquire the tools, background, and specialized expertise in statistics, pharmacokinetics, biomedical engineering, and other fields that are necessary to conduct a thorough evaluation of the risks and benefits of a new intended use that even roughly approaches that provided by FDA review (assuming that adequate data exist and that all the data are made publicly available), and it is unrealistic to suggest that a government-sponsored education campaign would provide this kind of multi-discipline expertise. In addition, an education campaign would not provide each health care provider or patient with the time needed to conduct such an evaluation of risks and benefits for every use of hundreds of medical products.[98] This suggested approach also does not account for the possibility that firms may present incomplete or unsubstantiated information, and that the health care provider or consumer would not be well positioned to uncover or weigh the significance of the absence of a full disclosure of all relevant data.[99]

- *Reminding health care providers of potential malpractice liability*. This proposed approach appears to be suggested as a way of making health care providers more cautious regarding prescribing/using medical products for unapproved uses. To the extent it discourages

[96] *See, e.g.*, FDA, *Truthful Prescription Drug Advertising and Promotion, at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm (last modified Dec. 16, 2016).

[97] *See* Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1593-94 (2014) ("The nation's experience prior to the 1962 [FD&C Act] amendments amply demonstrated that physicians could not distinguish between truthful and misleading claims of drug efficacy, in part because of misleading promotional statements. Even if didactic strategies for distinguishing among the types of claims made in off-label promotion and understanding the evidence base underlying them could be identified, along with strategies for effectively reaching every physician with this information, it is inconceivable that the government would appropriate funding at a level sufficient to create an effective counterweight to the $ 50 billion that pharmaceutical companies spend each year on promotion to physicians.") (citations omitted).

[98] *See* Brian S. Alper et al., *How much effort is needed to keep up with the literature relevant for primary care?*, 92 J MED LIBR ASS'N 429-37 (2004) (study on overall workload of systematically keeping up with the medical literature relevant to primary care estimated that it would require 627.5 hours per month).

[99] *See* Bates v. State Bar of Ariz., 433 U.S. 350, 383-84 (1977) (holding that limitations on advertising may be appropriate where the public lacks sophistication or a means of verifying information on a particular topic). *See also* Christopher Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 572 (2014) ("The truth or falsity of the drugmaker's promotional claims is unknown, largely because the drugmaker has declined to invest in making such a proof.").

all prescribing or use of medical products for unapproved uses by health care providers, this approach would not advance the interests behind allowing health care providers to determine the best treatment options for patients in specific circumstances, such as in treating diseases for which there are no approved treatments or in treating patients for whom all approved treatments have failed. In addition, like the previous example, it would allow firms to bypass the premarket review process for new intended uses and thereby undermine the significant government interests advanced by that process. Furthermore, by essentially shifting the responsibility and perhaps liability from the firm to the health care provider, this approach would not deter firms from developing biased presentations with the potential to mislead the listener.

- *Taxing firms more heavily for sales of products for unapproved uses than for approved uses.* This proposed approach would allow unrestricted sharing of information about unapproved uses of approved/cleared medical products, but attempt to retain some financial incentive for seeking FDA approval by taxing firms' sales for unapproved uses more than sales for approved uses. The proposal does not align with the government interests in part because it would affect all prescribing/use of medical products for an unapproved use equally – whether or not there were circumstances that warranted such prescribing/use.[100] Moreover, it would allow companies to substitute a tax payment for the cost of the robust scientific research needed to protect the public from injuries associated with inadequately studied and tested products. It is not apparent how such tax payments, which could simply become a cost of doing business and/or be directly passed along to patients, would in fact change firms' behavior or otherwise prevent, remedy or deter the significant public health harms that premarket review is designed to avert. This approach would also likely be impractical to administer and enforce because, as noted previously, it may be difficult to determine in many cases the particular use for which a product is being prescribed/used.

- *Permit promotion of unapproved uses listed in medical compendia.* This proposed approach would rely on medical compendia, which list information about drugs and already list certain unapproved uses of drugs as medically accepted. Medical compendia are developed through many sources, including for-profit individuals or companies and consortiums of recognized academic experts (e.g., the National Comprehensive Cancer Network). All compendia rely on medical literature so their decisions are not based on the same kind of data and information as FDA approval decisions.[101] Furthermore, publication bias is a well-known phenomenon, where trials with negative or unfavorable results often are not published, and thus

[100] *See* Aaron S. Kesselheim, *Off-label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J. L. & MED. 225, 252 (2011) ("[T]axing off-label use would indiscriminately affect evidence-based and non-evidence-based uses. It is also likely that taxation revenue could be incorporated into the price of the drug, and passed on to the consumers or insurers, negating their effect").

[101] Medical publications follow a prescribed format and present salient data and conclusions, but do not provide full, primary datasets to either the reader or to the journal's reviewers. Mike Mitka, *Off-Label Cancer Drug Compendia Found Outdated and Incomplete*, 301 JAMA 1645-1646 (2009) ("Investigators commissioned by the US Centers for Medicare & Medicaid Services (CMS) said compendia of medications used to justify off-label use for cancer treatments appear not to use systematic methods to review or update evidence. As a result, physicians using these compendia to determine treatment regimens for patients with cancer may not be prescribing the best medications for a particular case, and Medicare and other insurers may be paying for suboptimal care for such patients.").

may not be available to developers of compendia.[102] There is also the potential for firms to improperly influence compendia listings.[103] In contrast, FDA premarket review involves a much more in-depth and unbiased analysis of the underlying data and information. Compendia listings do not rely on this level of detail and are not comparable to an FDA approval.[104] This approach would permit firms to bypass the premarket review process for new intended uses once the product was listed in some compendia. By substituting the criteria used by the various compendia for the FDA premarket review process, this alterative would allow firms to market products for uses that lack robust scientific support and that have not been subject to rigorous scientific review, with the possibility for the introduction of bias. This approach would therefore undermine the government interests listed above, including incentivizing robust research by firms, requiring premarket safety and effectiveness review for each use, developing appropriate instructions for use, and protecting the integrity and reliability of promotional information regarding medical product uses.

- *Limiting evidence that could be considered relevant to intended use to speech that the government can prove is false or misleading.* This approach would limit the type of evidence that could be used to establish the intended use of a product to speech by firms that the government can prove is false or misleading. Under this approach, firms might be free to actively promote unapproved uses of approved/cleared medical products based on incomplete, unbalanced, or non-objective data or information unless and until the government established, after the communication occurred, that the communication was misleading. Essentially, claims would be legal until proven wrong, potentially after patients have been harmed.[105] Such an approach would undermine the current incentives to generate scientific evidence sufficient to establish safety and effectiveness for each intended use of a medical product. For example, the approach would likely incentivize exploratory, small, and less rigorous studies that are more likely to generate positive results. Once a firm has such positive preliminary results, they would be unlikely to perform additional studies to generate reliable evidence of safety or effectiveness.

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[102] *See supra* notes 21, 29, 58.

[103] *See, e.g.*, Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), *at* https://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal ("The United States further contends that Amgen used journal articles that were insufficient to support the safety and efficacy of the off-label uses at issue, and improperly obtained listings in medical compendia in an effort to establish that the off-label uses were medically accepted, and thereby eligible for coverage by federal health care programs."); Angela K. Green et al., *Time to Reassess the Cancer Compendia for Off-label Drug Coverage in Oncology*, 316 JAMA 1541 (2016) ("[T]here is limited transparency about how compendia are assembled or about conflicts of interest on the part of their contributors.").

[104] *See, e.g.*, Angela K. Green et al., *Time to Reassess the Cancer Compendia for Off-label Drug Coverage in Oncology*, 316 JAMA 1541-1542 (2016) ("A systematic review published in 2009 found that the quality of evidence cited in compendia for off-label cancer drug usage is less rigorous than the standards supporting FDA-approved drugs. This analysis of 14 off-label indications of cancer drugs found substantial limitations in the level, quantity, consistency, and timeliness of evidence among commonly used compendia. Evidence cited by the compendia was often not up-to-date and differed from evidence retrieved through an independent search by the authors. This raises concern that payers may be compelled to cover inadequately proven treatments for which the risks outweigh benefits. Despite the findings of this systematic review, this issue has not been addressed since then."), *citing* Amy P. Abernethy et al., *Systematic review: reliability of compendia methods for off-label oncology indications*, 150 ANN. INTERN. MED. 336-343 (2009).

[105] *See supra* note 95.

However, many medical products that look promising at early stages of development or clinical testing turn out not to provide any clinical benefit or cause harms when evaluated in larger clinical trials.[106] This approach might even be argued to open the door to statements by a "true believer" who truthfully represents he believes a product cures cancer without any scientific basis for that conclusion. Accordingly, this approach would undermine the requirements for premarket review of medical products for each of their intended uses and undermine all the interests advanced by the premarket review system and related provisions of the FDA Authorities.

[106] *See, e.g.*, Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016) (finding more than half of drugs entering late-stage clinical development fail during or after pivotal clinical trials, primarily because of inadequate efficacy, safety, or both). A few recent examples publicized after the November 9-10, 2016 public hearing of products that initially appeared to show promise but were later found to have safety or efficacy problems include the failure of Eli Lilly's experimental Alzheimer's drug, solanezumab, to demonstrate effectiveness and Juno Therapeutics' decision to place a clinical hold on its experimental leukemia drug following patient deaths. Pam Belluck, *Promising Drug for Alzheimer's Fails in a Trial*, N.Y. TIMES, Nov. 24, 2016, at A1; Anne Steele, *Juno's Stock Drops Following Two More Deaths in Cancer-Treatment Trial*, WALL ST. J., Nov. 23, 2016, *available at* http://www.wsj.com/articles/junos-stock-drops-following-two-more-deaths-in-cancer-treatment-trial-1479915925.

APPENDIX A
SUMMARY OF STATUTORY AND REGULATORY AUTHORITY BY PRODUCT CATEGORY

The FDA Authorities prohibit the introduction (or causing the introduction) into interstate commerce of a medical product that fails to comply with applicable requirements for approval, licensing, or clearance, or is otherwise misbranded or adulterated. These prohibitions include introducing (or causing the introduction) into interstate commerce of a medical product that is intended for a use that has not been approved or cleared by FDA, even if that same product is approved or cleared for a different use.

Below is an overview of the legal frameworks governing firms' communications regarding unapproved uses of medical products, including a discussion of the premarket review processes for each type of medical product. Despite the distinctions in the legal frameworks and associated processes, underlying each are the goals of spurring advances in medicine based on reliable scientific evidence and of ensuring the safety and effectiveness of medical products for each intended use.

A. Human Drugs

1. Premarket Review

The FD&C Act requires that all "new drugs" be approved by FDA before they may be distributed in interstate commerce (21 U.S.C. §§ 331(d) and 355(a)). A "new drug" is one that is "not generally recognized, among [qualified] experts . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ." (21 U.S.C. § 321(p)).[107] To obtain FDA approval for a new drug, a sponsor must submit a new drug application (NDA) that demonstrates that its product is safe and effective for each of its intended uses (21 U.S.C. § 355(a)).[108] Safety must be supported by "adequate tests by all methods

[107] The statute qualifies this provision with grandfather clauses that are unlikely to be met by any product marketed today. *See* 21 U.S.C. § 321(p)(1) (certain drugs marketed prior to the 1938 enactment of the FD&C Act) and Pub. L. No. 75-717, 52 Stat. 1040 (certain drugs marketed prior to the enactment of the 1962 amendments to the FD&C Act).

[108] *See also* Wash. Legal Found. v. Henney, 202 F.3d 331, 332 (D.C. Cir. 2000). In addition, the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act, which established an abbreviated new drug application (ANDA) approval process. An ANDA applicant relies on FDA's previous finding that the reference listed drug (RLD) – a drug previously approved under section 505(c) – is safe and effective. To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act). In addition, an ANDA applicant must provide sufficient information to show that the generic drug product has the same active ingredient(s), dosage form, route of administration, and strength as the RLD. An ANDA applicant must also demonstrate that its product has (with certain permissible differences) the same labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). The Agency must approve an ANDA unless it finds, among other things, that the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

reasonably applicable" (21 U.S.C. § 355(d)(1)). Effectiveness must be supported by substantial evidence, defined in section 505(d)(5) (21 U.S.C. § 355(d)(5)) and further explained in FDA regulations at 21 C.F.R. § 314.126.

"Substantial evidence" is a rigorous standard that requires scientific data from adequate and well-controlled clinical investigations (*see* 21 U.S.C. § 355(d)). This standard cannot be satisfied by impressions or beliefs of health care providers, reports lacking in details, or personal testimonials.[109]

Even for drugs that are not new drugs, and thus are not subject to the requirements of approval under section 505, safety and effectiveness must be supported by robust scientific evidence. For a drug to achieve "general recognition of safety and effectiveness," there must be the same quality and quantity of scientific data necessary to support the approval of an NDA, including substantial evidence consisting of adequate and well-controlled clinical investigations that establish the drug as effective.[110]

Through its premarket review, FDA determines that a new drug is (or is not) safe for each particular use under the conditions prescribed, recommended, or suggested in the product's labeling, e.g., dosage, route of administration, contraindications, and warnings.[111] This assessment requires a use-specific balancing of risks against benefits.[112]

As part of the process for approving an NDA, FDA also reviews and approves the labeling for inclusion on or within the package from which the drug is dispensed to help ensure that the labeling is accurate and conveys important information for the safe and effective use of the product for its approved use(s). This includes information about a drug's indications, dosage, precautions, warnings, and contraindications, as well as other information regarding the efficacy for each approved use (*see* 21 U.S.C. § 355(b)).[113]

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[109] *See* Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609, 618-19, 630 (1973); *see also* 21 C.F.R. § 314.126(e).

[110] *See* Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 629-631 (1973).

[111] Under certain circumstances, FDA may also consider additional risks and potential harms in determining whether a drug meets the relevant standard for marketing. For example, FDA may assess the risks of abuse or misuse of certain drugs, or the potential for harm to health from secondary exposure to certain drugs.

[112] *See* United States v. Rutherford, 442 U.S. 544, 555 (1979) ("Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.").

[113] The labeling that FDA reviews and approves for prescription drugs provides information for prescribers, but also includes information directed to ensuring that patients can use the drug safely and effectively. *See* 21 C.F.R. § 201.100(d)(3) and 21 C.F.R. § 201.57(c)(18) (patient counseling information). Under some circumstances, FDA may also determine that labeling for distribution directly to patients (a medication guide or patient package insert) is necessary as part of a risk evaluation and mitigation strategy (REMS) to mitigate the risks presented by a drug, including a biological product. *See* 21 U.S.C. § 355-1(e)(2). In addition, FDA may require FDA-approved patient labeling if the Agency determines that at least one of these conditions exists: (1) patient labeling could help prevent serious adverse effects; (2) the drug product is one that has serious risk(s) relative to benefit(s), and information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product; or (3) the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. *See* 21 C.F.R. § 208.1.

The Public Health Service Act (PHSA) establishes a premarket approval (referred to as "license" in the PHSA) process for biological products that is nearly identical to that for new drugs under the FD&C Act (*see* 42 U.S.C. § 262(i) for the definition of "biological product"). The PHSA prohibits the interstate distribution of a biological product without FDA approval (42 U.S.C. § 262(a)). A sponsor seeks FDA approval by submitting a biologics license application (BLA) (42 U.S.C. § 262(a)). To obtain approval, the sponsor must demonstrate, among other things, that the product is "safe, pure, and potent" (42 U.S.C. § 262(a)(2)(C)(i)(I)).[114] FDA approves a biological product for a particular use only when there is sufficient evidence, consisting of appropriate laboratory tests or controlled clinical data, to show that the product will be safe and effective for that use when administered in the manner approved (*see* 42 U.S.C. §§ 262(a)(2)(A) and 262(a)(2)(C)(i)(I); 21 C.F.R. §§ 600.3(p), 600.3(r), 600.3(s), and 601.2(d)). This premarket review and approval also involves FDA review and approval of the product's labeling (*see* 21 C.F.R. § 201.56). The standards for approval of biological products are construed similarly to the standards for approval of new drugs.[115]

2. Misbranding

All human drugs (including those that are biological products) are subject to the misbranding provisions of the FD&C Act, which makes it unlawful to misbrand drugs and to distribute misbranded drugs (21 U.S.C. §§ 331(a), (b), (c), (g), (k), and 352; 21 C.F.R. § 601.5(b)(1)(vi)). Among other things, a drug is misbranded if its labeling does not contain adequate directions for use (21 U.S.C. § 352(f)(1)). Adequate directions for use are "directions under which the layman can use a drug safely and for the purposes for which it is intended" (21 C.F.R. § 201.5). Because prescription drugs, by definition, are "not safe for use except under the supervision of a practitioner licensed by law to administer such drug" (21 U.S.C. § 353(b)(1)(A)), the labeling of a prescription drug cannot provide adequate directions for its safe use by laymen. However, FDA has exercised its authority under 21 U.S.C. § 352(f) to create regulatory exemptions from the requirements of section 502(f)(1) of the FD&C Act (21 U.S.C. § 352(f)(2)). Among the terms that must be met to satisfy these regulatory exemptions, a prescription drug must have labeling that provides adequate information for its safe and effective use by practitioners for all the purposes for which it is intended, including all purposes for which it is advertised or represented (*see* 21 C.F.R. §§ 201.100(c)(1), 201.100(d), 201.56, 201.57, and 201.80). For new drugs, this labeling also must be approved in an NDA (21 C.F.R. §§ 201.100(c)(2)), 201.100(d), and 201.115). Thus, an approved prescription drug that is intended for an unapproved use would be misbranded because the drug does not meet the regulatory exemptions from the requirement that its labeling bear "adequate directions for use."

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[114] A biological product may also be approved as a biosimilar after the firm demonstrates that the product is biosimilar to a biological product (the reference product) that has been shown to be safe, pure, and potent (42 U.S.C. § 262(k)).

[115] *See* Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, § 123(f), 111 Stat. at 2296, 2324 (1997) (codified at 21 U.S.C. § 355 note) (instructing FDA to "minimize differences in the review and approval" of drug and biological products); *see also* FDA, *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, 2-4 (May 1998), at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072008.pdf.

All drug labeling, as well as advertising for prescription drugs, is subject to additional misbranding provisions under the FD&C Act. For example, a drug is considered misbranded if its labeling is "false or misleading in any particular" (section 502(a) of the FD&C Act (21 U.S.C. § 352(a))). Similarly, a prescription drug is considered misbranded if its advertising fails to provide a true statement, including information in brief summary, regarding the product's side effects, effectiveness and contraindications, or if the advertising is otherwise false or misleading.[116]

B. Animal Drugs

1. Premarket Review

The FD&C Act and FDA regulations similarly prohibit firms from introducing a "new animal drug" into interstate commerce for any intended use that FDA has not determined to be safe and effective. A "new animal drug" is any drug that that is "intended for use for animals other than man" that is "not generally recognized, among [qualified] experts . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ." (21 U.S.C. § 321(v)). A new animal drug includes a drug that has already been approved for one or more uses and is accompanied by labeling that suggests an unapproved new use; in this situation, the drug would be an unapproved new drug with respect to that new use and any use of that drug would be deemed "unsafe" under section 512(a) of the FD&C Act (21 U.S.C. § 360b(a)).

To obtain approval for a new animal drug, a manufacturer must submit a new animal drug application (NADA) that demonstrates that the product is safe and effective for each of its intended uses, defined in section 512(d) of the FD&C Act (21 U.S.C. § 360b(d)) and explained in FDA regulations at 21 C.F.R. part 514. Safety and effectiveness must be established by "adequate tests by all methods reasonably applicable" that the "drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" (21 U.S.C. § 360b(d)(1)(A)).[117]

Section 201(u) of the FD&C Act provides that "safe" as used in section 512 of the FD&C Act "has reference to the health of man or animal." The determination of safety requires FDA to consider, among other relevant factors, "the probable consumption of such drug and any substance formed in or on food because of the use of such drug . . . ." (21 U.S.C. §360b(d)(2)(A)). Accordingly, FDA must consider not only the safety of the new animal drug to the target animal, but, where the new animal drug will be used in animals intended for food, also the safety to humans of substances formed in or on food as a result of the use of the new animal drug.

The statute further specifies that "substantial evidence" to establish effectiveness for approval means "evidence consisting of one or more adequate and well controlled investigations. . . by experts qualified by scientific training and experience to evaluate the effectiveness of the drug

[116] *See* section 502(n) of the FD&C Act (21 U.S.C. § 352(n)) and 21 C.F.R. § 202.1 (prescription drug advertising); *see also* section 201(n) of the FD&C Act (21 U.S.C. § 321(n)).

[117] In addition, the FD&C Act provides other premarket review processes for certain drugs intended for minor species or minor uses in major species. *See* 21 U.S.C. §§ 360ccc and 360ccc-1.

involved, on the basis of which it could fairly and reasonably 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" (21 U.S.C. § 360b(d)(3)).[118]

As part of the process for approving a new animal drug application, FDA also reviews and approves the labeling for inclusion on or within the package from which the drug is dispensed to help ensure that it is accurate and conveys important information related to the safe and effective use of the product for its intended use(s), such as indications, dosage, withdrawal, precautions, warnings, and contraindications, as well as information regarding the efficacy for each approved intended use (*see* 21 U.S.C. § 360b(b)).

One important way that the statutory frameworks applicable to human and animal drugs differ is that section 512 of the FD&C Act provides that an animal drug is deemed unsafe for any particular use or intended use of the drug unless there is an approval (or conditional approval or index listing) for that intended use "and such drug, its labeling, and such use conform to such approved application" (21 U.S.C. § 360b(a)). Animal drugs that are "unsafe" within the meaning of section 512(a) of the FD&C Act are adulterated under section 501(a)(5) of the Act (21 U.S.C. § 351(a)(5)). There is an exception, however, for certain extralabel uses of animal drugs. Sections 512(a)(4) and (5) provide that such extralabel use will not be considered "unsafe" (and therefore will not adulterate the new animal drug) when certain conditions are met, and the use complies with FDA regulations covering the extralabel use.[119]

2. Misbranding

All animal drugs are subject to the misbranding provisions of the FD&C Act, which makes it unlawful to misbrand drugs and to distribute misbranded drugs (21 U.S.C. §§ 331(a), (b), (c), (g), (k), and 352). Among other things, a drug is misbranded if its labeling does not contain adequate directions for use (21 U.S.C. § 352(f)(1)). Adequate directions for use are "directions under which the layman can use a drug safely and for the purposes for which it is intended" (21 C.F.R. § 201.5). Because prescription drugs, by definition, are "not safe for animal use except under the professional supervision of a licensed veterinarian" (21 U.S.C. § 353(f)(1)(A)(i)), the labeling of a prescription drug cannot provide adequate directions for its safe use by laymen. However,

[118] Section 512(d)(3) of the FD&C Act further provides examples of what may constitute an adequate and well-controlled investigation, including a study in a target species, a study in laboratory animals, any field investigation that may be required under section 512 and that meets the requirements of subsection (b)(3) if a presubmission conference is requested by the applicant, a bioequivalence study, or an in vitro study (21 U.S.C. § 360b(d)(3)(A)-(E)).

[119] Section 512(a)(4) and (5) of the FD&C Act permit a licensed veterinarian to prescribe an otherwise approved human or animal drug in a manner that is not in accordance with the approved labeling (an "extralabel use"), subject to certain conditions and prohibitions set by regulation (21 U.S.C. § 360b(a)(4)-(5), 21 C.F.R. § 530). This includes, but is not limited to: (1) use in species that are not listed in the labeling; (2) use for indications not listed in the labeling; (3) frequencies, or routes of administration other than those stated in the labeling; and (4) deviation from the withdrawal time indicated on the labeling (21 C.F.R. § 530.3(a)). Such uses are not deemed unsafe for purposes of 512(a)(1), and therefore do not misbrand the drug, provided they are prescribed by and used under the supervision of a licensed veterinarian, and all the provisions of 21 C.F.R. § 530 are followed and the uses are not otherwise prohibited under section 512(a)(4)(D) of the FD&C Act and 21 C.F.R. § 530.25.

FDA has exercised its authority under 21 U.S.C. § 352(f) to create regulatory exemptions from the requirements of section 502(f)(1) of the FD&C Act. Among the terms that must be met to satisfy these regulatory exemptions, a prescription new animal drug must be supplied with labeling that provides adequate information for its safe and effective use by practitioners for all the purposes for which it is intended, including all purposes for which it is advertised or represented (*see* 21 C.F.R. § 201.105(c)(1)). For new animal drugs, this labeling also must be approved in a new animal drug application (21 C.F.R. 201.105(c)(2) and 201.105(d); *see also* 21 C.F.R. § 201.115). Thus, an approved prescription animal drug that is intended for an unapproved use would be misbranded because the drug does not meet the regulatory exemptions from the requirement its labeling bear "adequate directions for use." Further, a use of an unapproved new animal drug is an "unsafe" use under 512(a), and is therefore adulterated as well as misbranded (21 U.S.C. §§ 360b(a) and 351(a)(5)).

All new animal drug labeling, as well as advertising for prescription drugs, is subject to additional misbranding provisions under the FD&C Act. For example, a drug is considered misbranded if its labeling is "false or misleading in any particular" (section 502(a) of the FD&C Act (21 U.S.C. § 352(a))). Similarly, a prescription drug is considered misbranded if its advertising fails to provide a true statement – including information in brief summary regarding the product's side effects, effectiveness, and contraindications – or if its advertising is otherwise false or misleading.

C. Devices Intended for Use in Humans[120]

1. Classification System and Premarket Review

As discussed further below, a device is adulterated or misbranded if, among other things, it is intended for a use that has not been approved or cleared by FDA even if that same product is approved or cleared for a different use. The type of premarket review pathway is determined by the degree of review and regulation that FDA deems necessary to provide a reasonable assurance of safety and effectiveness for a given device type. Although the premarket submission review pathways (e.g., approval application (PMA), *de novo*, and 510(k)) differ in various ways, they all fit within the same regulatory framework that enables FDA to ensure that devices on the market are ones that have been determined by FDA to have a reasonable assurance of safety and effectiveness for each and every use for which they are intended.

a. Class System

The Medical Device Amendments of 1976 (Pub. L. No. 94-295) directed FDA to issue regulations that classify all devices that were in commercial distribution at that time into one of three regulatory control categories: class I,[121] class II,[122] or class III,[123] depending upon the

[120] Premarket review requirements do not apply to devices intended for use solely in animals.

[121] Class I devices are subject to a comprehensive set of regulatory authorities called general controls that are applicable to all classes of devices (*see* section 513(a)(1)(A) of the FD&C Act (21 U.S.C. § 360c(a)(1)(A))). General controls apply to all three classes of medical devices; however, they are the only level of controls that apply to class I devices. General controls are described in sections 501 (adulterated devices), 502 (misbranded devices),

degree of regulation necessary to provide reasonable assurance of their safety and effectiveness, with class I requiring the least regulation and class III requiring the most regulation.[124]

Devices that were not in commercial distribution prior to the Medical Device Amendments of 1976 are automatically classified under section 513(f)(1) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval (discussed below) unless and until any such device is classified into class I or II under section 513(f)(2) or (f)(3) of the FD&C Act or FDA issues an order finding the device to be substantially equivalent (also discussed below), in accordance with the criteria in section 513(i) of the FD&C Act, to a legally marketed (predicate) device that does not require premarket approval (see sections 510(k), 513(f)(1)(A), and 513(i) of the FD&C Act).

Classification determinations must be based on an evaluation of the safety and effectiveness of the device considering (1) the persons for whose use the device is intended; (2) the intended conditions of use prescribed, recommended, or suggested in the labeling of the device; and (3) the probable benefits of the device as compared with the probable risks of its use.[125]

Moreover, the effectiveness and safety of the device must be determined on the basis of valid scientific evidence as set forth in section 513(a)(3) of the FD&C Act (21 U.S.C. § 360c(a)(3)) and further explained in FDA regulations at 21 C.F.R. § 860.7. "Valid scientific evidence" is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and

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510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports on devices), and 520 (general provisions respecting control of devices intended for human use) of the FD&C Act.

[122] Class II devices are devices for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls necessary to provide such assurance (*see* section 513(a)(1)(B) of the FD&C Act (21 U.S.C. § 360c(a)(1)(B))). Special controls are device-specific and include performance standards, post-market surveillance, patient registries, special labeling requirements, premarket data requirements, and guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the FD&C Act).

[123] Class III devices are devices for which general controls, by themselves, are insufficient and for which there is insufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device (*see* section 513(a)(1)(C) of the Act (21 U.S.C. § 360c(a)(1)(C))).

[124] This class system was intended to provide assurances of public health to patients and health care providers while not stifling device innovation: "After lengthy hearings and careful consideration, the Committee has developed a balanced regulatory proposal intended to assure that the public is protected from unsafe and ineffective medical devices, that health professionals have more confidence in the devices they use or prescribe, and that innovations in medical device technology are not stifled by unnecessary restrictions. The bill makes distinctions between those devices which are simple in design and represent little risk to health and those which are sophisticated and potentially hazardous." H.R. REP. NO. 94-853, at 12 (1976). Also, with respect to determining the regulatory status of a device, the legislative history of the FD&C Act states that "there may be instances in which a particular device is intended to be used for more than one purpose. In such instances, it is the Committee's intention that each use may, at the Secretary's discretion, be treated as constituting a different device for purposes of classification and other regulation." *Id*. at 14-15.

[125] *See* sections 513(a)(2) and (b) of the FD&C Act (21 U.S.C. §§ 360c(a)(2) and (b)); 21 C.F.R. § 860.7.

responsibly be concluded by qualified experts that there is a reasonable assurance of the safety and effectiveness of a device under its conditions of use.[126]

There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.[127] Further, there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.[128]

For example, when classifying *in vitro* diagnostic (IVD) devices,[129] FDA reviews the analytical and clinical performance information to evaluate the benefits and risks of the test and to determine whether the test will provide clinically significant results.

The class into which a device is placed reflects the level of premarket review necessary to provide a reasonable assurance of safety and effectiveness.

b. PMA, *De Novo*, and 510(k) Premarket Submissions

PMA approval is required by FDA before most class III devices can be legally marketed. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence[130] to assure that the device is safe and effective for its intended use(s). The PMA includes sections containing, among other things, technical data, non-clinical laboratory studies, and clinical investigations. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.[131]

For devices subject to PMA approval, labeling is reviewed and approved by FDA as part of the PMA review (*see* section 515(c)(1)(F) of the FD&C Act (21 U.S.C. § 360e(c)(1)(F))).

[126] *See* 21 C.F.R. § 860.7(c)(2). Sufficiently relevant and reliable real-world data could constitute valid scientific evidence, depending on the characteristics of the data, and may be appropriate for use in support of a premarket submission.
[127] *See* 21 C.F.R. § 860.7(d). The valid scientific evidence used to determine the safety of a device must adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.
[128] *See* 21 C.F.R. § 860.7(e).
[129] *See* 21 C.F.R. § 809.3(a).
[130] *See* 21 C.F.R. § 860.7(c)(2).
[131] *See* section 515(d) of the FD&C Act (21 U.S.C. § 360e(d)); 21 C.F.R. part 814 subpart C ("FDA Action on a PMA").

Devices of a new type that FDA has not previously classified based on the criteria at section 513(a)(1) of the FD&C Act and that are automatically classified into class III by operation of law, may be classified into class I or class II under the *de novo* process. If a sponsor believes its device is appropriate for classification into class I or class II and determines there is no predicate device, the submitter may submit a *de novo* request for classification[132] as the premarket submission in which the submitter provides information to demonstrate that general controls or general and special controls are sufficient to provide a reasonable assurance of safety and effectiveness for the device. FDA may decline to classify a device that is not of low-moderate risk or for which general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

If the submitter demonstrates that general controls, or a combination of general and special controls, are sufficient to provide a reasonable assurance of safety and effectiveness, FDA will grant the *de novo* request for classification and issue a written order classifying the specific device and device type in class I or class II. The device is granted marketing authorization subject to general controls and any identified special controls, and may serve as a predicate for future 510(k) submissions. FDA will publish a notice in the *Federal Register* announcing the classification and the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness. FDA will also publish a decision summary on the FDA website, which provides an overview of the data in support of the *de novo* submission.[133]

Devices granted marketing authority under *de novo* requests should be sufficiently understood to explain all the risks and benefits of the device such that all risks can be appropriately mitigated through the application of general controls or general and special controls to provide reasonable assurance of safety and effectiveness. Further, since devices classified under *de novo* requests may serve as predicates for future devices which can be appropriately regulated through the 510(k) pathway, FDA carefully considers the benefit-risk profile of these devices in the determination that there is reasonable assurance of safety and effectiveness.

Accordingly, if insufficient information exists to determine that general controls or general and special controls would provide reasonable assurance of safety and effectiveness for the device, the device cannot be classified as a class I or II device. Such a device would generally be subject to PMA review.[134]

The 510(k) review standard (substantial equivalence of a new device to a predicate device) differs from the PMA and *de novo* review standards. The 510(k) review standard is comparative,

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[132] *See* section 513(f)(2) of the FD&C Act (21 U.S.C. § 360c(f)(2)).

[133] Further information about decision summaries can be found on FDA's website, *Evaluation of Automatic Class III Designation (De Novo) Summaries, at* http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm232269.htm (last updated Dec. 22, 2016).

[134] *See* section 513(a)(1)(C) of the FD&C Act (21 U.S.C. § 360c(a)(1)(C)). *See also* section 513(f)(2)(A)(iv) of the FD&C Act (21 U.S.C. § 360c(f)(2)(A)(iv)) (stating that FDA has the authority to decline to undertake a classification request under the *de novo* pathway if FDA determines, among other things, that "the device submitted is not of low-moderate risk or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.").

whereas the PMA and *de novo* review standards rely on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review.[135] The standard for a determination of substantial equivalence in a 510(k) review is set out in section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)).[136,137]

During the 510(k) review, FDA considers the device's safety and effectiveness in its substantial equivalence determination (as discussed more fully below), and also in its evaluation of compliance with any applicable special controls, which FDA has determined to be necessary to provide a reasonable assurance of safety and effectiveness for the device type.

Safety and effectiveness are considered in two parts of the FDA's substantial equivalence review. First, FDA must find that the intended use of the device and its predicate are "the same." Under section 513(i)(1)(E)(i) of the FD&C Act (21 U.S.C. § 360c(i)(1)(E)(i)), for the purposes of substantial equivalence review, "[a]ny determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k)."

When a review of the indications for use and all other information in the proposed labeling submitted with a 510(k) supports an intended use that is the same as that of the predicate device, FDA will determine that the new device and predicate device have the same intended use. When a review of the labeling submitted with a 510(k) shows that the indications for use of a new device and predicate device differ, FDA must evaluate whether the new indications for use fall within the same intended use as that of the predicate device. In such cases, FDA determines

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[135] The legislative history of the Medical Device Amendments of 1976 indicates that: "The term 'substantially equivalent' is not intended to be so narrow as to refer only to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The Committee believes that the term should be construed narrowly where necessary to assure the safety and effectiveness of a device but not so narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness." H.R. REP. NO. 94-853, at 36 (1976).

[136] Section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)) states that:

> (i)(1)(A) For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term "substantially equivalent" or "substantial equivalence" means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device –
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> (i) has the same technological characteristics as the predicate device, or
>
> (ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.
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> (B) For purposes of subparagraph (A), the term "different technological characteristics" means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.

[137] In the Safe Medical Devices Act of 1990 (SMDA) (Pub. L. No. 101-629), Congress defined substantial equivalence in section 513(i) of the FD&C Act and required FDA to evaluate whether a new device is as safe and effective as a predicate device when there are technological differences between the devices.

the indications for use of the new device based upon review of the proposed labeling, and then may rely upon relevant clinical or scientific information that does not appear in the proposed labeling submitted with the 510(k) regarding the safety and effectiveness of the new indications for use.[138] Clinical data provided in support of any marketing application, including a 510(k) when those data are relevant to a substantial equivalence determination, should constitute valid scientific evidence as defined in 21 C.F.R. § 860.7(c)(2). Provided it constitutes valid scientific evidence, such data may include a: randomized, multi-arm, "blinded" study with concurrent sham (placebo) control; randomized, multi-arm, "blinded" study with concurrent ("active") control; non-randomized study with concurrent ("active") control; single-arm study with patient serving as own control; single-arm study with historical control (using patient-level data); single-arm study with literature control (historical control); single-arm study with objective performance criteria; single-arm study with performance goals; registry; observational study; systematic review (meta-analysis with patient-level data); meta-analysis based on summary information only; or literature summary.

Second, when comparing a new device to a predicate device, FDA must find that the two devices have "the same technological characteristics," or that a "significant change in the materials, design, energy source or other features of the device" does not raise different questions of safety and effectiveness and that the device is as safe and effective as the legally marketed predicate device.[139]

When evaluating whether a new device is as safe and effective as a predicate device, if the risks associated with the new device increase as compared to the predicate device, as explained in draft guidance,[140] FDA may still determine that the new device is substantially equivalent to the predicate device if, for example, FDA finds from a review of the new device's performance data that there are also increased benefits with the new device as compared to the predicate device. When looking at the increased risks posed by the new device, FDA may consider the degree of risk in comparison to the predicate device. FDA may also consider whether additional measures may help mitigate the increased risks. Depending on the increase in risk of the new device as compared to the predicate device, FDA may determine that the new device is not substantially equivalent to the predicate device, even despite increased benefits of the new device.

Although the 510(k) process involves a comparison of a new device to a predicate device rather than an independent demonstration of the new device's safety and effectiveness, as is required for a PMA and a *de novo* submission, in all these cases FDA's review process reflects a

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[138] *See* section 513(i)(1)(A)(ii)(I) of the FD&C Act (21 U.S.C. § 360c(i)(1)(A)(ii)(I)); 21 C.F.R. § 807.100(b). *See also* FDA, *The 510(k) Process: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], Guidance for Industry and Food and Drug Administration Staff* (July 2014) *at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf.

[139] *See* section 513(i)(1) of the FD&C Act (21 U.S.C. § 360c(i)(1)).

[140] *See* FDA, *Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics, Draft Guidance for Industry and Food and Drug Administration Staff*, 6 (July 2014), *at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM404773.pdf. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

determination of the level of control necessary to provide a "reasonable assurance of safety and effectiveness." The evidentiary standard, however, is different. In the 510(k) context, FDA generally relies, in part, on FDA's prior determination that a reasonable assurance of safety and effectiveness exists for the predicate device. Demonstrating basic similarities between a new device and a predicate device typically requires manufacturers to provide descriptive information such as a comparison of specifications, materials, and technology. In contrast, FDA generally evaluates differences between the new device and the predicate device to determine their effect on safety and effectiveness. It follows that the evidence necessary to show substantial equivalence will increase as differences between the new device and the predicate device increase if those differences significantly affect, or may significantly affect, safety or effectiveness (21 C.F.R. § 807.81).

FDA has determined that certain low-risk class I and class II devices do not require a 510(k) to provide a reasonable assurance of safety and effectiveness. These devices are said to be "510(k) exempt." These devices are exempt from complying with 510(k) requirements subject to certain limitations; however, they are not exempt from certain general controls. For example, 510(k)-exempt devices must:

- be suitable for their intended use
- be adequately packaged and properly labeled
- have establishment registration and device listing forms on file with FDA
- be manufactured under a quality system (with the exception of a small number of class I devices that are subject only to complaint files and general recordkeeping requirements)

2. Adulteration and Misbranding

The FD&C Act prohibits the introduction (or causing the introduction) into interstate commerce of an adulterated or misbranded device.

As discussed above, firms must obtain approval of a PMA for certain high risk, class III devices before introducing the device into interstate commerce (*see* sections 501(f)(1), 513, and 515 of the FD&C Act (21 U.S.C. §§ 351(f)(1), 360c, and 360e) and 21 C.F.R. §§ 814.20 and 814.39) or before introducing an already approved device into interstate commerce with the intent of marketing it for a new use. A device that lacks the necessary PMA approval is adulterated under section 501(f)(1)(B)(i) of the FD&C Act (21 U.S.C. § 351(f)(1)(B)(i)).

For most moderate-risk class I and class II devices, firms must obtain 510(k) clearance before introducing the device into interstate commerce, and before making a major change or modification in the intended use of a cleared device (*see* sections 502(o) and 510(k) of the FD&C Act (21 U.S.C. §§ 352(o) and 360(k)) and 21 C.F.R. § 807.81(a)(3)(ii)).[141] A device is

[141] Devices that are exempt from premarket notification requirements, generally because they are low risk, may be introduced into interstate commerce for the specifically exempt intended use(s) without obtaining FDA clearance

misbranded under section 502(o) of the FD&C Act (21 U.S.C. § 352(o)) if the firm fails to notify the Agency of the intent to introduce the device into commercial distribution as required by section 510(k) of the Act (21 U.S.C. § 360(k)). Additionally, a device that lacks the necessary 510(k) clearance is considered by operation of law to be a class III device that needs an approved PMA, and thus also is adulterated under section 501(f)(1)(B)(i) of the FD&C Act (21 U.S.C. § 351(f)(1)(B)(i)).

For certain low-risk class I and class II devices, firms are exempt from 510(k) clearance as long as, among other things, the device is for the same intended use as a legally marketed device of that generic type (*see* section 510(m)(2) of the FD&C Act (21 U.S.C. § 360(m)(2))). A 510(k)-exempt device that is marketed for an intended use not included in the regulation classifying that generic device type is no longer 510(k)-exempt and is an adulterated, unapproved class III device under section 513(f)(1) of the FD&C Act (21 U.S.C. § 360c(f)(1)).

The labeling and advertisement of devices also are subject to misbranding provisions under the FD&C Act. A device is misbranded if its labeling is "false or misleading in any particular" (section 502(a) of the FD&C Act (21 U.S.C. § 352(a))). Moreover, a restricted device[142] is considered misbranded if its advertising fails to provide adequate information regarding the product's safety and effectiveness, or is otherwise false or misleading (*see* sections 502(q) and (r) of the FD&C Act (21 U.S.C. § 352(q) and (r)); *see also* section 201(n) of the FD&C Act (21 U.S.C. § 321(n))).

(*see* sections 510(l) and (m) of the FD&C Act (21 U.S.C. § 360(l) and (m))). These devices, however, still remain subject to certain general controls such as labeling requirements and other post-market provisions of the FD&C Act. Changing the intended use of such a device generally requires 510(k) clearance and may, in certain situations, require a PMA.

[142] Under section 520(e) of the FD&C Act (21 U.S.C. § 360j(e)), the FDA is authorized to restrict the sale, distribution, or use of a device if there cannot otherwise be reasonable assurance of its safety and effectiveness. A restricted device can only be sold on oral or written authorization by a licensed practitioner or under conditions specified by regulation.

APPENDIX B
EXAMPLES WHERE COMMONLY ACCEPTED UNAPPROVED USES HAVE LED TO PATIENT HARM

A. Erythropoiesis Stimulating Agents (ESAs)

People with anemia have lower than normal amounts of circulating red blood cells, which contain hemoglobin that carries oxygen to body tissues. Anemia causes fatigue and shortness of breath, which adversely affects a person's ability to perform even normal daily activities. Health care providers often treat severe anemia with red blood cell transfusions.[143]

Erythropoiesis-Stimulating Agents (ESAs) (which include Epoetin alfa (marketed as Procrit, Epogen) and Darbepoetin alfa (marketed as Aranesp)) work by stimulating the bone marrow to produce red blood cells. They are currently approved for the treatment of anemia resulting from chronic kidney disease (CKD), chemotherapy, certain treatments for Human Immunodeficiency Virus (HIV), and also to reduce the number of blood transfusions during and after certain major surgeries.

ESAs have been widely used to treat anemia of cancer, regardless of whether or not a patient was undergoing chemotherapy, and have also been in nonanemic cancer patients undergoing chemotherapy and at dosing schedules other than those approved by FDA. At least the unapproved use for anemia of cancer was listed as a "medically-accepted indication" in one of the compendia used to determine coverage for certain federal health care programs.[144]

Subsequently, controlled trials of unapproved use of ESAs revealed decreased survival in cancer patients receiving ESAs and increased risks of cancer relapse.[145] FDA added a boxed warning to ESA products to warn about increased mortality and tumor progression for patients with cancer treated with ESAs. The warning also noted increased risk of serious cardiovascular events and thromboembolic events.

B. Atypical Antipsychotics

Most atypical antipsychotic drugs are approved for treatment of schizophrenia and bipolar disorder. However, they have been commonly used for the unapproved use of treating behavior problems in elderly patients with dementia. Subsequent controlled trials have revealed increased

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[143] *See* Sanjeev Sharma et al., *Transfusion of Blood and Blood Products: Indications and Complications*, 83 AM. FAM. PHYSICIAN 719 (2011).

[144] *See Erythropoiesis-Stimulating Agents: Continued Challenges*, 3 J. ONCOL. PRAC. 248 (2007).

[145] *See* Julia Bohlius et al., *Erythropoietin or Darbepoetin for Patients with Cancer – meta-analysis based on individual patient data (Review)*, COCHRANE DATABASE OF SYSTEMATIC REVIEWS, 3:CD007303 (2009); Brian Leyland-Jones et al., *Maintaining Normal Hemoglobin Levels with Epoetin Alfa in Mainly Nonanemic Patients with Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study*, 23 J. CLIN. ONCOL. 5960 (2005); Michael Henke et al., *Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial*, 362 LANCET 1255 (2003); *Erythropoiesis-Stimulating Agents: Continued Challenges*, 3 J. ONCOL. PRAC. 248 (2007).

mortality resulting from this use, primarily resulting from deaths due to cardiovascular events and infectious disease.[146] These products now bear a boxed warning noting the risks of using them to treat elderly patients with dementia.

C. Premarin/Prempro

Starting in the 1980s and continuing through the 1990s, estrogen use steadily increased among women, in part due to publication of numerous reports presenting observational evidence suggesting a lower incidence of coronary heart disease in estrogen users.[147] During this time, doctors extensively prescribed the estrogen drug Premarin and the estrogen plus progestin drug Prempro for long-term use in women in the hope of preventing the increased risk of coronary heart disease that follows menopause.[148]

FDA first approved Wyeth Pharmaceutical's estrogen product, Premarin, to treat menopausal symptoms, including severe hot flashes, in 1942.[149] In 1995, FDA approved Wyeth Pharmaceuticals' estrogen plus progestin drug, Prempro, to treat menopausal symptoms and prevent postmenopausal osteoporosis.[150] However, FDA did not approve any estrogen products to prevent coronary heart disease or other chronic diseases as no manufacturer produced evidence showing such drugs were safe and effective for this use.[151]

In 1997, when use of Premarin and Prempro to treat coronary artery disease was finally studied as part of the Women's Health Initiative (WHI) – a large government-sponsored randomized placebo-controlled trial – results showed these drugs increased risks of adverse health events in women.[152] Results of the Prempro study showed an increased risk of breast cancer, heart attack, stroke, blood clots in the lungs and legs, and dementia in women using Prempro when compared to a placebo group.[153] Given this conclusion, WHI halted the planned 8-year study after just 5

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[146] *See, e.g.* Donovan T. Maust et al., *Antipsychotics, Other Psychotropics, and the Risk of Death in Patients with Dementia: Number Needed to Harm*, 72 JAMA PSYCHIATRY 438-445 (2015).

[147] Marcia L. Stefanick, *Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration*, 118 AM. J. MED. 64, 67 (2005).

[148] Declaration of Rachel E. Sherman, MD, Par Pharmaceutical, Inc. v. United States, 1:11-cv-1820 (D.D.C. Jan. 11, 2012).

[149] In 1986, FDA also announced that Premarin was effective for prevention of osteoporosis in postmenopausal women. *See* FDA, *Conjugated Estrogens - Letter from Dr. Janet Woodcock*, (May 5, 1997), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm168836.htm.

[150] FDA, *Drugs@FDA.gov: FDA Approved Drug Products Prempro (estrogens, conjugated; medroxyprogesterone acetate) NDA*, *at* http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020527 (last visited Dec. 20, 2016).

[151] FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm.

[152] FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm; National Institutes of Health, *WHI Study Finds No Heart Disease Benefit, Increased Stroke Risk With Estrogen Alone*, (Apr. 13, 2004), *at* https://www.nhlbi.nih.gov/news/press-releases/2004/whi-study-finds-no-heart-disease-benefit-increased-stroke-risk-with-estrogen-alone.

[153] FDA, *Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women*, (Apr. 30, 2009), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339 htm.

years and recommended that doctors not prescribe Prempro to postmenopausal women for cardiovascular protection.[154] WHI also halted the Premarin study early after finding an increased risk of stroke and blood clotting in women using Premarin when compared to a placebo group.[155] After reviewing the WHI findings and recommendations, the Data and Safety Monitoring Board[156] for the trial concluded that, given the risks of the drug, Premarin was not a viable intervention for prevention of chronic diseases, including prevention of chronic heart disease.[157]

After release of the WHI study results, FDA issued a statement encouraging manufacturers to revise estrogen- and progestin-containing drug labels to reflect the risks of unapproved use.[158] By January 2003, FDA and Wyeth revised Premarin and Prempro's labeling to include a boxed warning stating that estrogens and estrogen-plus-progestin therapies should not be used for prevention of cardiovascular disease.[159] FDA also released a guidance document reporting the results of the WHI study, encouraging drug sponsors to seek FDA approval of estrogen drugs only at the lowest doses and exposures possible, and warning against unapproved use of Prempro and Premarin.[160] In 2005, FDA published a second guidance document recommending labeling changes for estrogen drug products, including revising Patient Information leaflets with information about possible side effects and a clear warning to not use estrogen drugs to reduce risks associated with heart disease, such as heart attacks or strokes.[161] FDA has also modified the approved indications for Premarin and Prempro to clarify that these drugs should only be

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[154] Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321, 325 (2002); FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331 htm.

[155] National Institutes of Health, *WHI Study Finds No Heart Disease Benefit, Increased Stroke Risk With Estrogen Alone*, (Apr. 13, 2004), *at* https://www.nhlbi.nih.gov/news/press-releases/2004/whi-study-finds-no-heart-disease-benefit-increased-stroke-risk-with-estrogen-alone.

[156] The Data and Safety Monitoring Board is a committee of experts, with no vested interest in a specific treatment, who are responsible for reviewing ongoing trial data and ensuring the safety of human subjects enrolled in the clinical trials. Data and Safety Monitoring Boards are required for multi-site clinical trials with interventions that entail risk(s) to participants. *See* U.S. Department of Health and Human Services, *Data and Safety Monitoring Boards in NIH Clinical Trials: Meeting Guidance, But Facing Some Issues*, (June 2013), *at* http://osp.od.nih.gov/sites/default/files/resources/oei-12-11-00070.pdf.

[157] Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321, 325 (2002).

[158] FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm; FDA, *Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women*, (Apr. 30, 2009), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm.

[159] FDA, *Prempro/Premphase (conjugated estrogens/medroxyprogesterone acetate tablets)*, *at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153358 htm (last updated Aug. 20, 2013).

[160] FDA, *Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation* (Jan. 2003), *at* http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM135338.pdf.

[161] FDA, *Draft Guidance for Industry, Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling* (Nov. 2005), *at* http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM135336.pdf.

used when the benefits clearly outweigh the risks and advised health care providers to prescribe these drugs to women at the lowest dose and shortest duration possible.[162]

D. Tambocor and Enkaid

FDA approved the antiarrhythmic drugs Tambocor (flecainide), manufactured by 3M Pharmaceuticals, and Enkaid (encainide), manufactured by Bristol-Myers Laboratories, in 1985 and 1986, respectively, to treat life-threatening and symptomatic ventricular arrhythmias.[163] The drug labeling specifically noted the drugs had not been tested in post-heart-attack patients and there was no evidence to show either drug improved patient survival.[164] FDA did not approve either drug for use in patients without symptoms of ventricular arrhythmias.[165]

However, immediately after approval many physicians began prescribing antiarrhythmic drugs such as Tambocor and Enkaid for the unapproved treatment of asymptomatic ventricular arrhythmias, primarily increased rates of ventricular premature beats in patients who had recently experienced heart attacks. Asymptomatic ventricular arrhythmias are associated with decreased survival in such patients.[166] These patients did not exhibit symptoms of ventricular arrhythmias as indicated on the FDA-approved labeling; rather they had abnormal electrocardiograms showing ventricular arrhythmias.[167] Many in the medical community hoped that using Tambocor and Enkaid to reduce asymptomatic ventricular arrhythmias would improve survival of patients who recently experienced heart attacks.[168]

This unapproved use was so widespread that in 1987, the National Institutes of Health (NIH) launched the Cardiac Arrhythmia Suppression Trial (CAST) to investigate the effectiveness of antiarrhythmic drugs in post-heart attack patients.[169] NIH intended recruitment for CAST to last three years but discontinued the study of antiarrhythmic drugs after only two years when preliminary findings showed the risk of death was 2.5 times greater for patients in the treatment

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[162] FDA, *Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women*, (Apr. 30, 2009), *at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339 htm.

[163] *See* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

[164] *See* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

[165] *See* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

[166] Declaration of Rachel E. Sherman, MD, Par Pharm., Inc. v. United States, 1:11-cv-1820 (D.D.C. Jan. 11, 2012).

[167] *See* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

[168] Declaration of Rachel E. Sherman, MD, Par Pharm., Inc. v. United States, 1:11-cv-1820 (D.D.C. Jan. 11, 2012).

[169] FDA, *Promotion of Unapproved Drugs and Medical Devices: Statement of William B. Schultz*, (1996), *at* http://www.fda.gov/newsevents/testimony/ucm115098 htm. *See also* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

versus control group.[170] The trial's Data and Safety Monitoring Board[171] also recommended this arm of the study be halted finding that it was unlikely these drugs could show a benefit in post-heart attack patients.[172]

Because of the CAST study, 3M Pharmaceuticals and Bristol-Myers notified doctors that Tambocor and Enkaid should only be prescribed for patients with life-threatening arrhythmias, and revised the drug labeling to include this warning.[173] Bristol-Myers announced in September 1991 that it was withdrawing Enkaid from the market given continuing uncertainty regarding the implications of the CAST study, and the increasing availability of alternative therapies.[174] While Tambocor remained on the market after publication of the CAST results, FDA required 3M Pharmaceuticals to add two boxed warnings to the drug label cautioning patients who experienced a recent heart attack or suffered from chronic atrial fibrillation not to use the drug.[175]

[170] *See* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.
[171] *See supra* note 156.
[172] Debra S. Echt et al., *Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial*, 324 NEW ENG. J. MED. 781 (1991).
[173] *See* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.
[174] *See* News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), *at* http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.
[175] *See* ABRAMS' CLINICAL DRUG THERAPY: RATIONALES FOR NURSING PRACTICE 464 (Geralyn Frandsen & Sandra Smith Pennington eds., 10th ed. 2014).

APPENDIX C
EXAMPLES OF PRODUCTS MARKETED FOR UNAPPROVED USES THAT CAUSED HARM

A. Aranesp (Amgen, Inc.)

Aranesp, manufactured by Amgen, is one of the ESAs discussed above, approved for treatment of anemia associated with chronic renal failure and for the treatment of chemotherapy-induced anemia in patients.

Amgen later sought FDA approval for a third indication for Aranesp – to treat anemia caused by cancer itself (as opposed to anemia caused by chemotherapy). FDA did not approve Amgen's application for this indication as Amgen failed to provide sufficient evidence demonstrating Aranesp was safe and effective for this indication.[176] Despite not receiving approval, Amgen began promoting Aranesp to treat anemia caused by cancer, as well as the use of less frequent, larger doses of the drug (which also had not been approved).[177] Sales representatives promoted the unapproved use to health care providers with "the very same studies that the FDA had rejected as insufficient to support the safety and efficacy of those off-label uses, when Amgen had applied to expand Aranesp's label to encompass them."[178]

Meanwhile, in January 2007, an Amgen-sponsored trial studying Aranesp showed that Aranesp increased the number of patient deaths when compared to a placebo group.[179] Other studies suggested similar results.[180] FDA issued a safety alert in February 2007 warning that Aranesp was not only ineffective in reducing the need for red blood cell transfusions in anemic cancer patients not receiving chemotherapy, but that the drug also caused a higher rate of patient deaths

[176] Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), *at* http://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal.

[177] Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), *at* http://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal.

[178] Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), *at* http://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal.

[179] Sean Harper, M.D., Amgen, *Aranesp (darbepoetin alfa) Dear Healthcare Professional Letter*, (Jan. 26, 2007), *at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153899 htm.

[180] FDA, *Information for Healthcare Professionals: Erythropoiesis Stimulating Agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)]*, (Nov. 8, 2007), *at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126481.htm.

compared to the standard of care.[181] In light of these findings, FDA also required Aranesp to bear a boxed warning to advise the public of these risks.[182]

B. Seprafilm (Genzyme Corp.)

In 1996, FDA approved Genzyme Corporation's Seprafilm.[183] Seprafilm is a thin film indicated for use in patients undergoing abdominal or pelvic laparotomy as an adjunct intended to reduce the incidence, extent, and severity of postoperative adhesions between the abdominal wall and the underlying viscera such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures.[184] A laparotomy is a surgical procedure that involves making an incision into the abdominal wall that allows the surgeon to gain access to and visualize the internal organs using standard surgical instruments.[185] By contrast, laparoscopy is a surgical technique in which short, narrow tubes are inserted into the abdomen through smaller incisions; Seprafilm has never been FDA-approved for use in laparoscopic surgical procedures.[186]

Between 2005 and 2010, in response to diminishing sales due to a diminishing number of laparotomies being performed, Genzyme sales representatives taught doctors and other staff to alter Seprafilm into a "slurry" – a new medical device that lacked an approved application for premarket approval – for use in laparoscopic surgeries by inserting a catheter filled with the mixture into the body and squirting it into the abdominal cavity.[187] Genzyme also distributed promotional material that implied Seprafilm had been proven safe and effective for use in gynecologic cancer surgeries, even though Seprafilm's labeling cautioned that the device had not been clinically evaluated in the presence of malignancies.[188]

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[181] *See* FDA, *Aranesp (darbepoetin alfa) February 2007*, *at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150817 htm (last updated Aug. 27, 2013).

[182] *See* FDA, *Aranesp (darbepoetin alfa) February 2007*, *at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150817 htm (last updated Aug. 27, 2013).

[183] *See* FDA, *Premarket Approval (PMA) Database: Seprafilm P950034*, *at* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P950034 (last visited Dec. 23, 2016).

[184] *See* FDA, *Premarket Approval of Genzyme Corporation's Seprafilm Bioresorbable Membrane – ACTION*, (Aug. 12, 1996), *at* http://www.accessdata fda.gov/cdrh_docs/pdf/p950034.pdf (last visited Dec. 23, 2016).

[185] Department of Justice, *Information*, United States v. Genzyme Corp., No 8:15-cr-352-JSM-AEP, (M.D. Fla. Sept. 3, 2015), at https://www.justice.gov/opa/file/767301/download (last visited Dec. 23, 2016).

[186] Department of Justice, *Information*, United States v. Genzyme Corp., No 8:15-cr-352-JSM-AEP, (M.D. Fla. Sept. 3, 2015), at https://www.justice.gov/opa/file/767301/download (last visited Dec. 23, 2016).

[187] *See* Department of Justice, *Genzyme Corp. to Pay $22.28 Million to Resolve False Claims Allegations Related to "Slurry" Used in Patients*, (Dec. 20, 2013), *at* https://www.justice.gov/opa/pr/genzyme-corp-pay-2228-million-resolve-false-claims-allegations-related-slurry-used-patients; *Deferred Prosecution Agreement*, United States v. Genzyme Corp., No 8:15-cr-00352-JSM-AEP-1, (M.D. Fla. Aug. 31, 2015), *at* https://www.justice.gov/opa/file/767286/download.

[188] *See* Department of Justice, *Genzyme Corporation to Pay $32.5 Million to Resolve Criminal Liability Relating to Seprafilm*, (Sept. 3, 2015), *at* https://www.justice.gov/opa/pr/genzyme-corporation-pay-325-million-resolve-criminal-liability-relating-seprafilm; *Deferred Prosecution Agreement*, United States v. Genzyme Corp., No 8:15-cr-00352-JSM-AEP-1, (M.D. Fla. Aug. 31, 2015), *at* https://www.justice.gov/opa/file/767286/download; Department of Justice, *Information*, United States v. Genzyme Corp., No 8:15-cr-352-JSM-AEP, (M.D. Fla. Sept. 3, 2015), at https://www.justice.gov/opa/file/767301/download (last visited Dec. 23, 2016).

C. Depakote (Abbott Laboratories)

In 1983, FDA approved Abbott Laboratories' drug Depakote to treat patients suffering from epileptic seizures.[189] Subsequently, in 1996, FDA approved Depakote to treat bipolar mania and for prevention of migraines.[190] Abbott sponsored a study of Depakote for treatment of agitation in elderly patients with dementia, but that trial was discontinued in 1999 after subjects experienced an increase in drowsiness, dehydration, and anorexia.[191] Abbott also sponsored two trials to study Depakote for treatment of schizophrenia, but both failed to show patients benefited from Depakote when compared to a control group. Abbott waited nearly two years to share these study results with its sales representatives and approximately four years to publish the results.[192]

Despite these study results, from 1998 through 2006, Abbott sales staff reportedly targeted nursing home employees to promote unapproved uses of Depakote, including for treatment of agitation and aggression in elderly patients suffering from dementia.[193] According to Department of Justice allegations, the company also marketed Depakote for treatment of schizophrenia in nursing homes from 2001 until 2006.[194]

D. Neurontin (Warner-Lambert)

In 1993, FDA approved Warner-Lambert's drug Neurontin as an adjunctive or supplemental medication to control partial onset seizures in adults.[195] In 1996, Warner-Lambert sought FDA approval to use Neurontin as the sole drug (monotherapy) for epileptic seizures, and sought an increase in Neurontin's effective dose range and maximum recommended dose. FDA did not approve the indication, stating that Warner-Lambert did not provide sufficient evidence to support approval of Neurontin as a monotherapy,"[196] and FDA would not approve the changes in

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[189] In re Abbott Depakote S'holder Derivative Litig., 909 F. Supp. 2d 984, 989 (N.D. Ill. 2012).
[190] In re Abbott Depakote S'holder Derivative Litig., 909 F. Supp. 2d 984, 989 (N.D. Ill. 2012). *See also* FDA, *Drugs@FDA.gov: FDA Approved Drug Products Depakote (divalproex sodium) NDA*, *at* http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018723 (last visited Dec. 21, 2016).
[191] In re Abbott Depakote S'holder Derivative Litig., 909 F. Supp. 2d 984, 989 (N.D. Ill. 2012); *see also* Department of Justice, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), *at* http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote.
[192] Department of Justice, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), *at* http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote.
[193] Department of Justice, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), *at* http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote.
[194] Department of Justice, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), *at* http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote.
[195] Alicia Mack, *Examination of the Evidence for Off-Label Use of Gabapentin*, 9 J MANAGED CARE PHARM. 559 (2003).
[196] David Kessler Expert Report, In re Neurontin Mktg., Sales Practices and Prod. Liab. Litig., *available at* 2008 WL 7018942 (D. Mass. July 31, 2008).

dose because controlled trials failed to provide evidence that higher doses of Neurontin are more effective than those recommended.[197] In 1996, the firm sought FDA approval of Neurontin as a monotherapy for partial seizures in adult patients not previously treated with an antiepileptic drug. However, in 1997, FDA declined to approve the additional use because Warner-Lambert again failed to provide evidence showing Neurontin was a safe and effective monotherapy for partial seizures, as required to support FDA approval of a new indication.[198]

Despite FDA's decision, Warner-Lambert marketed Neurontin as monotherapy to treat epileptic seizures and a wide array of other ailments – including broad neuropathic pain, migraine headache, and bipolar disorder – all of which were unapproved uses of the drug.[199] This marketing occurred despite there being no scientific evidence supporting use of Neurontin to treat many of these diseases or conditions. For example, Warner-Lambert promoted Neurontin as an effective treatment for bipolar disorder, even though a scientific study conducted between 1996 and 1997 demonstrated that a placebo worked as well or better than the drug.[200] Warner-Lambert itself estimated that "only about ten percent of Neurontin prescriptions that year were for the FDA-approved on-label uses for epilepsy or postherpetic neuralgia, and that more than a third of prescriptions were for unapproved treatment of neuropathic pain, migraine or headache, or bipolar disorder."[201]

E. Atypical Antipsychotics

Antipsychotic drugs are one of the top selling classes of pharmaceuticals. In 2008, sales of antipsychotic drugs exceeded $10 billion in retail U.S. pharmacies, representing the largest expenditure for any single drug class.[202] FDA generally approves these drugs for narrow indications, such as treatment of schizophrenia or bipolar disorder in adults. However, despite FDA approving these drugs to treat disorders that affect a small minority of the U.S. population, drug manufacturers have marketed antipsychotic drugs for unapproved uses, with serious public health risks and consequences, as the examples below illustrate.

[197] In re Neurontin Mktg. & Sales Practices Litig., No. 04-CV-10739-PBS, 2011 WL 3852254, at *6 (D. Mass. Aug. 31, 2011) , aff'd, 712 F.3d 21 (1st Cir. 2013).
[198] David Kessler Expert Report, In re Neurontin Mktg., Sales Practices and Prod. Liab. Litig., *available at* 2008 WL 7018942 (D. Mass. July 31, 2008).
[199] In re Neurontin Mktg. & Sales Practices Litig., No. 04–CV–10739–PBS, 2011 WL 3852254, at *1 (D. Mass. Aug. 31, 2011).
[200] In re Neurontin Mktg. & Sales Practices Litig., No. 04-CV-10739-PBS, 2011 WL 3852254, at *12 (D. Mass. Aug. 31, 2011) aff'd, 712 F.3d 21 (1st Cir. 2013).
[201] In re Neurontin Mktg. & Sales Practices Litig., 712 F.3d 21, 28 (1st Cir.), *cert. denied sub nom.*, Pfizer Inc. v. Kaiser Found. Health Plan, Inc., 187 L. Ed. 2d 594 (2013).
[202] Rosanne Spector, *Evidence lacking for widespread use of costly antipsychotic drugs, says researcher*, (Jan. 6, 2011), *at* http://med.stanford.edu/news/all-news/2011/01/evidence-lacking-for-widespread-use-of-costly-antipsychotic-drugs-says-researcher html.

1. Zyprexa (Eli Lilly)

FDA approved Zyprexa, manufactured by Eli Lilly, in 1996 for treatment of schizophrenia.[203] In 2000, FDA also approved Zyprexa for the treatment of bipolar disorder.[204]

In 1999, Eli Lilly began promoting Zyprexa for a number of unapproved uses in nursing homes and assisted living facilities.[205] Eli Lilly marketed Zyprexa for treatment of agitation, aggression, hostility, dementia, Alzheimer's dementia, depression, and generalized sleep disorder in elderly patients.[206] In 2000, Eli Lilly began promoting Zyprexa to primary care physicians – even though these physicians do not typically treat schizophrenia or bipolar disorder.[207] Eli Lilly trained sales staff to promote Zyprexa to primary care physicians for the unapproved treatment of anxiety, irritability, depression, nausea, Alzheimer's disease, and other mood disorders.[208]

Around this time, FDA received clinical trial information showing elderly patients taking Zyprexa had in increased risk of death due to cardiovascular and infectious diseases. In addition, these trials showed Zyprexa had little or no benefit in reducing dementia-related symptoms and caused weight gain, increased cholesterol levels, and diabetes. Studies found that unapproved use of Zyprexa was responsible for widespread adverse effects and many deaths.[209]

In 2005, FDA issued a public health advisory warning that use of antipsychotic medications, such as Zyprexa, was associated with increased mortality in elderly patients. FDA also required a boxed warning be added to Zyprexa stating that "[e]lderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at increased risk of death compared to placebo."[210]

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[203] FDA, *Drugs@FDA.gov: FDA Approved Drug Products Zyprexa (olanzapine) NDA, at* http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020592 (last visited Dec. 20, 2016).

[204] FDA, *Drugs@FDA.gov: FDA Approved Drug Products Zyprexa (olanzapine) NDA, at* http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020592 (last visited Dec. 20, 2016).

[205] Department of Justice, *Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), *at* http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html.

[206] Department of Justice, *Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), *at* http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html.

[207] Department of Justice, *Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), *at* http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html.

[208] Department of Justice, *Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), *at* http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html.

[209] FDA, *Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances*, (Apr. 11, 2005), *at* http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171.

[210] FDA, *Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances*, (Apr. 11, 2005), *at* http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171.

2. Geodon (Pfizer)

In 2001, FDA approved Geodon, manufactured by Pfizer, for treatment of schizophrenia.[211] However, Pfizer promoted Geodon for treatment of many conditions not approved by FDA, including treatment of depression, mood disorder, anxiety, aggression, dementia, attention deficit hyperactivity disorder, obsessive-compulsive disorder, autism, and post-traumatic stress disorder, in both children and adults.[212] Pfizer hired physicians across the U.S. to help promote unapproved Geodon use in children by giving promotional lectures encouraging doctors to prescribe the drug to children, despite the fact that Geodon was not approved for use in children, and to prescribe the drug at substantially higher amounts than the approved dosages.[213]

3. Seroquel (AstraZeneca)

FDA approved Seroquel, manufactured by AstraZeneca, to treat symptoms of psychotic disorders, for short-term treatment of bipolar mania, and for treatment of bipolar depression.[214] Between 2001 and 2006, AstraZeneca widely promoted Seroquel to psychiatrists and other health care providers for unapproved uses. AstraZeneca marketed Seroquel for treatment of aggression, Alzheimer's disease, anger management, anxiety, attention deficit disorder, bipolar maintenance, dementia, depression, mood disorder, post-traumatic stress disorder, and sleeplessness, despite the fact FDA has not found Seroquel to be safe and effective for these indications. AstraZeneca marketed Seroquel to doctors who do not typically treat schizophrenia or bipolar disorder, including doctors who treat the elderly, primary care physicians, pediatric and adolescent physicians, and to doctors working in long-term care facilities and prisons. The company promoted unapproved uses of Seroquel through company-sponsored continuing medical education programs and recruited doctors to serve as authors of articles that were ghostwritten by medical literature companies and about studies the doctors in question did not conduct.[215]

4. Abilify (Bristol-Myers Squibb)

In 2002, FDA approved Abilify, manufactured by Bristol-Myers Squibb Company (BMS), for treatment of schizophrenia. Abilify was subsequently approved for other indications. However, BMS promoted Abilify for treatment of conditions not approved by FDA, including use in elderly patients with symptoms consistent with dementia as well as for unapproved uses in

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[211] FDA, *Drugs@FDA.gov: FDA Approved Drug Products Geodon (ziprasidone hydrochloride) NDA, at* http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020825 (last visited Dec. 20, 2016).

[212] Department of Justice, *Pharmaceutical Company Pfizer, Inc. to Pay $301 Million for Off-Label Drug Marketing*, (Sept. 2, 2009), *at* http://www.justice.gov/archive/usao/pae/News/2009/sep/pfizerrelease.pdf.

[213] Department of Justice, *Pharmaceutical Company Pfizer, Inc. to Pay $301 Million for Off-Label Drug Marketing*, (Sept. 2, 2009), *at* http://www.justice.gov/archive/usao/pae/News/2009/sep/pfizerrelease.pdf.

[214] FDA, *Drugs@FDA.gov: FDA Approved Drug Products Seroquel (quetiapine fumurate) NDA, at* http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020639 (last visited Dec. 20, 2016).

[215] Department of Justice, *Pharmaceutical Giant AstraZeneca to Pay $520 Million for Off-label Drug Marketing*, (Apr. 27, 2010), *at* http://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing.

children.[216] In 2006, Abilify received a boxed warning against its use in the treatment of dementia-related psychosis. The warning states: "Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis."[217]

F. Metacam (Boehringer Ingelheim Vetmedica, Inc.)

In 2003, FDA approved the use of Metacam (meloxicam) oral tablets as a non-steroidal anti-inflammatory drug (NSAID) for the control of pain and inflammation associated with osteoarthritis in dogs.[218] The following year, FDA approved Metacam for use as a subcutaneous injection in both cats and dogs.[219] Although cats are particularly sensitive to NSAIDs due to a limited ability to break them down compared to other species,[220] at that time there were no NSAIDs available to treat pain and inflammation in cats. FDA therefore balanced the risks against the benefits and approved Metacam for cats only as a single-dose, one-time injection prior to surgery for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration.[221]

In a tolerance study submitted to FDA in 2004 to support approval of Metacam, Boehringer Ingelheim Vetmedica, Inc., the manufacturer, found serious risks regarding long-term oral Metacam use in cats. The purpose of the study was to assess the tolerance in cats following multiple doses of Metacam over a period of 10 days. The study concluded that Metacam, "when initially dosed as a subcutaneous injection followed by oral dosing for nine days at [$\geq$ 0.14 mg per pound] was associated with severe adverse effects, including death."[222]

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[216] Delaware State Government Press Release, *Forty-Three Attorneys General Reach Consumer Protection Settlement With Bristol-Myers Squibb Company Over Abilify Marketing* (Dec. 8, 2016), *at* http://news.delaware.gov/2016/12/08/a1/; Department of Justice, *Bristol-Myers Squibb to Pay More Than $515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing* (Sept. 28, 2007), *at* https://www.justice.gov/archive/opa/pr/2007/September/07_civ_782 html.

[217] Abilify Prescribing Information (last revised Aug. 2016), *at* http:// www.accessdata.fda.gov/drugsatfda_docs/label/2016/021436s041,021713s032,021729s024,021866s026lbl.pdf.

[218] FDA, *Freedom of Information Summary, NADA 141-213 Metacam*, (Apr. 15, 2003), *at* http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118006.pdf.

[219] FDA, *Freedom of Information Summary, NADA 141-219 Metacam*, (Oct. 28, 2004), *at* http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118027.pdf.

[220] FDA, *Over-the-Counter Pain Relievers for People—Are They Safe for Pets?*, *at* http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm392732.htm#OTC (last updated Oct. 26, 2016).

[221] *See* FDA, *Freedom of Information Summary, NADA 141-219 Metacam*, (Oct. 28, 2004), *at* http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118027.pdf; FDA, *NADA Number: 141-219*, *at* http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=141-219 (last visited Dec. 21, 2016).

[222] FDA, *Freedom of Information Summary, NADA 141-219 Metacam*, (Oct. 28, 2004), *at* http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118027.pdf.

After Metacam was approved on a limited basis for use in cats, the manufacturer then began promoting Metacam for unapproved uses. In an April 2005 Notice of Violation letter, FDA cited a free CD that the manufacturer was distributing to veterinarians titled "Pain: How to Understand, Recognize, Treat, Stop."[223] The CD mailer included the photographic images of a parrot, guinea pig, cat, reptile, and dog, suggesting that Metacam was safe and effective for uses that had never been demonstrated.

By September 2010, FDA had received hundreds of adverse event reports associated with oral dosing of Metacam, including reports of several feline deaths, including from euthanization, and numerous reports of kidney failure.[224] Based on these reports, FDA asked the manufacturer to add a boxed warning to Metacam explicitly stating that "[r]epeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats."[225]

[223] FDA, *Notice of Violation letter to Boehringer Ingelheim Vetmedica, Inc.*, (Apr. 19, 2005), *at* http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/ucm042460.pdf.

[224] FDA, *CVM ADE Comprehensive Clinical Detail Report Listing*, (Jan. 1, 1987-Apr. 30, 2013), *at* http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM055409.pdf (last visited Dec. 20, 2016).

[225] *See* FDA, *Information about the Boxed Warning on METACAM® (meloxicam) Labels*, *at* http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm472976.htm (last updated Nov. 17, 2015).