Systemic, Societal, and Legal Developments Require Changes To FDA's Regulation of Manufacturer Speech

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Executive Summary

This White Paper has been prepared by the Medical Information Working Group (MIWG), a coalition of research-based biopharmaceutical and medical technology developers and manufacturers. The MIWG was formed in 2006 to improve the federal regulatory framework and enforcement climate affecting manufacturer dissemination of information about prescription drugs, biological products, and medical devices, including information about new uses of approved products. The MIWG and its members have made numerous submissions to FDA, including two citizen petitions (2011 and 2013) requesting clarification of and substantive changes to the existing regulatory framework. On June 6, 2014, FDA granted both petitions and announced both targeted changes and a "comprehensive review of the regulatory regime governing communications about medical products" as requested by the MIWG.[1] The MIWG appreciates FDA's ongoing efforts to address the issues raised in its submissions. The MIWG was pleased to hear comments by FDA officials at the Food and Drug Law Institute's Annual Conference this past April, stating that the Agency is aware of the evolving First Amendment jurisprudence, as well as changes in how information is conveyed and health care is delivered, and is committed to evaluating the regulatory scheme in light of those developments. The purpose of this White Paper is to address key outstanding issues as FDA officials conduct their comprehensive review.[i]

"Off-Label" Use. Once FDA has authorized a prescription drug or medical device for marketing, the product must be accompanied by FDA-

[i] The White Paper is not intended as an exhaustive summary of MIWG proposals or positions. We have, for example, submitted comments to FDA on a variety of guidance documents and in response to comment solicitations (e.g., on the Medical Policy Council agenda and "scientific exchange," see 78 Fed. Reg. 16,679 (Mar. 18, 2013) and 76 Fed. Reg. 81,508 (Dec. 28, 2011)). Those comments are not recapitulated here. Nor do we address in this White Paper certain other issues identified by FDA officials as currently under review, such as the level of substantiation required for "out-of-label" communications.

approved labeling bearing information necessary for safe and effective use. After FDA approval or clearance of a drug or device, a practitioner may, in treating patients, prescribe and use the product for indications and under circumstances not described in the indications and usage section of the FDA-approved labeling. Uses not set forth in the indications and usage section are referred to as "off-label" uses, and information not set forth in labeling is often referred to as "off-label" information. These terms encompass both new indications and information that supplements an indication, such as information regarding dosing, use in subpopulations, and use in combination with other drugs. FDA is not authorized to and does not interfere with off-label use within the context of medical or surgical practice. The standard of care often may require uses that are not included in a product's approved labeling, and in many instances a "new" use may be as well-established by scientific data as labeled uses. For some diseases, off-label uses either are the only therapies available, or are the therapies of choice, particularly in certain areas of practice.

Recognizing that off-label use is a key aspect of quality patient care, Congress has mandated that certain federal health care programs, such as Medicare Part B, Medicare Part D, and Medicaid cover off-label uses that are "medically accepted" as that term is defined by applicable statutes and guidance.[2] These programs also have discretion to cover other off-label uses. As a matter of necessity, federal programs and their private counterparts exercising their discretionary authority make coverage and payment decisions using sources of information other than FDA-approved labeling, and these sources may not satisfy the regulatory standards that the Agency uses in making marketing authorization decisions.

Practitioners and patients also need meaningful access to a wide range of accurate, science-based information to inform health care decisions.

Manufacturers often have unique access to information of great public health importance, and also often the ability and the incentive to advance the scientific process through contributions to scientific exchange and investments in the processes of science themselves. This fact, and the inherent limitations of FDA-approved labeling, including, for example, the fact that advances in medical knowledge generally precede labeling revisions, mean that there must be room in the regulatory scheme for manufacturers to communicate broadly to various stakeholders without limiting the information they provide to that which appears in approved labeling.

FDA's regulatory approach to industry communications about off-label uses of medical products is built on a handful of regulations and statutory provisions that in many cases are more than 50 years old. As discussed in Part I, in recent years, seismic shifts in the structure of the health care delivery system, in patient involvement in health care decisions, and in the law have affected the context in which FDA administers its legislatively granted authorities.

- **Shifts In Health Care Delivery.** Public and private payors increasingly emphasize value in health care and reward providers that deliver high-quality care to their patients. To provide the best care, meet performance benchmarks, and assess value, payors and practitioners need a wealth of information, some of which does not appear in FDA-approved labeling.

- **Increased Patient Involvement In Health Care Decisions.** Technological advances are enabling patients to play a bigger role in their health care decisions, and indeed, enhanced access to information about medical products and treatments helps health care practitioners and patients engage in well-informed conversations about the available range of health care choices and make decisions based upon accurate and up-to-date

information.[ii] It is critical that health care practitioners and their patients have the benefit of access to truthful and non-misleading information about medical products and are equipped to make health care decisions that best serve the patient, even where some of that information is not contained in the FDA-approved product labeling.

- **Changes In The Law.** Manufacturer speech about medical treatments is entitled to a high level of protection under the United States Constitution. The courts have recognized that, under the First Amendment, manufacturers must be recognized as valuable contributors to available information about health care in the modern technological age. Both the First Amendment and the Due Process Clause of the Fifth Amendment require "precision" and "narrow specificity" in content regulation, and these standards are more demanding where, as in the case of the Federal Food, Drug, and Cosmetic Act (FDCA), violations are punishable criminally. In short, FDA can regulate manufacturer speech only through precise, clear rules, and those rules must be appropriately tailored and well-defined to avoid chilling protected manufacturer speech.

Key MIWG Proposals. Part II sets forth key MIWG proposals, some of which have been advanced in prior submissions, that we continue to believe merit careful assessment by agency officials. These proposals are as follows:

- Proposal #1 – Amend the Regulations Recognizing "Scientific Exchange" in 21 C.F.R. §§ 312.7(a) & 812.7 and Create a New Regulation Recognizing

[ii] FDA imposes differing requirements on manufacturer communications according to intended audience, with consumer-, HCP-, and payor-directed materials subject to different sets of standards in recognition of the different levels of training and experience of those respective audiences. Access to health care information is necessary for patients to engage in well-informed conversations with their HCPs about the range of health care choices available to them, and HCPs and payors have specialized information needs that may differ from those of patients. We do not here address whether FDA should permit less manufacturer communication to patients on the ground that they lack the training or experience necessary to evaluate the quality of that information, except to note that there may be legal or other impediments to an approach that distinguishes according to intended audience.

"Scientific Exchange" Outside the Investigational Context. For many years, FDA has explicitly recognized that the law does not forbid a manufacturer from engaging in "scientific exchange," a type of non-promotional communication about drugs and medical devices that is important for the public health. This speech includes scientific findings disseminated by or on behalf of product developers about investigational products and new uses of marketed products. The main purpose of Proposal #1 is to clearly delineate when communications qualify as scientific exchange so that manufacturers and FDA can know in advance whether a proposed scientific communication is permissible scientific exchange, or is subject to regulation as advertising or labeling. The MIWG proposes revisions to 21 C.F.R. §§ 312.7 and 812.7, which are found in FDA regulations governing investigational products, to clarify when the scientific exchange concept applies in the investigational context. In addition, recognizing that scientific exchange is constitutionally protected and applies more broadly, the MIWG also proposes a new regulation to clarify when scientific exchange applies outside the investigational context.

- Proposal #2 – Issue New Interpretive Guidance Confirming that "Labeling" Is Defined by 21 C.F.R. § 1.3(a) and 21 U.S.C. § 321(m). The purpose of this proposal is to bring much-needed clarity to the definition of "labeling," which defines the main category of manufacturer communication that FDA is empowered to regulate under the law. Currently, manufacturers do not have clear guidance as to the types of communications that are within this key statutory definition, and the lack of clarity undermines the ability of payors, practitioners, and patients to receive high-quality information about drugs and medical devices.

- Proposal #3 – Amend the Regulatory Definitions of "Intended Use" in 21 C.F.R. §§ 201.128 & 801.4. The purpose of Proposal #3 is to assure that manufacturers and FDA operate from a common understanding, consistent with the relevant legislation and case law, regarding the types of evidence that can be used in a specific type of enforcement action against a manufacturer for "off-label promotion" of a drug or medical device. This evidence, which is referred to as evidence of "intended use", has been the subject of significant confusion and controversy over the years. Clarifying the definition of this important concept would support effective enforcement of the law by assuring that manufacturers have a clear understanding of the types of communications that can be used as evidence against them in these enforcement actions, while avoiding an undue chill on truthful and non-misleading speech.

As with the other proposals, the ultimate objective is to bring clarity to the regulatory scheme to support effective enforcement while avoiding an undue chill on truthful and non-misleading speech. These proposals are intended to ensure that FDA's regulatory approach adequately reflects recent social and legal developments, while preserving the Agency's ability to require manufacturers to support adequately the efficacy of drugs, biological products, and medical devices for all the uses for which they are promoted.

Implications of MIWG Proposals. The proposals outlined in this White Paper and in prior MIWG submissions would promote and protect the public health and advance patient care by establishing a clearly articulated and appropriately regulated role for manufacturers to provide scientifically accurate, clinically relevant information to patients, caregivers, and providers. They would also allow manufacturers to provide reliable economic analyses to payors and managed care organizations to support prescribing, product selection, and coverage and reimbursement decisions. The MIWG is not seeking

any alterations to FDA's existing high standards for the premarket review of new medical products. Nor is the MIWG requesting changes that would allow promotion of a new use without FDA first finding that the product is safe and effective for that use. Under the MIWG's proposed approach, FDA would retain its authority over promotional labeling, advertising, and statements that may be used as evidence of a new intended use, while manufacturers could make available through other channels accurate, science-based data and information to inform health care decision-making.

In sum, as we explain, nothing we are asking FDA to consider would interfere with the Agency's ability to engage in effective regulation. Our proposals would, however, bring greater clarity and coherence to the regulatory framework for medical products, and provide better access to the full range of data sources key stakeholders need to make sound, well-informed health care decisions.

Introduction

> "Advances in medical knowledge and practice inevitably precede labeling revision."
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> 40 Fed. Reg. 15,392, 15,394 (Apr. 7, 1975)

Once FDA has authorized a prescription drug or medical device for marketing, the product must be accompanied by FDA-approved labeling bearing information necessary for safe and effective use.[3] This labeling is not intended to be, and indeed cannot be, comprehensive.

In developing a new medical product, the manufacturer determines the use for which the product will be investigated—first in the laboratory and then in clinical trials.[4] Decisions relating to the use under investigation reflect a variety of considerations, including the likelihood that the product will have an appropriate risk/benefit profile in that use, the potential market for the product for that use, and the feasibility of designing and completing clinical trials of the product for that use. If the product is ultimately approved by FDA, its labeling contains information about the use for which the product has been studied and found "safe and effective." Medical products, however, once approved for any use, may be—and often are—prescribed for other uses. Uses not set forth in labeling are referred to as "off-label" uses, and information not set forth in labeling is often referred to as "off-label" information.[5]

A product's approved uses, which are set forth in the approved labeling, thus differ from its actual or known uses. FDA regulations require that the approved labeling for a new drug "contain a summary of the essential scientific information needed for the safe and effective use of the drug."[6] The labeling, however, cannot simultaneously provide a fully substantiated set of clinically relevant facts about the labeled use of a product and also set forth all that might be known in the medical community about potentially beneficial

uses. In other words, because "advances in medical knowledge and practice inevitably precede labeling revision,"[7] approved labeling "cannot be both authoritative and avant-garde."[8]

Once a drug or device has been approved for marketing, a practitioner may, in treating patients, prescribe and use the product for indications and under circumstances not described in the FDA-approved labeling.[9] FDA is not authorized to and does not interfere with off-label use within the context of medical or surgical practice.[10] So long as a practitioner complies with state medical practice standards—including the use of due care—he or she may depart from the conditions of use set forth in approved labeling for a drug or device. As FDA has acknowledged, the "[s]tandard of care may include uses or treatment regimens that are not included in a product's approved labeling[.]"[11]

Practitioners often depart from the conditions of use in FDA-approved labeling "[b]ecause the pace of medical discovery runs ahead of the FDA's regulatory machinery," rendering off-label uses the "'state-of-the-art' treatment."[12] In many instances a "new" use may be as well-established by scientific data as labeled uses. Where off-label use constitutes the standard of care, non-use can raise malpractice concerns—making such use not just lawful but indeed effectively mandatory.[13] For some diseases, off-label uses either are the only therapies available, or are the therapies of choice, particularly in certain areas of practice.[14]

Oncologists, in particular, vary the conditions of use set forth in approved labeling because cancer patients "are regularly faced with few approved treatment options, especially if the first treatment didn't work."[15] Many uses of cancer drugs "are common in clinical practice, but are not listed in approved product labeling, despite the fact that they appear to be supported by published data from clinical studies."[16] "Approximately half of the

uses of anticancer chemotherapy drugs are for indications other than those referenced in the United States Food and Drug Administration approved label."[17] "[A] drug that is effective in treating one type of cancer is often found to be effective in treating other types of cancer," even though it may not have been approved for use with all of those types.[18] As the American Society of Clinical Oncology stated in a letter to FDA in 2002, "the gold standard of care for many cancers frequently involves the off-label use of approved drug products."[19] FDA itself has recognized that oncologists in daily practice use drugs off-label based on published data and prior clinical experience.[20]

In psychiatry, as well, multiple treatment attempts and methods may be necessary before a successful therapy can be found for a patient, and a drug that is approved to treat one condition may also treat a related, but unlabeled, one. Patients are treated based on symptoms rather than on specific diagnoses, and there are even psychiatric disorders for which no approved drug has an indication, such that off-label use is the only option for drug therapy.[21] Even if FDA has approved a drug for a particular condition, the patient may fall outside the labeled patient population, or might need a higher or lower dosage. As a result, uses of approved drugs in ways that depart from approved labeling are common in psychiatry.

Recognizing that off-label use is a key aspect of quality patient care, Congress has mandated that certain federal health care programs, such as Medicare Part B, Medicare Part D, and Medicaid, cover off-label uses that are "medically accepted."[22] In addition, such programs are authorized in their discretion to reimburse for other "off-label treatments."[23] As a matter of necessity, federal programs and their private counterparts exercising their discretionary authority make product selection, coverage, and payment decisions using sources of information other than FDA-approved labeling, and

these sources may not satisfy the regulatory standards that the Agency uses in making product approval decisions.

To make sound health care decisions, payors, practitioners, and patients need accurate, science-based information. Manufacturers often have both unique access to such information, and the ability and the incentive to contribute to scientific exchange and invest in science itself. The regulatory scheme must leave room for manufacturers to communicate broadly to various stakeholders, without limiting the information they provide to the FDA-approved labeling.

I. The Need for Changes to the Regulatory Regime

A. Seismic Shifts in Health Care

For many years, organizations that pay for care, utilizing formularies to manage their drug spend,[iii] have played a unique and important role in health care. Their coverage and reimbursement decisions can significantly influence the care that a patient receives.

> "[P]rivate and public payers are embracing a new perspective on health care payment and delivery—one that emphasizes value over volume and rewards providers that deliver high-quality care."
>
> DHHS, 2013 Annual Progress Report to Congress: National Strategy for Quality Improvement in Health Care

Payors routinely look beyond FDA-approved labeling to assess products and try to identify the most cost-effective ways to achieve desired health outcomes.[24] A heterogeneous mix of information informs coverage and reimbursement decisions, including comparative outcomes and price information as well as early information about investigational products.[25] In many cases, this information is not set forth in approved labeling because it concerns clinical endpoints, dosing regimens, or patient populations, including patient subgroups, for which the drug or device has not been FDA-approved. In addition, information of interest to payors often is derived from meta-analyses, uncontrolled observational studies, and other sources that, under FDA's current approach. would not necessarily be considered sufficient to support statements in FDA-approved labeling.[26] See Table 1.

[iii] These entities may include population health decision-makers such as integrated delivery networks (IDNs), treatment guideline and pathway developers, and compendium publishers.

Table 1. Key Stakeholders Turn to Different Sources of Information About FDA-Regulated Products

FDA Standards	Health Care Practitioners	Payors
• "Adequate and well-controlled" clinical investigations (drugs) *21 C.F.R. § 314.126* • "Valid scientific evidence" (devices) *21 C.F.R. § 860.7*	• "Information contained in [the] labeling and other adequate scientific data" available to them *37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972)*	• Experimental studies (e.g., randomized controlled trials), pragmatic clinical trials (e.g., controlled studies within clinics), prospective non-experimental studies (e.g., registry studies and cohort studies), retrospective analyses (e.g., claims analyses and medical record analyses), decision modeling (e.g., decision tree, Markov model, and budget impact model), and systematic reviews (e.g., meta-analyses) *See Anthony Wang et al., US Payer Perspectives on Evidence for Formulary Decision Making, 8 J. Oncology Practice 22s, 22s-24s (2012).*

This phenomenon is not limited to the private sector. Government health care programs must cover off-label uses in some cases, and in others they are permitted to cover off-label uses but are not required to do so. Specifically, Congress has mandated that Medicare and Medicaid provide reimbursement for uses that are considered "medically accepted," including off-label uses supported by certain compendia.[iv] Moreover, Medicare Parts B and D must reimburse drugs used in anti-cancer chemotherapeutic regimens for other off-label treatments if, consistent with certain criteria established by CMS, the carrier or the plan determines that the use is supported by medical literature, and state Medicaid agencies may cover off-label, off-compendia uses of drugs unless the state Medicaid agency exercises its discretion to restrict such coverage.[27]

[iv] MIWG member companies also are aware of CMS's informal policy of reimbursing for off-label uses when the use is off-label by virtue of the drug's dosing or combination use.

The TRICARE program permits coverage for off-label uses if they are medically necessary and shown by reliable evidence to be safe, effective, and in accordance with nationally accepted standards of practice.[28] Under the Federal Employees Health Benefits Program (FEHBP), HMO plans must provide coverage for off-label use of covered medications when prescribed in accordance with generally accepted medical practice by a Plan doctor, and fee-for-service plans must provide coverage for off-label uses of covered medications if medically necessary, appropriate for the patient's condition, and prescribed for such use by a Plan doctor.[29]

CMS has also recognized that local contractors use information derived from compendia and peer-reviewed medical literature to inform decisions about coverage of off-label treatment regimens, and CMS has taken steps to ensure that recognized compendia are complete with respect to listings of off-label uses.[30] In addition, requests for National Coverage Determinations must include comprehensive information including scientific evidence supporting all clinical indications for a product under the Medicare program.[31] Private payors regularly follow the federal government's lead and reimburse for medically accepted interventions, including those not set out in FDA-approved labeling.

Moreover, both "private and public payors are embracing a new perspective on health care payment and delivery—one that emphasizes value over volume and rewards providers that delivery high-quality care."[32] More and more, payment for medical services is "contingent upon demonstrating progress in meeting established performance thresholds."[33] The ACA initiated a number of these pay-for-performance initiatives. For instance, it required a "value-based payment modifier" for Medicare that includes "a differential payment to a practitioner or group of practitioners . . . based upon the quality of care furnished compared to cost."[34] The ACA also provides for "shared savings

program[s]" in which providers who form groups known as accountable care organizations (ACOs) can share in cost savings to Medicare, provided they meet certain performance standards.[35] The ACA also instituted a "value-based purchasing program" that provides for increased payments to hospitals when they meet or exceed performance standards.[36] Likewise, many private payors have shifted their focus to outcome-based payments. Performance-based pay is fast becoming a major factor in the health care delivery system.

This emphasis on value in health care is increasingly shared by physician specialty groups. The American Society of Clinical Oncology "is developing a scorecard to evaluate drugs based on their cost and value," and the American College of Cardiology and the American Heart Association recently announced a plan to use cost data to rate the value of treatments in clinical practice guidelines and performance standards.[37] The cardiology societies have, likewise, stressed that practitioners should weigh the value of the therapies they select, explaining that "the idea that doctors should ignore costs is unrealistic because they . . . have to consider the financial burden placed on the patient, if not society."[38]

The ACA also introduced a number of measures specifically aimed at engaging patients in treatment decisions. The National Quality Strategy was established in accordance with the ACA's directive to set priorities that will "have the greatest potential for improving health outcomes, efficiency, and patient-centeredness of health care for all populations."[39] In 2011, the Department of Health and Human Services (HHS) established six such priorities, one of which is "[e]nsuring that each person and family is engaged as partners in their care."[40] Pursuant to this goal, patients and caregivers share in the decision-making process regarding their course of treatment.

PCORI was established pursuant to the ACA.[41] PCORI is a public-private entity formed "to assist patients, clinicians, purchasers, and policy-

makers in making informed health decisions by advancing the quality and relevance of evidence."[42] The ACA instructs PCORI to disseminate research findings "with respect to the relative health outcomes, clinical effectiveness, and appropriateness of . . . medical treatments [and] services."[43] PCORI has begun to devise a research agenda to support the development of new data and analysis comparing treatment options and is developing standards for the conduct of real-world evidence (RWE) studies and other non-RCT study designs, including systematic reviews and observational studies.[44] PCORI "is not required to communicate information in a manner consistent with FDA-approved labeling of regulated products."[45] Patient-centeredness was also a focus of the President's Council of Advisors on Science and Technology (PCAST), which identified as "the most significant change . . . that all healthcare should be organized around the needs and specific characteristics of the patient, not around those of the hospital, doctor's office, insurance company, or electronic health record vendor."[46]

The influence of value-oriented factors in shaping health care delivery has increased the need for current and reliable information provided by medical product developers about new uses in at least two significant ways. First, in order to provide the best care and meet performance benchmarks, practitioners need information, including information that does not appear in FDA-approved labeling. Second, in order for practitioners to assess value, they must be able to compare the cost and effectiveness of various courses of treatment. The scientific data and analyses informing these judgments may include evidence generated by comparative effective research and other information not included in FDA-approved labeling. Practitioners may also appropriately consider information from studies and analyses that do not meet FDA's requirements for approval.[47]

B. Increased Patient Involvement in Health Care Decisions

Patients today are increasingly involved in decisions relating to their health care. In the past, patients looked almost exclusively to practitioners to fulfill their informational needs.[48] Now, however, a great deal of information that used to flow from practitioner to patient reaches patients directly from a wide variety of sources. "In response to changing societal expectations, the role of the FDA has evolved from providing information aimed solely at the health-care provider to communicating health-related information directly to patients and the general public."[49]

Technological advances are enabling patients to play a bigger role in their health care decisions,[50] and the Internet has become the primary driver in patients' information-seeking behavior and expectations.[51] In almost every aspect of their lives, patients can look to the Internet for instant access to real-time information about products and services.[52] A recent survey found that a majority of Americans have looked online for health care information,[53] and indeed, "[a] growing number of patient-consumers are . . . actively engaged, accessing the Internet for health information before even thinking about going to a doctor."[54] In addition to websites geared exclusively toward providing health care information, social networks such as Facebook and Twitter are becoming important resources for patients making health care decisions, as are blogs and online reviews of medical products and services.[55] The Internet has become an invaluable tool for patients to educate themselves, and

"In response to changing societal expectations, the role of the FDA has evolved from providing information aimed solely at the health-care provider to communicating health-related information directly to patients and the general public."

P. Seligman & S. Osborne, Perspectives on Early Communication of Drug Risks to the Public, 85 Clin. Pharm. & Therapeutics 335 (2009).

it facilitates patient engagement with practitioners and other patients regarding health concerns.

Patients' efforts to become more engaged in their own course of treatment are meaningful only if the decisions made in conjunction with their health care practitioners are based upon complete, accurate, and up-to-date information. Although the Internet can be a valuable source of information both for patients and for practitioners, the quality of the information available online varies widely and misinformation abounds, in part because manufacturers—the very entities who know most about a particular product—are currently prohibited from sharing information that is not included in the FDA-approved labeling, while others may engage in such communications regardless of how well- or ill-informed they might be.

The case for enhanced access to information about medical products is also buttressed by the health care system's increased focus on patient-centered care. Informed health care decision-making is critical to this endeavor, and practitioners and the patients they serve need comprehensive information to decide which therapeutic options are best under the circumstances. As discussed above, the ACA introduced a number of initiatives focusing on patient-centered care, which was also a focus of the President's Council of Advisors on Science and Technology (PCAST) Report. The Council recognized as "the most significant change . . . that all healthcare should be organized around the needs and specific characteristics of the patient, not around those of the hospital, doctor's office, insurance company, or electronic health record vendor."[56] For the concept of patient-centered care to have real meaning, patients must be involved in their own care and be empowered to work with their health care practitioners to make decisions that comport with their own preferences and values, based on information that is accurate and relevant.[57] A regulatory regime that inhibits the availability of such information

simply because it is not included in the FDA-approved labeling is incompatible with the goal of patient-centeredness and undermines access to current and valid scientific analysis—the type often concentrated in the hands of product manufacturers.

C. Legal Developments

Society's growing recognition of the need for widespread dissemination of accurate data and analysis to inform decisions of all sorts, including health care decisions, has been reflected in the evolution of controlling legal precepts of the First Amendment right of free expression. FDA, no less than any other government entity, must adhere to these constitutional principles.[58]

In the early years of its development, commercial speech protection operated at a protective level far below that of scientific and other traditionally protected noncommercial speech (e.g., political speech). Since at least the early 1990s, however, the courts have dramatically increased the protection afforded to commercial speech. Indeed, the government has not prevailed in the Supreme Court in a case involving suppression of commercial speech in many years—and this includes situations in which government, through FDA, has sought to regulate commercial expression in the name of protecting health.[59]

The high level of protection given to commercial speech complements the protection the courts have recognized in the context of scientific speech—like political expression, an area of traditionally protected noncommercial speech that has long been outside the scope of regulation. Much of the information that is at stake in the debate over "off-label promotion" is within the scope of these two categories—protected commercial speech and protected scientific speech.

1. First Amendment Protection of "Core" Scientific Speech

It has, for many years, been beyond dispute that "core" scientific speech is entitled to robust protection under foundational First Amendment principles. Indeed, scientific speech "reside[s] at the core of the First Amendment."[60]

Medicine, like other fields of scientific endeavor, requires free interchange among multiple viewpoints over time. "[O]pen debate is an essential part of both legal and scientific analyses. . . . Scientific conclusions are subject to perpetual revision. . . . The scientific project is advanced by broad and wide-ranging consideration of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so, and that in itself is an advance."[61] Science is cumulative, iterative, and self-correcting: each individual discovery is founded on the work of, and is subject to analysis and criticism from, others. Scientific and medical progress depends on the free flow of information about past discoveries, and on the comments, analyses, criticism, and other findings associated with those discoveries. The system, to operate effectively, requires the robust participation of multiple speakers reflecting differing points of view.[62]

Scientists practice "a discipline that seeks, but never finds, absolute truth," using a "variety of criteria to evaluate data in conditions that provide less than total certainty."[63] An opinion that is "regarded as valid" at a particular moment in time can become "invalid" if additional information emerges that conflicts with the earlier information or opinion and is "more credible."[64] "Physicians," in particular, "must make decisions in the face of uncertainty and without . . . [the] luxury of awaiting further information."[65] Because of the nature of clinical practice, they must rely on a wide range of information sources and, critically, on their own judgment in weighing those sources given the circumstances of a particular case. The medical and scientific literature on which physicians commonly rely contains conflicting observations, uncertain

conclusions, retractions, and public challenges. The findings of one study may be replicated by a subsequent study, or may be discredited, and often seemingly disparate data sets are reconsidered in the secondary literature (e.g., systematic reviews).

Whereas physicians consider a multitude of information sources and rely on their own judgment and experience in making treatment decisions, regulatory authorities consider data derived from a much narrower range of sources—mainly, randomized controlled trials (RCTs). After FDA has "judg[ed] the safety and effectiveness of drugs and the truthfulness of their labeling," health care practitioners are "responsible for making the final judgment as to which, if any, of the available drugs" will be prescribed "in the light of the information contained in their labeling and other adequate scientific data available . . . ."[66] Because medical practice requires making judgments beyond the clinical trials leading to regulatory approval, clinicians must often consider information from non-regulatory sources.

> "Do people sit down and call up the labeling for a drug they are familiar with and read it? Probably not, not very often anyway. So it is the translation of labeling by commercial sponsors that is an important component of education, or could be."
>
> Dr. Robert Temple, ODE I, Cardiovascular and Renal Drugs Advisory Committee, June 15, 2005.

From FDA's perspective, approved labeling serves as <u>the</u> source of permissible statements in promotional labeling and advertising. Yet labeling does not always contain the most up-to-date (or even the most accurate) information about the use of a medical product. For physicians to use their "best knowledge and judgment" in the use of approved drugs, they must have access to information that has not been reviewed by FDA or set forth in approved labeling. Moreover, physicians at a minimum must have access to all data generated to support product approval,

even if such information is not directly reflected in the product's indication statement. Manufacturers often have unique access to information of great public health importance, and also often the ability and the incentive to advance the scientific process through contributions to scientific exchange and investments in the processes of science themselves.

Thus, by its very nature, scientific speech occupies a critically important role in clinical decision making by supplementing the authoritative safety and efficacy information set forth in FDA-cleared or -approved labeling. Because of its societal value, scientific speech has long been recognized as residing at the core of First Amendment-protected speech, and the Supreme Court has recently recognized that manufacturer speech is subject to a high level of protection even when it is commercial in nature.

2. First Amendment Protection of Commercial Speech

In recent years, Supreme Court decisions have adopted three key principles in the commercial speech arena: (1) the respect that democracy dictates for the citizen's ability to make self-governing choices on the basis of truthful and open debate applies to the choice of lawful commercial products and services, in much the same way as it applies to citizen choices made in other social realms; (2) regulatory agencies no longer have free reign to restrict expression, even when matters of health are involved; and (3) the First Amendment generally prohibits the government from singling out speech for regulation based on its content or the identity of the speaker. These three guiding precepts set the constitutional parameters for FDA's authority to regulate the speech of product developers and manufacturers. The case law makes clear that, to be valid as a matter of constitutional law, FDA's efforts to regulate the speech of such firms must comport with these principles.

The first precept emphasizes that FDA cannot, consistent with the First Amendment, seek to forbid accurate speech that relates to lawful activity. While the Court's protection of commercial speech has been expanding for many years, the first watershed in the development of the doctrine came in the 1996 case of 44 Liquormart v. Rhode Island.[67] There Justice Stevens, announcing the judgment of the Court, concluded that when the commercial speech sought to be regulated or suppressed is truthful and advocates lawful purchase, governmental restriction of that speech is categorically unconstitutional as a violation of the First Amendment. Such bans, Justice Stevens reasoned, "usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth. The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good."[68] Thus, Justice Stevens argued that the First Amendment is designed to prevent government from manipulating citizen behavior, not through free and open debate but rather through the selective suppression of speech advocating lawful action.

Although, in 44 Liquormart, Justice Stevens spoke for a plurality of the Court, no Supreme Court decision since 44 Liquormart is in any way inconsistent with Justice Stevens' reasoning or conclusion, and on more than one occasion a majority opinion has expressed a similar sentiment. For example, in Edenfield v. Fane,[69] the Court reasoned:

> The commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish. Some of the ideas and information are vital, some of slight worth. But the general rule is that the speaker and the audience, not the government, assess the value of the information presented.

Even in Thompson v. Western States Medical Center, a 2002 case involving a governmental attempt to protect health interests by suppressing commercial speech, the Court stated: "We have . . . rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information."[70]

This anti-paternalism rationale—long accepted in every other area of speech regulation—is especially applicable to truthful speech by drug and device manufacturers. Much of that information is provided directly to professionals, who are undoubtedly equipped to judge the merits of the content. Even when communication is directed to lay audiences, the manufacturer's products may not be purchased except through an expert filter, since a prescription is required for any purchase. All that communication to lay audiences accomplishes, then, is to empower the individual as a participant in his or her health care. Such a goal is fully consistent with traditional values fostered by the First Amendment—values which have now been recognized as applicable to the regulation of even purely commercial speech.

The second precept makes clear that FDA's assertion of a competing interest in protecting the public health cannot trump the interest in making available accurate information to inform health care decision making. First, the Supreme Court's decision in Western States in 2002, cited above, should have put an end to such thinking. Moreover, the relatively recent decision of the Second Circuit in United States v. Caronia,[71] construing the FDCA not to authorize the FDA to prohibit truthful off-label advertising in order to avoid a First Amendment violation, is further evidence that the First Amendment now plays an important role in protecting commercial speech concerning health. The court in Caronia emphasized the importance of the free flow of information regarding new uses for prescription products, observing that "in the fields of

medicine and public health, 'where information can save lives,' it only furthers the public interest to ensure that all decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed."[72]

The statement by the Caronia court underscores the need to assure the widespread availability of speech by manufacturers about their products. Today, it is easy for a consumer to find on the Internet countless statements of advice about the proper uses of medical products—both for and against—without any assurance that the information has any basis in fact or the speaker is a responsible and informed commentator. To be sure, the First Amendment makes regulation of this "Wild West" form of free and open communication constitutionally difficult, if not legally impossible. But that fact makes all the more important the need for those who are truly informed about both the benefits and dangers of those powerful products to be permitted to communicate with both professionals and the public. And no one is more informed on those subjects than the manufacturers.

The government still retains full authority to regulate false or misleading commercial expression regarding the use of prescription products. But outside of that limited area, it is now clear that government's regulatory authority over commercial expression is similar to its extremely limited power to regulate scientific, political, and other traditionally protected forms of speech.

Recognition of this important point underscores the third guiding precept of modern commercial speech law: FDA may not discriminate in its regulation of expression between speech by manufacturers on the one hand and speech by non-manufacturers on the other hand. This directive was unambiguously established by the Supreme Court in its 2011 decision in Sorrell v. IMS Health, Inc.[73] There the Court ruled that a Vermont law limiting pharmaceutical manufacturers' speech violated the First Amendment. The statute in question restricted pharmacies' ability to sell or disclose information

about physicians' prescribing practices by preventing pharmaceutical manufacturers from using prescriber information for marketing purposes absent doctor's consent. The Court, noting that many doctors found targeted promotion made on the basis of such information instructive and helpful, held the law unconstitutional because it failed to impose similar restrictions on academic researchers' use of the same information. Because the statute discriminated between categories of speakers, the Court held that it was subject to heightened scrutiny. Thus, the Court established beyond question that in order to justify selective regulation of pharmaceutical manufacturer speech while at the same time permitting identical speech by other speakers, the government would need to satisfy a demanding standard. After Sorrell, then, the government must overcome a high bar to justify singling out manufacturer speech.

Developments in the protection of commercial speech in general and the protection of speech by FDA-regulated manufacturers in particular have sought to keep pace with the information explosion in recent years. The courts have recognized that, under the First Amendment, these manufacturers must be recognized as valuable contributors to available information about health care in the modern technological age.

Finally, the MIWG acknowledges and shares the government's interest in ensuring that information regarding drugs and medical devices is of high quality. Further, the MIWG believes that it should be clear to health care practitioners what information regarding a drug and medical device has been reviewed and approved by the Agency. First Amendment protections afforded to manufacturer speech need and should not be sacrificed, however, to achieve these goals.

3. Protection Afforded By The Due Process Clause of the Fifth Amendment

Not only the First Amendment but also the Due Process Clause of the Fifth Amendment require "precision" and "narrow specificity" in content regulation, and these standards are more demanding where, as in the case of the FDCA, violations are punishable criminally. "Because First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity."[74] The First Amendment requires speech restrictions to be clear and precise, because "[u]ncertain meanings inevitably lead citizens to 'steer far wider of the lawful zone' than if the boundaries of the forbidden areas were clearly marked."[75] A further foundational principle thus emerges from the case law interpreting the Due Process Clause—that FDA can regulate manufacturer speech only through precise, clear rules, and those rules must be appropriately tailored and well-defined to avoid chilling manufacturer speech.

Most recently, in the 2012 FCC v. Fox Television Stations (Fox II)[76] decision, the Supreme Court held that the Federal Communications Commission could not apply a new interpretation of a broadly worded law to activities that took place before the Commission had provided notice of its new interpretation. In so holding, the Court underscored the need for federal regulatory agencies to promulgate rules that are (1) comprehensible, and (2) not so open-ended that it is impossible to predict how they will be applied.[77]

In Fox II, the Supreme Court reviewed the FCC's interpretation of a federal statute prohibiting broadcasters from using "obscene, indecent, or profane language."[78] In 2001, the FCC concluded that "whether . . . material dwells on or repeats at length descriptions of sexual or excretory organs or activities" was a factor in the indecency analysis.[79] In 2004, the FCC adopted a new interpretation according to which even "fleeting" (non-repeated)

expletives and nudity constituted prohibited material under the statute.[80] At issue were "notices of apparent liability" issued by the FCC to two broadcasters that had aired shows containing fleeting expletives or nudity before the new interpretation had been communicated to the public.[81] The Court held that "[t]he Commission's lack of notice to [broadcasters] that its interpretation had changed" violated the Due Process Clause of the Fifth Amendment by failing "'to provide a person of ordinary intelligence fair notice of what is prohibited.'"[82]

Fox II points up the importance of Due Process principles in FDA's regulation of manufacturer speech about off-label uses. First, the current regulatory framework is not sufficiently clear, as members of the MIWG emphasized in their July 2011 citizen petition. Second, the Court emphasized that fair notice principles operate with greater force "when applied to . . . regulations that touch upon 'sensitive areas of basic First Amendment freedoms.'"[83] As it is beyond dispute that FDA's regulation of manufacturer speech under the FDCA also implicates the Free Speech Clause, the decision indicates that fair notice requirements are even more stringent.[84]

The constitutional issues highlighted in Fox II extend beyond off-label speech, affecting the full range of questions that industry confronts in an effort to make operational decisions about disseminating product information in the absence of clear FDA rules. In the past, FDA has announced various initiatives to provide the necessary clarity, announcing plans to revise existing guidance and develop new guidance and to resolve questions created by First Amendment case law.[85] Those initiatives appeared to signal FDA's commitment to enhancing the regulatory framework by establishing clear, predictable rules applicable to manufacturer speech, but their promise was never fully realized as concrete policy changes in the form of proposed regulatory changes were never even published for comment.

Currently, industry must piece together FDA's policy on off-label communications through an array of warning and untitled letters, podium statements, non-binding guidance (much of which exists only in draft form), and non-public communications such as telephone calls, emails, and advisory comments. No concise set of rules or guidelines exists. As a result, important questions remain regarding the rules applicable to manufacturer communications, both on- and off-label.

> "While it may be true that companies in industries that operate with few regulatory constraints are aware of their legal obligations and the steps they must take to comply, "the pharmaceutical industry operates under a unique set of restraints . . . ."
>
> Public Citizen v. U.S. Dep't of Health & Human Servs., No. 11-1681 (BAH), Mem. Op. 16 (Sept. 5, 2014).

The MIWG welcomes FDA's decision to grant its July 2011 and September 2013 citizen petitions. At the same time, however, the actions taken by FDA in response to the petitions have not addressed the issues raised by the MIWG in a sufficiently responsive manner. Interested parties may continue to look to the courts for answers, and many are certain to argue that the continued lack of clarity and the associated chilling effects by themselves create a dispute that is eligible for judicial review. The litigation risk aside, however, we cannot imagine that FDA officials would prefer a regulatory scheme characterized by ambiguity and surprise to one carefully developed by the Agency and characterized by clarity and predictability. For these reasons, and in light of the evolving case law, precise, narrowly specific rules governing manufacturer speech should be provided by the Agency as soon as is practicable.

II. MIWG Proposals

In recent years, the Medical Information Working Group has articulated an agenda intended to identify for FDA those aspects of the existing regulatory framework that require modification in view of the developments described in the previous section of this White Paper. We have also commented on various FDA proposals, some of which were issued by the Agency to respond to MIWG member requests. In 2012, for example, the MIWG submitted comments to the Agency in response to a new draft guidance providing recommendations on manufacturer responses to unsolicited requests—a draft guidance that itself was published in response to a request made by MIWG members in a citizen petition filed with FDA in July 2011. All of the MIWG's submissions on these issues—which have covered a wide range of open regulatory questions involving policy, statutory, and constitutional questions of significant importance—have been made to public dockets and reflect the MIWG's intention to identify necessary changes and outline an approach that would better align the regulatory scheme with legal and constitutional limitations while protecting and promoting the public health.

Despite the investment of significant attention to these issues over a sustained period, and notwithstanding the progress that the Agency's leadership has made in recognizing the importance of issues relating to the regulation of manufacturer speech in a rapidly evolving environment, the MIWG believes that the policy documents that FDA has issued over the past several years continue to fall short. Notably, FDA officials have continued to articulate the same rationale favoring the regulatory status quo, even as those same officials assert that the Agency, at the highest levels, recognizes the need for change.[86]

Whatever the explanation, it is evident that, although the MIWG recognizes the strides FDA has made in acting on the agenda items identified in our prior submissions—from requesting public input on its policies regarding "scientific exchange" to updating the safe harbor on unsolicited requests, among other issues—much work remains to be done in conforming those actions to the relevant policy and legal imperatives.

This White Paper is intended to help close the gap, by setting forth the key changes that the MIWG believes are necessary to align the regulatory scheme sufficiently with relevant legal considerations and to assure that FDA's regulatory approach adequately reflects the changes in the external environment described in this White Paper. Specifically, the MIWG's proposals redefine "scientific exchange" and clarify the definitions of "labeling" and "intended use" to give manufacturers a clear ability to communicate important information about their products to meet the informational demands of the changing external environment, as outlined in Part I of this White Paper. Without implementation of these proposals, manufacturer speech will still be chilled, because avenues for communicating such information will not be clearly delineated.

The proposals discussed in this document reflect a common theme: the importance of clearly defining the scope of manufacturer communications over which FDA has authority, by delineating—in a manner consistent with statutory and constitutional limitations—the lines between categories of manufacturer communication that FDA is empowered to regulate and those types of communication that are outside FDA's purview. Moreover, the MIWG's proposals construe the terms "labeling," intended use," and "scientific exchange" in a manner that is consistent with the FDCA and the Constitution.[v]

[v] Further, the MIWG's proposals adopt the approach of the Second Circuit in Caronia. In that decision, the Second Circuit applied the principle of constitutional avoidance, construing the FDCA in a manner

This White Paper does not address other important issues that have been the subject of prior MIWG comment, such as the regulatory standards that apply to communications that are within FDA's "promotion" authority. The MIWG has submitted a wide range of documents to FDA on a multitude of issues, and this White Paper is not intended as an exhaustive summary of all of them.[vi]

Part II of the White Paper, below, sets forth the changes that we believe are necessary to the existing regulatory scheme, in addition to those that FDA has already announced and on which the MIWG has already commented.

that would not raise First Amendment concerns. 703 F.3d 149, 160 (2d Cir. 2012). Similarly, the MIWG's proposals construe the terms "labeling," "intended use," and "scientific exchange" in a manner to avoid a First Amendment violation.

[vi] In addition, individual MIWG member companies and their representatives (including trade associations) may separately propose changes to the regulatory scheme; those changes are not included in this White Paper.

Proposal #1 Amend the Regulations Recognizing "Scientific Exchange" in 21 C.F.R. §§ 312.7(a) & 812.7 and Create a New Regulation Recognizing "Scientific Exchange" Outside the Investigational Context.

Requested Actions

Revise 21 C.F.R. §§ 312.7(a) and 812.7 as follows:[vii]

21 C.F.R. § 312.7(a)

(a) *Promotion of an investigational new drug*. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug~~, including dissemination of scientific findings in scientific or lay media~~. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(1) To be part of the full exchange of scientific information, a statement must (i) make clear that the drug is investigational; (ii) make no claims that the drug has been proven to be safe or effective; and (iii) be truthful and non-misleading when measured against

[vii] Proposed deletions are reflected by struck text, and proposed additions are noted by underlining. Emphasis shown by italics appears in the original regulations.

information available on the drug at the time the statement was made.

(2) Examples of communications and activities considered to be part of the full exchange of scientific information include, but are not limited to: (i) dissemination of scientific findings in scientific or lay media; (ii) publication of results of scientific studies; (iii) letters to the editor in defense of public challenges; and (iv) investigator conferences.

21 C.F.R. § 812.7

(a) A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

(1~~a~~) Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.

(2~~b~~) Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

(3~~c~~) Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall

promptly terminate the investigation.

(4d) Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

(b) This section is not intended to restrict the full exchange of scientific information concerning the device. Rather, its intent is to restrict promotional claims of safety or effectiveness of the device for a use for which it is under investigation and to preclude commercialization of the device before it is approved for commercial distribution.

(1) To be part of the full exchange of scientific information, a statement must (i) make clear that the device is investigational; (ii) make no claims that the device has been proven to be safe or effective; and (iii) be truthful and non-misleading when measured against information available on the device at the time the statement was made.

(2) Examples of communications and activities considered to be part of the full exchange of scientific information include, but are not limited to: (i) dissemination of scientific findings in scientific or lay media; (ii) publication of results of scientific studies; (iii) letters to the editor in defense of public challenges; and (iv) investigator conferences.

Create new 21 C.F.R. § x.x as follows:

21 C.F.R. § x.x

(a) Manufacturers, packers, and distributors (firms) of drugs and medical devices may engage in the full exchange of scientific information concerning a drug or device candidate or a new use for a lawfully marketed drug or device.

(b) To be part of the full exchange of scientific information, a statement must (i) make clear that the drug or device candidate or new use for a lawfully marketed drug or device has not been approved or cleared by FDA; (ii) make no claims that the drug or device candidate or new use for a lawfully marketed drug or device has been proven to be safe or effective; and (iii) be truthful and non-misleading when measured against information available at the time the statement was made.

(c) Examples of communications and activities considered to be part of the full exchange of scientific information include, but are not limited to: (1) communication, both proactive and reactive, of scientific or medical information or findings, including communication of such information by field-based personnel in scientific, medical, or clinical development departments of firms and communication of such information by personnel in these departments to payors who are carrying out their responsibilities for the

selection and coverage of drugs or devices for managed care or other similar organizations; (2) communication, both proactive and reactive, of information regarding a firm's research and development efforts, including communications to facilitate investigator-initiated research and communications regarding specific drug or device candidates and new uses of drugs or devices lawfully marketed in the United States; and (3) communication, both proactive and reactive, of health care economic information, including communication of such information delivered by or on behalf of the health care economic or health outcomes departments of firms to payors who are carrying out their responsibilities for the selection and coverage of drugs or devices for managed care or other similar organizations. For purposes of this provision, "health care economic information" means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug or device to the use of another drug or device, to another health care intervention, or to no intervention.

Rationale

FDA regulations prohibit a drug manufacturer from representing in a promotional context that an investigational new drug or device is safe or effective. FDA has not issued a comprehensive, binding statement as to the contours of this provision. Moreover, although the "scientific exchange"

concept is included in FDA's drug regulations, no regulation in Part 812 refers to "scientific exchange" about investigational medical devices. FDA has, however, provided some commentary on the meaning of "scientific exchange."

In a 1987 preamble, FDA indicated that, to qualify as "scientific exchange," statements must: (1) make clear that a drug is investigational; (2) make no claims that a drug has been proven to be safe or effective; and (3) be truthful and non-misleading when measured against available information on the drug.[87] FDA also referred to several examples of permissible scientific exchange: "publishing results of scientific studies, letters to the editor in defense of public challenges, investigator conferences."[88]

In a proposed rule in 1977, FDA affirmed medical device manufacturers' entitlement to engage in scientific exchange.[89] FDA has never issued a corresponding final rule, however, although in succeeding years the Agency continued to recognize "scientific exchange" in the context of medical devices.[viii] The MIWG's proposed revisions to the regulations are intended to codify the pertinent preamble language and address the gaps in this rulemaking record.

In addition, FDA regulations do not address a firm's ability to engage in scientific exchange outside of the investigational context. The existing regulations addressing scientific exchange—21 C.F.R. §§ 312.7 and 812.7—are found in 21 C.F.R. Parts 312 and 812, which govern investigational

[viii] CDRH alluded to scientific exchange in a series of warning letters issued in the 1990s, stating in each letter: "Although FDA does encourage the full exchange of scientific information concerning investigational devices, including dissemination of scientific findings through scientific/medical publications or conferences, safety and efficacy conclusions and statements of a promotional nature are inappropriate." A guidance document published in 1999 did not clarify the scope of permissible scientific exchange for devices, although it did make clear that manufacturers could "make known through a notice, publication, display, mailing, exhibit, announcement, or oral presentation the availability of an investigational device for the purpose of obtaining clinical investigators to participate in a clinical study involving human subjects." Guidance for Industry and FDA Staff on Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects 1 (Mar. 1999).

drugs and devices, respectively. Scientific speech, however, is entitled to robust protection under the First Amendment, and the concept of scientific exchange applies more broadly than only to drugs and devices subject to investigation. For example, the concept applies to discussion of new uses of lawfully marketed drugs or devices, even if these new uses are not being investigated pursuant to 21 C.F.R. Parts 312 and 812. The concept also applies to discussion of information that supplements an approved use, such as information regarding dosing, use in a different patient population, use in a subpopulation, or use in combination with another drug. The MIWG, therefore, proposes a new regulation that clearly acknowledges a firm's ability to engage in scientific exchange outside the investigational context.

The new regulation would also clarify the applicability of "scientific exchange" to important practices. FDA has repeatedly recognized the value that field-based professionals add to the communication of medical and scientific information.[ix] The Agency has, for example, required the use of medical science liaisons (MSLs) to fulfill communication and practitioner training requirements associated with various products' Risk Evaluation and Mitigation Strategies (REMS). FDA has also indicated that MSLs may communicate off-label information in certain contexts (e.g., to share risk information in connection with REMS requirements, to respond to questions about off-label use data). FDA has, however, never addressed more broadly the ability of MSLs proactively to communicate information that does not appear in FDA-approved product labeling.[90] Nor has FDA specifically affirmed that "scientific exchange" includes proactive communications and repeated dissemination of information that goes beyond initial publication or presentation of study results (e.g., new retrospective analyses of pivotal trial data). Neither limitation is set forth in the

[ix] Note that under Sorrell v. IMS Health, 131 S. Ct. 2653 (2011), speaker-based restrictions will be subject to elevated scrutiny.

language of the regulations, but the absence of FDA guidance on these aspects of MSL communications has created a chilling effect.

Beyond field-based medical communications, manufacturers proactively communicate regarding their research and development efforts, commonly referred to as the product "pipeline." Pipeline discussions are critical to industry operations, as they not only spur investment in new projects, but also are fundamental to aid the research collaborations often necessary to ensure successful clinical development programs. The information, which may be directed to potential investors or clinical investigators, clinicians, researchers, and insurers (including government payors), may take various forms, but often refers to specific product candidates and new uses of marketed products. Whether posted on company websites, discussed at conferences, or communicated in other fora, these pipeline presentations represent scientific exchange because they focus on the dissemination of data regarding development-stage products.

Manufacturers frequently provide grant monies for, or products to be used in, investigator-initiated research that advances medical or scientific knowledge about their products. Aside from this limited support from the company, investigators assume responsibility for all aspects of their research, including protocol development, institutional and regulatory approval, study conduct, data analysis, and communication of results.[91] To facilitate investigator-initiated research, manufacturers may sponsor websites or host online portals that allow potential investigators to learn more about the company's research interests and the criteria for collaboration, as well as permit the submission of clinical trial protocols and grant applications for the company's review. Similar to the pipeline presentations discussed above, these websites may contain information about new uses of marketed products, as well as information about investigational products. While the Department of Justice

has alleged that manufacturer support of investigator-initiated research has constituted off-label promotion, FDA has never (to our knowledge) commented on these websites or other kinds of manufacturer communication about investigator-initiated research.[92]

"Scientific exchange" also properly includes many manufacturer communications to payors, and FDA regulations should be amended to make that point explicit.[93] Moreover, the Agency should establish a binding interpretation of the FDCA that expressly recognizes manufacturers' entitlement to communicate scientific information to payors. The FDCA, as it was amended by Section 114 of the FDA Modernization Act of 1997, addresses manufacturer communications directed to formulary committees and analogous entities, but the statute does not address the dissemination of economic information through non-promotional channels, such as scientific exchange.

Creating a new regulation recognizing scientific exchange outside the investigational context as suggested above would help to ensure that payors have access to the full range of information that they need to make sound, well-informed decisions and clarify that scientific, medical, and health care economic information may be shared with payors in the context of scientific exchange, for both drugs and medical devices.

Related Submissions

- Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011)
- Comments re: Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868 (Mar. 27, 2012)
- Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013)

Proposal #2 Issue New Interpretive Guidance Confirming that "Labeling" Is Defined by 21 C.F.R. § 1.3(a) and 21 U.S.C. § 321(m).

Requested Action

Issue new guidance affirming that (1) "labeling" is defined by 21 U.S.C. § 321(m) and 21 C.F.R. § 1.3(a), and (2) FDA interprets 21 C.F.R. § 202.1(l)(2) solely to exclude the listed items from the scope of the Agency's prescription drug advertising rules in 21 C.F.R. Part 202, and not to define "labeling."

Rationale

The FDCA establishes specific rules for "labeling." For the FDA regulatory scheme to respond to the shifts described in Part I of this White Paper, FDA's interpretation of the statutory definition of "labeling," which defines the manufacturer communications to which those specific rules apply, must leave manufacturers with sufficient latitude to respond to the needs of various stakeholders for a wide range of product-related and other information, without limiting that information to the FDA-approved labeling. In the past, FDA has advanced broad and vague interpretations of "labeling," to the extent that manufacturers cannot reliably discern—in advance of embarking on a proposed course of conduct—whether their truthful, non-misleading, scientifically supported communications about medical products are subject to the statutory "labeling" rules or outside the scope of those rules. Clarity in the scope of application of these rules is critical not only to providing adequate information to inform health care decisions, but also for facilitating manufacturer compliance and FDA's effective enforcement of the law.

Section 502(a) of the FDCA provides that "[a] drug or device . . . shall be deemed to be misbranded . . . [i]f its labeling is false or misleading in any particular."[94] For this provision to apply, a false or misleading statement

must appear in a communication that qualifies as "labeling." According to Section 505(a) of the FDCA, "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) [new drug application (NDA)] or (j) [abbreviated new drug application (ANDA)] is effective with respect to such drug."[95] Whether a product is a "new drug" depends on the content—in particular the "conditions prescribed, recommended, or suggested"—of its labeling.[96] Section 502(f)(1) of the FDCA provides that a drug or device "shall be deemed to be misbranded" unless its labeling contains "adequate directions for use."[97]

Section 201(m) of the FDCA defines labeling to include written, printed, or graphic matter "accompanying" a product.[98] When it was enacted, the term "labeling" was understood to mean the written material that is inside the package of a product.[99] This made sense, because the case law at the time also reflected the "package insert" understanding of "labeling."[100]

In 1948, in United States v. Kordel, the Supreme Court held that a manufacturer cannot evade the statutory "labeling" requirements simply by sending drugs and "literature" in two separate shipments.[101] The Court held that materials shipped separately can constitute "labeling"—regardless of physical proximity—when they "perform[] the function of labeling."[102] The Court provided the following guidance in determining whether a "display of . . . matter" performs the "function" of labeling:

- "Nowhere else [is] the purchaser advised how to use [the article]."
- "It constitute[s] an essential supplement to the label attached to the package."
- "[I]t supplements or explains [the product], in the manner that a committee report of the Congress accompanies a bill."

- The materials and products are "interdependent; they [are] parts of an integrated distribution program."[103]

The Court made clear that not all "written, printed, or graphic matter" that merely mentions a product qualifies as "labeling." To qualify as "labeling," the "matter" must satisfy the "functional" test, which includes the criterion that it constitute an essential supplement to the label. FDA regulations similarly explain that "labeling" under Section 201(m) "furnishes or purports to furnish information for use or . . . prescribes, recommends, or suggests a dosage for the use of the drug."[104]

Properly construed, "labeling" does not include any "written, printed, or graphic matter" that merely mentions a specific product. An appropriately constrained definition of "labeling" would enable manufacturers to understand in advance which of their "written, printed, or graphic" communications would be subject to regulation by FDA, ultimately opening up new channels of truthful, non-misleading communication as required by the First Amendment.

To achieve the objective of establishing a clear definition of "labeling" that is more consistent with the First and Fifth Amendments, with the relevant statutory language, and with Kordel, FDA would not have to amend its existing regulations. Two regulatory provisions are relevant:

- 21 C.F.R. § 1.3(a), the general regulation defining "labeling" for all FDA-regulated products, states: "Labeling includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce"; and

- 21 C.F.R. § 202.1(l)(2), in FDA's prescription drug advertising regulations, sets forth an extensive list of items that are deemed to be "labeling."

In the past, FDA has cited § 202.1(l)(2) as though it functioned as a regulatory interpretation of the statutory definition of "labeling" in Section 201(m) of the FDCA.[105] As a result of those and other statements, manufacturers believed that virtually any type of written communication in which they engaged could be regulated as promotional "labeling" by FDA. Such communications could not include information about new uses because of the statutory prohibitions governing "labeling." Recently, however, the government has explained that § 202.1(l)(2) does not define "labeling," but rather operates to exclude the listed communications from the definition of "advertising" in the FDCA.

> Section 202.1(l)(2) was issued pursuant to 21 U.S.C. § 352(n), which governs prescription drug advertising. By its terms, Section 352(n) excludes "any printed matter which the Secretary determines to be labeling * * * ." Section 202.1(l)(2), which lists items that "are hereby determined to be labeling," was issued to implement this exclusion. In keeping with the terms of Section 352(n), its purpose is to limit the domain of the Act's prescription drug advertising requirements, by making clear what kinds of materials are not subject to those requirements. It was never meant to suggest that the items in the list will be regulated as labeling without regard to Kordel's construction of "accompanying," and it has not been applied by FDA in that manner.[106]

This more recent interpretation is the correct one, as it accords better with the statute as it has been construed by the courts. Moreover, a clear, limited definition of "labeling" would remove existing regulatory impediments to

manufacturers' use of existing channels of communication to provide accurate, science-based information to payors, health care practitioners, and patients.

Related Submissions

- Comments re: Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868 (Mar. 27, 2012)
- Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013)

Proposal #3 Amend the Regulatory Definitions of "Intended Use" in 21 C.F.R. §§ 201.128 & 801.4.

Requested Action

Amend 21 C.F.R. §§ 201.128 and 801.4 as follows:[x]

21 C.F.R. § 201.128

(a) The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122 refer to the objective intent, as shown by labeling claims, advertising matter, or analogous oral statements, of the persons legally responsible for the labeling of drugs or persons acting by or on behalf of such persons. ~~The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.~~The words *intended uses* do not refer to the subjective intent of any person. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, ~~a packer, distributor, or seller intends an article for different uses than those~~

[x] Proposed deletions are reflected by struck text, and proposed additions are noted by underlining. Emphasis shown by italics appears in the original regulations.

~~intended~~ an article has different intended uses because of labeling claims, advertising matter, or analogous oral statements by its packer, distributor, or seller than those made by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. ~~But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.~~

(b) A person legally responsible for the labeling of a human prescription drug does not violate section 502(f)(1) of the Act, unless such person or a person acting by or on behalf of such person recommends or suggests in labeling claims, advertising matter, or analogous oral statements the use of the drug for an indication that differs from the drug's indication as stated in the drug's labeling pursuant to 21 C.F.R. § 201.100.

(c) Scientific exchange, as defined in 21 C.F.R. § 312.7 and 21 C.F.R. § x.x, does not provide evidence of intended use.

21 C.F.R. § 801.4

(a) The words *intended uses* or words of similar import in §§ 801.5, 801.119, and 801.122 refer to the objective intent, as shown by labeling claims, advertising matter, or analogous oral statements, of the persons legally responsible for the labeling of devices or persons acting by or on behalf of such persons. ~~The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.~~ The words *intended uses* do not refer to the subjective intent of any person. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, ~~a packer, distributor, or seller intends an article for different uses than those intended~~an article has different intended uses because of labeling claims, advertising matter, or analogous oral statements by its packer, distributor, or seller than those made by the person from whom he received the devices, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. ~~But if a manufacturer knows, or has~~

~~knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.~~

(b) A person legally responsible for the labeling of a prescription device does not violate section 502(f)(1) of the act, unless such person or a person acting by or on behalf of such person recommends or suggests in labeling claims, advertising matter, or analogous oral statements the use of the device for an indication that differs from the device's indication as stated in the device's labeling pursuant to 21 C.F.R. § 801.109.

(c) Scientific exchange, as defined in 21 C.F.R. § 812.7 and 21 C.F.R. § x.x, does not provide evidence of intended use.

Rationale

The MIWG proposes that FDA make clear the distinction between "scientific exchange" on the one hand, and communications that qualify as "labeling" or "advertising," or that can create a new "intended use" under the FDCA, on the other. The distinction is of paramount importance as without it conceivably any manufacturer statement could be subject to regulation—with attendant content restrictions that would run counter to the informational needs of stakeholders, as discussed above. Moreover, the enforcement environment for manufacturers in recent years has been characterized by the unpredictable and indiscriminate invocation of the "intended use" doctrine. Manufacturers, in

particular, cannot predict with certainty whether their non-promotional, scientific communications—especially field-based scientific communications—will be regarded by the Department of Justice or other regulators and enforcers as "evidence of intent" or "evidence of intended use." As discussed below, the relevant law does not permit either approach. Providing the clarification that the MIWG requests would assure that manufacturers have available to them adequate alternative communication channels which are not promotional in nature, without unduly constraining effective enforcement of the law.

- A new intended use can be created only by promotional claims.

A new use can be created only by a manufacturer's (or other seller's) claims as to that use. Under the current regulatory language, despite the general rule that intended use is based on the manufacturer's "expressions," a new intended use can also be created when a drug or medical device "is to be used" off-label.[107] Under the latter theory, a manufacturer would be in violation of the misbranding provisions of FDCA, despite the absence of promotion of a new use, if the manufacturer merely was on constructive notice of the new use—in the terms of the regulations, if the manufacturer had "knowledge of facts that would give him notice."

Problems with this interpretation were identified from the moment of its inception more than sixty years ago. Manufacturers submitted comments on the proposed rule objecting to the possibility of liability based solely on a known new use. They objected, as well, to the asserted obligation to seek approval for a new use that they did not recommend.[108] FDA thus "has repeatedly stated that it may only regulate claimed uses of drugs. . . ."[109] The Agency has also stated that "not all speech or actions by a manufacturer regarding an unapproved use is [sic] taken by FDA to be evidence of intended use."[110] Prosecutors have nevertheless sought to invoke FDA's regulatory definitions of intended use to support FDCA liability based on a manufacturer's mere

knowledge that its product is being used off-label.[111] Manufacturers therefore have difficulty in evaluating a wide range of proposed business practices that clearly should be lawful, but could be regarded by prosecutors as evidence in a misbranding action under the FDCA because they involve off-label uses that are in no way promoted but are actually or constructively known to them. In addition, manufacturers are regularly accused of violating the FDCA for communications that are properly regarded as scientific exchange.

Read correctly, §§ 201.128 and 801.4 do not support liability in the absence of claims. The regulations, in their respective fourth sentences, refer to the article being "offered and used" off-label. As a result, no new intended use should arise from actual use in the absence of "an offer"—that is, promotion of the use. Moreover, it is impossible for manufacturers to avoid knowledge of the actual, off-label uses to which their products are being put. Nevertheless, without the definitional clarity, the only recourse a manufacturer has to manage its potential liability based on the knowledge-based intended use theory would be to try and stamp out off-label uses—interference with medical practice that conflicts with FDA policy and could undermine patient care.

Other novel theories of intended use are similarly invalid. Because, as the text of FDA's regulations makes clear, "intended use" is an objective rather than a subjective standard, internal company documents reflecting a subjective desire that a product be used off-label cannot be used as evidence of a misbranding or other FDCA violation. Indeed, "courts have always read . . . 'intended' to refer to specific marketing representations."[112] Courts have also made clear that statements must be disseminated to the public to create new intended uses.[113] Thus, intended use not only excludes "subjective intent," but also requires evidence of statements that were actually made to the public.

Consequently, intended use cannot be determined according to just any source. In the past, to support a broad interpretation of intended use,

FDA has invoked case law stating that intended use may be based on statements in labeling, advertising, or "any other relevant source." Most recently, FDA invoked such a case in its June 6, 2014, response to the MIWG's citizen petitions, citing Action on Smoking and Health v. Harris,[114] to support the point that intended use can be established, in part, by the manufacturer's or distributor's subjective intent.[115] Such reliance is misplaced, because courts have invoked the "other relevant source" language, which originated in Hanson v. United States,[116] exclusively in cases in which there were manufacturer promotional claims.[117] Rather, intended use is created by a manufacturer's promotional claims, as the relevant regulatory text and case law make clear.

- To create a new intended use, a claim must prescribe, recommend, or suggest a product for a new indication (that is, a different recognized disease or health condition).

The text of 21 C.F.R. §§ 201.128 and 801.4 refers to a product's "purpose" and to its "conditions, purposes, or uses." The text thus makes clear that statements that do not "prescribe, recommend, or suggest" use of a product for an entirely new indication are not "off-label" statements within the meaning of the FDCA. Other FDA commentary is consistent with this approach, confirming that communication qualifies as prohibited off-label promotion only if it prescribes, recommends, or suggests a product for "a use that is not included in the approved labeling . . . ."[118] On the other hand, although FDA has stated that not every conceivable departure from approved labeling was included in the "off-label" category, the Agency has failed to explain when an "out of label" use constituted an "off-label" use.[119]

Manufacturers therefore are left to speculate as to whether their communications about departures from approved labeling could give rise to FDCA liability, and the lack of meaningful a priori definitions or interpretative guidance from FDA chills truthful and non-misleading manufacturer speech

about new uses of approved products. By amending 21 C.F.R. §§ 201.128 and 801.4 as provided above, FDA would make clear that a manufacturer's statements that do not encourage use of a product for an entirely new indication are not "off-label" statements.

Related Submission

- Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013)

III. Implications Of The MIWG Position

Does The MIWG's Proposed Approach Represent A Frontal Assault On The Regulatory System For Drugs And Medical Devices?

No, it does not. The MIWG's approach represents a carefully crafted, measured strategy, on which we encourage FDA to draw, to improve the existing regulatory and enforcement climate so that it (1) provides clear, enforceable rules that enable and encourage voluntary compliance, and (2) responds to major changes in the way health care is delivered, stakeholders assess clinical options, and patients make treatment decisions.

Much of the MIWG's suggested approach derives from FDA's own statements acknowledging the limitations of its authority. In recent litigation, FDA has recognized important limiting principles:

1. FDA does not regulate "promotion," but rather has authority with respect to "labeling" and "advertising"—statutorily defined categories that together are sometimes more conveniently referred to as "promotion."[120] Press releases, for example, are not in and of themselves subject to regulation as "labeling."[121]

2. Statements that do not prescribe, recommend, or suggest a use are not subject to regulation by FDA. Consequently, a manufacturer is entitled to (among other things) provide "appropriate warnings about the adverse consequences of an off-label use," and doing so does not "trigger[] the prohibitions on distributing a product for an unapproved use and misbranding a product for failure to provide adequate directions for use."[122]

3. "Intended use" is not created merely by a "manufacturer's knowledge that an approved product was being prescribed by doctors" for a new use; by the fact that a physician to whom "on-label" use information is being provided also can or even frequently does encounter clinical scenarios in which a product could be used "off-label";[123] or by the manufacturer's practice of teaching its representatives about potential off-label uses.[124]

These statements and other basic precepts that we believe are the subject of widespread agreement, both within and outside of the Agency, have informed the MIWG's suggested strategy for changes that should be incorporated directly into the relevant regulatory provisions to help align the regulatory scheme with constitutional limitations.

The MIWG's proposed approach focuses on:

- Bringing much-needed clarity to long-standing FDA policies that have been established over the past several decades to allow manufacturers to engage in limited, carefully controlled non-promotional dissemination of certain kinds of "off-label" information, such as responses to unsolicited requests. The MIWG is asking that FDA define historically undefined terms and bring much-needed coherence, consistency, and rationality to these safe harbors, which have not been comprehensively reconsidered in recent years, despite the obvious need for such reconsideration. FDA has acknowledged that these policies require updating, and the MIWG has been actively engaged in commenting on FDA's proposals and otherwise providing input to agency officials as they refine and improve upon the relevant regulations and guidance documents.

- Assuring that FDA's regulatory activities are consistent with the statutory authority conferred on the Agency by Congress under the FDCA, through targeted clarifications and improvements to various regulations and guidance documents addressing the scope of the "labeling," "advertising," and "intended use" provisions. These provisions define the categories of manufacturer speech over which FDA can lawfully assert regulatory control, and clarity in their contours is critical to the effective functioning of the regulatory system.

- Better aligning FDA's regulatory approach with the limitations imposed on the Agency by the First and Fifth Amendments. Constitutional principles make clear that the existing regulatory and enforcement climate exhibits significant infirmities that, if challenged in court, likely would result in judicial decisions against government regulation.

Manufacturers need to be able to determine in advance with reliability and precision the rules that apply to their communications, so that they can consistently assure that those communications comply with applicable legal requirements. Under the current approach, such assurance is impossible because of the interpretive questions that remain unresolved by FDA in clear, binding rules.

Under the MIWG's proposals, the existing prohibitions on so-called off-label promotion would continue to apply to all claims regarding a product made in "labeling" and "advertising," or in other communications that create an "intended use," including sales representatives' oral statements. Moreover, other statutory and regulatory requirements applicable to these specific types of manufacturer communications, such as the requirement that these communications be truthful and non-misleading, would continue to apply. This is consistent with the FDA's authority over manufacturer communications, which is defined with reference to the "labeling" and "advertising" provisions of the

FDCA, and to the regulatory definition of "intended use" in 21 C.F.R. §§ 201.128 (drugs) and 801.4 (devices). FDA's interpretation of these terms would be as described in the MIWG's proposal.

In addition, the MIWG supports the disclosure of the off-label nature of a particular new use when a manufacturer is appropriately communicating about the new use.

Will Practitioners Use Drugs Off-Label When Better, Approved Alternatives Are Available?

The MIWG is advocating for freer dissemination of accurate, science-based data and analyses. The ultimate objective of the MIWG's proposed changes is to promote and protect the public health and advance patient care by establishing a clear and appropriately regulated role for manufacturers to provide scientifically accurate, clinically relevant information. As a consequence, information provided in line with the MIWG's suggestions would not steer practitioners away from approved uses when such use would result in better patient care. Instead, the changes proposed by the MIWG would merely help practitioners gain access to comprehensive, accurate, and up-to-date information to guide health care decision-making.

If a practitioner chooses to prescribe a product in a manner that is not fully consistent with the FDA-approved labeling, he or she must do so only when sound evidence and valid scientific reasoning support it.[125] State medical practice standards function to assure that practitioners comply with these obligations.[126]

Will Practitioners Mistake "Off-Label" Uses For Approved Uses?

The MIWG supports the disclosure of the off-label nature of a particular new use when a manufacturer is communicating about the new use in accordance with a safe harbor. For example, in asking FDA to clarify its

position on scientific exchange, the MIWG proposes that FDA state that, to qualify as scientific exchange, statements must, among other things, make clear that a use or product is not FDA-approved or -cleared. The MIWG also supports the requirement in the draft guidance on unsolicited requests that a response to a non-public request include, among other things, "[a] prominent statement notifying the recipient that FDA has not approved or cleared the product as safe and effective for the use addressed in the materials provided."[127] Similarly, the MIWG supports the requirement in the draft guidance on distributing scientific and medical publications that such publications be accompanied by "a prominently displayed and permanently affixed statement disclosing," among other things, "[t]hat some or all uses of the manufacturer's drugs or devices described in the information have not been approved or cleared by FDA . . ."[128]

Will Unsafe Drugs Reach The Market?

The MIWG's proposals leave premarket review intact. The MIWG agrees that manufacturers should be required appropriately to study the safety and effectiveness of their products and, when required, demonstrate such safety and effectiveness to FDA. Because the MIWG's proposed plan does not alter or weaken the Agency's premarket review program, unsafe drugs will not reach the market as a result of FDA's implementation of the MIWG's proposals.

Will Manufacturers Be Permitted To Promote Their Products For Any Use Once They Obtain Initial Approval?

No. Under the MIWG's proposals, the existing prohibitions on so-called off-label promotion would continue to apply to all claims regarding a product made in "labeling" and "advertising," or in other communications that create an "intended use," including sales representatives' oral statements. This is consistent with the FDA's authority over manufacturer communications, which is defined with reference to the "labeling" and "advertising" provisions of the FDCA, and to the regulatory definition of "intended use" in 21 C.F.R. §§ 201.128 (drugs) and 801.4 (devices). FDA's interpretation of these terms would be as described in the MIWG's proposal.

Under the proposals, manufacturers would be free to communicate new-use information through communications that do not constitute "labeling" or "advertising" and that do not create a new "intended use," as these terms are defined by the FDCA and FDA regulations as described in the MIWG's proposal. These "other" communications are non-promotional and outside the scope of FDA's authority. Such communications include, among other things, responses to unsolicited requests, scientific exchange, industry-supported scientific and educational activities, and dissemination of reprints, medical textbooks, and clinical practice guidelines. In addition, communications listed in 21 C.F.R. § 202.1(l)(2) would be outside the scope of FDA's authority, unless they qualify as labeling under 21 U.S.C. § 321(m), 21 C.F.R. § 1.3(a), and applicable case law.

Will Sales Representatives Be Entitled To Say Anything They Like To Encourage Off-Label Use?

FDA can regulate statements by sales representatives through the "intended use" regulation, 21 C.F.R. §§ 201.128 (drugs) and 801.4 (devices) and Section 502(f)(1) of the FDCA. Under the claims-based interpretation of 21 C.F.R.

§§ 201.128 and 801.4, sales representatives' oral statements can create a new "intended use." If any "intended use" is a new use, the product would be misbranded, because it lacks adequate directions for that new use.[129] Sales representatives therefore would be unable to promote off-label use under the MIWG's proposals.

Will Manufacturers Be Free To Engage In The Widespread Marketing Of Their Products Without Regard For The FDA-Approved Labeling?

Under the MIWG's proposal, the existing prohibitions on so-called off-label promotion would continue to apply to all claims regarding a product made in "labeling" and "advertising," or in other communications that create an "intended use," including sales representatives' oral statements. This is consistent with the FDA's authority over manufacturer communications, which is defined with reference to the "labeling" and "advertising" provisions of the FDCA, and to the regulatory definition of "intended use" in 21 C.F.R. §§ 201.128 (drugs) and 801.4 (devices). FDA's interpretation of these terms would be as described in MIWG's proposal.

Approved labeling is not intended to be, and cannot be, comprehensive. Product labeling reflects information gathered from the clinical studies and other sources forming the basis of FDA's approval decisions. Sponsors initiating studies sometimes impose rigorous selection criteria (e.g., excluding patients with multiple disease conditions), which can narrow the scope of the information that these trials provide. Once marketed, however, a product is used in a real-world setting by a larger number of patients. As a consequence, the understanding of a product's risk/benefit profile continues to evolve long after the text of the labeling has been set. Before changes in understanding can be reflected in product labeling, however, they must be submitted to FDA and reviewed in a lengthy supplemental process according to regulatory standards established decades ago. A great deal of scientifically

valid information about drug products may not qualify for inclusion in labeling. Approved labeling often omits important information or lags behind current medical understanding.

Given these limitations, manufacturers must be permitted to communicate information that is not included in FDA-approved labeling. The MIWG's proposals are limited to providing further clarity in the regulatory scheme, to enable manufacturers to engage in non-promotional communications that convey accurate out-of-label data and information to a variety of audiences to facilitate sound health care decisions. They do not provide for off-label promotion as FDA has defined it.

Appendix

The slide deck contained herein was used by MIWG representatives during a meeting with FDA officials on November 6, 2014. The slide deck is intended to summarize key points in this White Paper and in other MIWG submissions to FDA.

November 6, 2014

Medical Information Working Group (MIWG)

The MIWG is a coalition of research-based biopharmaceutical and medical technology developers and manufacturers:

- Allergan, Inc.
- Amgen Inc.
- Bayer Healthcare Pharmaceuticals Inc.
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Eli Lilly & Company
- Genentech, Inc.
- GlaxoSmithKline LLC
- Johnson & Johnson
- Novartis Pharmaceuticals Corporation
- Novo Nordisk, Inc.
- Pfizer, Inc.
- Sanofi US

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MIWG Mission

- To clarify and modernize the federal regulatory and enforcement construct governing manufacturer dissemination of truthful, non-misleading, scientifically supported information about prescription drugs, biological products, and medical devices, including:
  - Information about investigational products;
  - Information about new uses of approved/cleared products; and
  - "Out-of-label" information, such as comparative clinical/economic information intended to inform decision-making by payers, formulary committees, or other similar entities.

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Agenda

- **The Need for Change**
- Implications of the MIWG Proposals
- MIWG Proposals
  - Clarify "scientific exchange"
  - Facilitate payer-directed communications under FDAMA 114
  - Clarify "labeling"
  - Clarify "intended use"
- The Case for Rulemaking
- Advisory Opinion Process

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The Need for Change

- Seismic Shifts in Healthcare
  - Healthcare decision-makers, including public and private payers and others in the managed care realm, increasingly emphasize value-oriented factors
- Increased Focus on Patient-Centeredness
  - Informed health care decision-making—based on complete, accurate, and up-to-date information—is critical to this endeavor
- Legal Developments
  - Recent court decisions reinforce key First and Fifth Amendment principles:
    - Content- and speaker-based restrictions are presumptively invalid. Sorrell v. IMS Health, Inc., 131 S. Ct. 2653, 2667 (2011).
    - Restrictions on speech must be sufficiently clear to provide regulated parties with notice as to what conduct is permissible or impermissible. FCC v. Fox Television Stations, 132 S. Ct. 2307 (2012).

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Agenda

- The Need for Change
- **Implications of the MIWG Proposals**
- MIWG Proposals
  - Clarify "scientific exchange"
  - Facilitate payer-directed communications under FDAMA 114
  - Clarify "labeling"
  - Clarify "intended use"
- The Case for Rulemaking
- Advisory Opinion Process

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Implications of the MIWG Proposals

- The MIWG's approach does not represent an attack on the approval process.
- Under the MIWG's proposals, FDA would continue to have regulatory authority over product claims in "labeling" and "advertising," or in other communications that create an "intended use," including sales representatives' oral statements.
- Moreover, these types of manufacturer communications would continue to be subject to specific FDA requirements, including the substantiation requirement and the requirement that these communications be truthful and non-misleading.

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Implications of the MIWG Proposals
• To be clear, the MIWG supports:
– the drug approval process
– liability for false or misleading statements
– the need for adequate directions for truly new intended uses
– appropriate regulations governing truthful, non-misleading scientific exchange
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Agenda

- The Need for Change
- Implications of the MIWG Proposals
- **MIWG Proposals**
  - Clarify "scientific exchange"
  - Facilitate payer-directed communications under FDAMA 114
  - Clarify "labeling"
  - Clarify "intended use"
- The Case for Rulemaking
- Advisory Opinion Process

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MIWG Proposals

- The MIWG proposes:
  - To develop a definition of "scientific exchange" that truly allows free exchange of scientific information; and
  - To clarify the channel for communication of health care economic information to payers.
- To accomplish these goals, the definitions of "labeling" and "intended use" need to be clarified.
- Under the current regulatory scheme, manufacturers sometimes cannot distinguish between "scientific exchange" and communications that qualify as "labeling" or "advertising" or create a new "intended use."
- The lack of clarity regarding the concept of "scientific exchange" chills speech and hinders manufacturers' ability to provide critical information about their products to meet the informational demands of the changing external environment.
- As will be discussed, much can be accomplished by codifying language from a 1987 preamble, which specifies when a communication qualifies as "scientific exchange."

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Scientific Exchange

- Lack of clarity in the "scientific exchange" regulation chills speech and hinders access to important information
  - Does scientific exchange encompass field-based communications (e.g., by MSLs)?
  - Does the communication have to satisfy "recency" or "newsworthiness" criteria not explicit in the regulation?
- FDA should amend regulations to:
  - Codify 1987 preamble, i.e., to qualify as scientific exchange, a statement must
    - Make clear that the product or use is investigational
    - Make no conclusory claims that the product or use has been proven safe or effective
    - Be truthful and non-misleading when measured against information available at the time the statement was made
  - Confirm applicability to medical devices
  - Confirm applicability to non-IND approved drugs and devices (e.g., for information relating to new uses or further exploration of already approved uses)
  - Cover, e.g.: MSLs, pipeline information, information supporting investigator-initiated research, payer interactions
- Clarity needed to distinguish between "scientific exchange" and communications that may:
  - Qualify as "labeling" or "advertising;" or
  - Create a new "intended use" under the FDCA

Payer-Directed Communications: FDAMA 114

- FDAMA 114
  - HCEI communicated to payers and similar entities does not require substantial evidence if directly related to an approved indication
- FDA should publish guidance addressing:
  - What is HCEI?
  - When is HCEI "directly related" to an approved indication?
  - Who is the permitted audience for HCEI?
  - What constitutes "competent and reliable scientific evidence" (CARSE) supporting HCEI?

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Payer-Directed Communications: FDAMA 114 (cont'd)

- What is HCEI?
  - Encompasses all components of analysis, including inputs, assumptions, methods, and results
  - Can involve a number of techniques, e.g.,
    - Economic modeling, cost minimization, cost effectiveness, comparative effectiveness, cost utility, cost benefit, cost of illness
  - Clinical components can be generated using evidence from different sources or using different types of methodologies, e.g.,
    - Randomized clinical trials, pragmatic clinical studies, meta-analyses, observational studies, case studies, patient-reported outcomes, epidemiologic studies, prescription claims database analyses, and outcomes research

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Payer-Directed Communications: FDAMA 114 (cont'd)

- What is "directly related" to an approved indication?
  - The phrase "directly relates" signifies that Congress intended for HCEI to include communication relating to the labeled indication, even if it varies from the approved labeling, so long as the communication does not claim that the drug has been approved for, or is safe and effective for, an entirely "new use" of the drug as defined in 21 C.F.R. § 201.128.
- HCEI is "directly related" to an approved indication when:
  - Based on data explicitly cited in labeling
  - Based on economic/health outcomes not in label if outcomes are shown by competent and reliable evidence to flow from use of product for approved indication

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Payer-Directed Communications: FDAMA 114 (cont'd)

- Who is the permitted audience?
  - A "formulary committee, or other similar entity" encompasses any individual, group of individuals, or entity responsible for contributing toward, advising, or facilitating organizational decisions directed at selecting the drugs that may be used within a certain population of patients, improving population health, lowering health care costs, or improving patient experience through the availability or management of pharmaceutical treatments or programs.
  - "Managed care or other similar organizations" includes entities that make coverage or payment decisions regarding drugs provided to patients, have some level of financial responsibility for patient care, or are responsible for selecting drugs offered to patients.
  - "[I]n the course of . . . carrying out its responsibility for the selection of drugs" means provided to inform drug-selection decisions for a population of patients.

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Payer-Directed Communications: FDAMA 114 (cont'd)

- What is CARSE?
  - The CARSE standard is flexible, and it is not appropriate to define the criteria that particular studies, analyses, or materials disseminated pursuant to FDAMA 114 must satisfy
  - CARSE includes "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results." FTC v. Iovate Health Sciences USA, Inc., No. 10-cv-587, at 8 (W.D.N.Y. 2010).
  - Components of the HCEI analysis, including those involving clinical information, are not required to meet the substantial evidence standard applicable to stand-alone clinical claims

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Labeling

- To accommodate scientific exchange, FDA should narrow the current, overly broad interpretation of labeling, e.g.,
  - Statements that 21 C.F.R. § 202.1(l)(2) sets forth an extensive list of items deemed to be labeling
- Manufacturers have been told that virtually any type of written communication could be regulated as labeling by FDA
- Properly construed, "labeling" does *not* include any written, printed, or graphic material that contains a product name
  - FDCA § 201(m): "labeling" means written, printed, or graphic matter "accompanying" a product
  - United States v. Kordel
    - The Court held that written materials comprise "labeling" when they: (1) have the same origin as the drug; (2) have the same destination; (3) are designed for use in the sale and distribution of the drug; and (4) have a "textual relationship" or "constitute[ ] an essential supplement" to the label.

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Labeling (cont'd)

- Clear definition of "labeling" required for:
  - Consistency with FDCA and Kordel
  - First and Fifth Amendment requirements
- FDA should confirm "labeling" is defined by 21 C.F.R. § 1.3(a) and interpret it in a manner that is consistent with Kordel
  - 21 C.F.R. § 202.1(l)(2) does not define labeling, but operates to exclude the listed communications from the definition of "advertising"
  - No need to amend these regulations

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Intended Use

- Unclear what sources of information may create a new intended use under FDA regulations
  - §§ 201.128 and 801.4 refer to the drug/device being "offered and used" off-label, but
  - Also mention a manufacturer's knowledge
  - Prosecutors invoke regulatory interpretations that penalize mere knowledge
- FDA should amend regulations to clarify that a new "intended use":
  - Can be created only by labeling statements, advertising matter, or analogous oral statements
    - As distinguished from communications that are not promotional (e.g., scientific exchange) or are not outward-facing (e.g., internal company communications)
  - Is not evidenced by:
    - Actual or constructive knowledge that a product may be used off-label
    - Subjective intent

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Agenda

- The Need for Change
- Implications of the MIWG Proposals
- MIWG Proposals
  - Clarify "scientific exchange"
  - Facilitate payer-directed communications under FDAMA 114
  - Clarify "labeling"
  - Clarify "intended use"
- **The Case for Rulemaking**
- Advisory Opinion Process

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Under First And Fifth Amendment Principles, FDA Can Regulate Manufacturer Speech Only If It Does So With "Precision"—Which Guidance Does Not, and Cannot, Provide

- FCC v. Fox Television Stations, Inc., 132 S. Ct. 2307 (2012) (Fox II), confirms that due process "fair warning" considerations apply with special force in the First Amendment context
  - "A fundamental principle in our legal system is that laws must give fair notice of conduct that is forbidden or required. .... This requirement of clarity in regulation is essential to the protections provided by the Due Process Clause of the Fifth Amendment." 132 S. Ct. at 2317.
  - The Supreme Court's "fair notice" jurisprudence recognizes two due process requirements:
    - "[F]irst, that regulated parties should know what is required of them so they may act accordingly," and
    - "[S]econd, [that] precision and guidance are necessary so that those enforcing the law do not act in an arbitrary or discriminatory way." Id.
  - "When speech is involved, rigorous adherence to those requirements is necessary to ensure that ambiguity does not chill protected speech." Id.
    - See also id. at 2318 ("The vagueness of [a content-based regulation of speech] raises special First Amendment concerns because of its obvious chilling effect.").

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The Case For Proceeding By Rulemaking, Rather Than Guidance

- Only regulations provide the "fair notice" required by the Due Process Clause
  - Guidance documents are generated by processes that do not lend themselves to compliance with Due Process requirements.
  - As comments indicate, draft guidances issued by FDA recently have lacked precision, are sometimes unclear, and have made an already murky regulatory environment even more restrictive.
- Regulating by rule rather than guidance would enable FDA to reduce its litigation risk and encourage voluntary compliance
  - Enforcement efforts are hampered if underlying legal norms are subject to challenge on Due Process grounds.
  - Manufacturers cannot comply as readily if they are unaware of FDA's regulatory expectations.
- The public health is better served by clear, precise requirements that avoid chilling clinically important information dissemination

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Agenda

- The Need for Change
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- MIWG Proposals
  - Clarify "scientific exchange"
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  - Clarify "intended use"
- The Case for Rulemaking
- **Advisory Opinion Process**

23

Improved Advisory Procedures Are Needed to Encourage Voluntary Compliance

- The Need: Binding agency advice is particularly critical for FDA-regulated companies, given the ambiguity and complexity in the regulatory and enforcement environment
- MIWG Proposals:
  - Provide responses to requests for advisory comments under 21 C.F.R. § 202.1(j)(4) within 30 days
  - Implement binding advisory opinion process
- An FDA task force previously rejected MIWG's request to implement a binding advisory opinion process

> "The request for FDA to issue binding advisory opinions may place inappropriate restrictions on FDA's ability to respond to emerging issues to best protect and promote the public health. . . . The Task Force is not recommending changes to current practice."
>
> FDA Transparency Initiative: Improving Transparency to Regulated Industry 44 (Jan. 2011)

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Summary of MIWG Positions

Type of Speech	Applicable Standards	Examples
Scientific Exchange	• Truthful and non-misleading • Disclose that product or use is not FDA-approved • No claims of safety or effectiveness	• Information supporting investigator-initiated research • MSL communications • Pipeline information • Payer interactions • Rebuttals of comparative effectiveness research
Advertising/Labeling/Evidence of Intended Use	• Truthful and non-misleading • Other regulatory requirements as applicable (e.g., substantiation, fair balance, adequate directions for use)	• Journal ads • Promotional websites • Analogous oral statements
HCEI to Formulary Committees or Other Similar Entities	• Competent and reliable scientific evidence (CARSE) • Directly related to the approved indication • Shared with formulary committees or other similar entities	• Prescription claims database analyses comparing economic consequences of various treatments • Economic modeling to estimate savings (e.g., reduced length of hospital stay) associated with a drug

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Endnotes

[1] Letter from Leslie Kux, Assistant Commissioner for Policy, FDA to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014).
[2] See 42 U.S.C. §§ 1396r-8(d)(1)(B)(i), (k)(3), (k)(6), 1395w-102(e)(1), (e)(4), 1395x(t)(2); Medicare Benefit Policy Manual Ch. 15, § 50.4.5.
[3] 21 U.S.C. §§ 352(f)(1), 353(b)(1); 21 C.F.R. §§ 201.100(c), 801.109(c).
[4] 21 C.F.R. §§ 312.23(a)(3)(iv)(b), 312.20(b)(2), 312.25(a).
[5] 59 Fed. Reg. 59,820, 59,820 (Nov. 18, 1994) ("The uses that are approved by the agency are sometimes referred to as 'labeled' uses because they appear in the product's approved labeling. Uses that do not appear in the labeling and are not approved by the agency are referred to as 'unapproved,' 'unlabeled,' 'off-label,' or 'extra-label' uses.").
[6] 21 C.F.R. § 201.56(a)(1).
[7] See 40 Fed. Reg. 15,392, 15,394 (Apr. 7, 1975) ("[T]he labeling of a marketed drug does not always contain all the most current information available to physicians relating to the proper use of the drug in good medical practice. Advances in medical knowledge and practice inevitably precede labeling revision."); see also Draft Guidance for Industry: Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices 2, 5-6 (June 2014) (acknowledging "the inherent limitations of the premarket risk assessment," observing that a wide variety of studies and analyses can inform a drug's safety profile, and "recogniz[ing] that the safety profile of a drug evolves throughout its lifecycle as the extent of exposure to the product increases and that it can be helpful for health care practitioners to receive significant new risk information about an approved product in a timely manner," the Agency proposed recommendations for the dissemination of "new risk information that rebuts, mitigates, or refines risk information in approved labeling.").
[8] Robert Temple, Legal Implications of the Package Insert, 58 Med. Clinics of N. Am. 1151, 1155 (1974).
[9] See, e.g., 21 U.S.C. § 396; 21 C.F.R. § 312.2(d); 48 Fed. Reg. 26,720, 26,733 (June 9, 1983); 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972).
[10] See Guidance for Industry: Development and Use of Risk Minimization Action Plans § IV.D (Mar. 2005) (FDA lacks "authority . . . to control decisions made by qualified healthcare practitioners to prescribe products for conditions other than those described in FDA-approved labeling, or to otherwise regulate medical or surgical practice."); 68 Fed. Reg. 6,062, 6,071 (Feb. 6, 2003) (quoting 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972)).
[11] Draft Guidance for IRBs, Clinical Investigators, and Sponsors: Informed Consent Information Sheet 9 (July 2014).
[12] Richardson v. Miller, 44 S.W.3d 1, 13 n.11 (Tenn. Ct. App. 2000); see also J.H. Beales III, New Uses for Old Drugs, in Competitive Strategies in the Pharmaceutical Industry (Robert B. Helms ed., 1996) (reporting that off-label uses that later come to be recognized by the FDA appear in official compendia on average 2.5 years before FDA recognition).
[13] See Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 349-51 & n.5 (2001); Washington Legal Found. v. Friedman, 202 F.3d 331, 333 (D.C. Cir. 2000); see also 1997 Annual Meeting of the AMA, 4, Reports of the Council on Scientific Affairs (stating that "the prescribing of drugs for unlabeled uses is often necessary for optimal patient care").
[14] Susan G. Poole & Michael J. Dooley, Off-Label Prescribing in Oncology, 12 Support Care Cancer 302 (2004); see also Bryan A. Liang & Tim Mackey, Reforming Off-Label Promotion to Enhance Orphan Disease Treatment, Science, Jan. 15, 2010, at 273.
[15] Am. Cancer Soc'y, Off-Label Drug Use, http://tinyurl.com/p575mqo.
[16] Guidance for Industry: FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products 1 (Dec. 1998).
[17] ASCO, Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications, 24 J. Clin. Onc. 3206 (2006).
[18] Am. Soc'y of Clinical Oncology (ASCO), Drug Approval and Labeling, http://tinyurl.com/o64owuz.
[19] Letter from Joseph S. Bailes, M.D., Chair, Clin. Practice Comm., ASCO to Dockets Management Branch 1, Docket No. 02N-0209 (Sept. 13, 2002) (emphasis added).

[20] See Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer 4 (Jan. 2004).
[21] See Kavi K. Devulapalli & Henry A. Nasrallah, An Analysis of the High Psychotropic Off-Label Use in Psychiatric Disorders, 2 Asian J. Psych. 29 (2009); see also Christopher M. Wittich et al., Ten Common Questions (and Their Answers) About Off-label Drug Use, 87 Mayo Clin. Proc. 982 (2012); see also E. Horowitz et al., Off-Label Use of Sodium Valproate for Schizophrenia, 9 PLoS One 1 (2014).
[22] See 42 U.S.C. §§ 1396r-8(d)(1)(B)(i), (k)(3), (k)(6), 1395w-102(e)(1), (e)(4), 1395x(t)(2); Medicare Benefit Policy Manual Ch. 15, § 50.4.5.
[23] 42 U.S.C. §§ 1396r-8(d)(1)(B)(i), (k)(6), (g)(1)(B)(i).
[24] See Jeroen P. Jansen et al., Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons for Good Research Practices: Part 1, 14 Value in Health 417, 418, 427 (2011) (indicating that indirect treatment comparisons, network meta-analyses, and observational studies can be useful guides for reimbursement decisions in the absence of "robustly designed RCTs . . . compar[ing] all interventions of interest," which "are almost never available").
[25] See Alan M. Garber & Harold C. Sox, The Role of Costs in Comparative Effectiveness Research, 29 Health Affairs 1805, 1805-06, 1810 (2010) (indicating that "insurers . . . will surely make heavy use of the research" generated pursuant to ACA's directives, which "will include studies of systems of health care delivery, such as comparisons of different workplace wellness programs to prevent the effects of chronic disease," as well as PCORI's CER).
[26] See, e.g., Louis P. Garrison Jr. et al., A Flexible Approach to Evidentiary Standards For Comparative Effectiveness Research, 29 Health Affairs 1812, 1815-16 (2010) (indicating that the research generated by PCORI, which can include a wide variety of non-registration quality studies, could be useful to "various decision makers in formulating practice guidelines and determining what interventions to cover and how much to pay for them").
[27] See 42 U.S.C. §§ 1396r-8(d)(1)(B)(i), (g)(1)(B)(i), (k)(6), 1395w-102(e)(1), (e)(4), 1395x(t)(2)(B)(ii)(II); Medicare Benefit Policy Manual Ch. 15, § 50.4.5.
[28] See 32 C.F.R. § 199.4(g)(15); see also TRICARE Policy Manual 6010.57-M Ch. 8, § 9.1, 2.2.5 (Sept. 8, 2011).
[29] See Office of Personnel Management (OPM), Carrier Letter No. 2011-10a ("You must also provide benefits for 'off-label' use of covered medications when prescribed in accordance with generally accepted medical practice by a plan doctor"); OPM, Carrier Letter No. 2014-12(a) ("The Policies established in prior years remain in effect unless we have stated otherwise"); see also OPM, Carrier Letter No. 2014-13, at 1 ("[A]s with all covered benefits, the treatment or services must be medically necessary and appropriate for the member's condition"); OPM, Carrier Letter No. 1999-16, Call Letter Enclosure-FFS ("[B]enefits must be provided for 'off-label' use of covered medication [sic] if prescribed for such use by a Plan doctor"); OPM, Carrier Letter No. 2013-09(b) ("Benefit policies from prior years remain in effect unless otherwise noted").
[30] 72 Fed. Reg. 66,222, 66,304, 66,305 (Nov. 27, 2007).
[31] 78 Fed. Reg. 48,164, 48,166 (Aug. 7, 2013).
[32] See 2013 Annual Progress Report to Congress: National Strategy for Quality Improvement in Health Care, available at http://tinyurl.com/ok28hfk.
[33] Id. at 7.
[34] 42 U.S.C. § 1395w-4(p)(1).
[35] See id. § 1395jjj(a)(1), (d)(2).
[36] See id. §1395ww(o).
[37] Andrew Pollack, Cost of Treatment May Influence Doctors, N.Y. Times, Apr. 17, 2014, at A1.
[38] Id.
[39] 42 U.S.C. § 280j(a)(2)(B)(i).
[40] 2013 Annual Progress Report to Congress: National Strategy for Quality Improvement in Health Care, at 4, available at http://tinyurl.com/ok28hfk.
[41] See 42 U.S.C. § 1320e(b)(1).
[42] Id. § 1320e(c).
[43] Id.
[44] See id. § 1320e(d)(6)(C), (2)(A).

[45] Garrison, supra note 26 at 1816 (observing that PCORI "may communicate information that includes a more direct assessment of value than some decision makers, such as product manufacturers, are allowed to address").
[46] Executive Office of the President, President's Council of Advisors on Science and Technology, Realizing the Full Potential of Health Information Technology to Improve Health Care for Americans: The Path Forward, at 24 (Dec. 2010).
[47] See Garrison, supra note 26, at 1812-13 (observing that "[t]he Affordable Care Act recognizes that comparative effectiveness research will include systematic reviews and observational studies, as well as randomly controlled trials" and noting that "evidentiary standards might be quite dissimilar" when FDA is assessing whether to approve a drug or device and when a provider is determining when to recommend a procedure).
[48] See 63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998) ("Health care professionals bear the primary responsibility of informing individuals about patient-specific benefits, risks, and directions for using prescription medication."); Pamela Hartzband & Jerome Groopman, Untangling the Web — Patients, Doctors, and the Internet, 362 New England J. Med. 1063, 1064 (2010) ("Information traditionally flowed from doctor to patient; the physician described the genesis and course of a disease and the options available for treating it.").
[49] See P.J. Seligman & S.F. Osborne, Perspectives on Early Communication of Drug Risks to the Public, 85 Clinical Pharmacology & Therapeutics 335 (2009).
[50] See Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices 3 (Dec. 2011) ("The rapid growth of the Internet, including social media tools and other emerging technologies, has made it easier for both consumers and health care professionals to quickly seek information about medical conditions and treatments.").
[51] See Pamela Hartzband & Jerome Groopman, Untangling the Web — Patients, Doctors, and the Internet, 362 New England J. Med. 1063, 1063 (2010) ("But nothing has changed clinical practice more fundamentally than one recent innovation: the Internet.").
[52] Randale C. Sechrest, The Internet and the Physician-Patient Relationship, 468 Clin. Orthop. Relat. Res. 2566, 2569 (2010).
[53] Robin A. Cohen & Patricia F. Adams, Use of the Internet for Health Information: United States, 2009, National Center for Health Statistics Data Brief (July 2011).
[54] See William H. Frist, Connected Health And The Rise Of The Patient-Consumer, 33 Health Affairs 191, 192 (2014) ("A growing number of patient-consumers are already actively engaged, accessing the Internet for health information before even thinking about going to a doctor."); see also W. Ed Hammond et al., Connecting Information To Improve Health, 29 Health Affairs 285, 285 (2010) (discussing the demand for instant "access to complete and comprehensive data for decision making").
[55] See Ronen Rozenblum & David W. Bates, Patient-centered healthcare, social media and the internet: the perfect storm?, 22 BMJ Quality & Safety 183, 184 (2013) ("Facebook has become a significant source of health care information, such as specific data about health conditions and healthcare facilities, and blogs have become a powerful communication tool to disseminate health information and engage patients with their health care."); see also Health Research Institute, Customer experience in the pharmaceutical sector: Getting closer to the patient, at 6 (Nov. 2013), available at http://tinyurl.com/kjsv5md (describing the growing importance of social media and online patient reviews).
[56] Executive Office of the President, President's Council of Advisors on Science and Technology, Realizing the Full Potential of Health Information Technology to Improve Health Care for Americans: The Path Forward, at 24 (Dec. 2010).
[57] See Lygeia Ricciardi et al., A National Action Plan To Support Consumer Engagement Via E-Health, 32 Health Affairs 376, 377 (2013) ("Many studies have shown that engaged patients—those who actively seek to know more about and manage their own health—are more likely than others to participate in preventive and healthy practices, self-manage their conditions, and achieve better outcomes.").
[58] R.J. Reynolds Tobacco Co. v. FDA, 845 F. Supp. 2d 266, 276 (D.D.C. 2012) ("Congress must pass laws, and the FDA must implement final rules, that are consistent with the requirements of the Constitution.").
[59] Thompson v. W. States Med. Ctr., 535 U.S. 357 (2002).
[60] Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 62 (D.D.C. 1998), vacated in part, 202 F.3d 331 (D.C. Cir. 2000); Board of Trustees v. Sullivan, 773 F. Supp. 472, 474 (D.D.C. 1991) ("[T]he First

Amendment protects scientific expression and debate just as it protects political and artistic expression."); Miller v. California, 413 U.S. 15, 34 (1973) (The First Amendment protects speech that has "serious . . . scientific value").

[61] Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 596-97 (1993).

[62] "[T]he constant process of questioning, testing, updating, and sometimes replacing received wisdom is the hallmark of good science . . . ." Eugene Volokh, In Defense of the Marketplace of Ideas, 97 Va. L. Rev. 595, 597 (2011).

[63] Brief amici curiae of Professors Kenneth Rothman, Noel Weiss, James Rocins, and Raymond Neum, 61 U.S.L.W. 3284 (1992), in Daubert v. Merrell-Dow Pharm. Inc., 509 U.S. 579 (1993).

[64] 21 C.F.R. § 202.1(e)(6)(iii). The regulatory standards for the adjudication of clinical trials as sources of efficacy data for new drugs make explicit that those investigations are properly evaluated according to contemporary scientific standards; as knowledge regarding trial design evolves, so too does FDA's approach to the regulatory review of those data sources. Id. § 314.126.

[65] Lars Noah, Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community, 44 Ariz. L. Rev. 373, 382 (2002).

[66] 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972).

[67] 517 U.S. 484 (1996).

[68] Id. at 503.

[69] 507 U.S. 761, 767 (1993).

[70] Thompson, 535 U.S. at 374.

[71] 703 F.3d 149 (2d Cir. 2012).

[72] Id. at 167.

[73] 131 S. Ct. 2653 (2011).

[74] Reno v. ACLU, 521 U.S. 844, 874 (1997); Keyishian v. Bd. of Regents of the U. of N.Y., 385 U.S. 589, 604 (1967); see also Buckley v. Valeo, 424 U.S. 1, 76-77 (1976).

[75] Grayned v. City of Rockford, 408 U.S. 104, 109 (1972) (quoting Baggett v. Bullitt, 377 U.S. 360, 372 (1964)).

[76] 132 S. Ct. 2307 (2012).

[77] Id. at 2317 (Due process principles require "[f]irst, that regulated parties should know what is required of them so they may act accordingly; second, precision and guidance . . . so that those enforcing the law do not act in an arbitrary or discriminatory way.") (citing Grayned, 408 U.S. at 108-109).

[78] 18 U.S.C. § 1464.

[79] Fox II, 132 S. Ct. at 2313 (quoting In re Industry Guidance on Commission's Case Law Interpreting 18 U.S.C. § 1464 and Enforcement Policies Regarding Broadcast Indecency, 16 FCC Rcd. 7999).

[80] Id. at 2314.

[81] Id.

[82] Id. at 2318 (quoting United States v. Williams, 553 U. S. 285, 304 (2008)).

[83] Id. (quoting Baggett v. Bullitt, 377 U.S. 360, 372 (1964)).

[84] Id. ("When speech is involved, rigorous adherence to [fair notice] requirements is necessary to ensure that ambiguity does not chill protected speech.").

[85] 62 Fed. Reg. 14,912 (Mar. 28, 1997); 67 Fed. Reg. 34,942 (Mar. 16, 2002).

[86] See Michael McCaughan, Acknowledging Caronia: FDA Takes The First Step To Rethinking Off-Label Policy, The RPM Report, May 1, 2014 (quoting CDER Director Janet Woodcock's statement at the Food and Drug Law Institute's (FDLI's) Annual Conference in April 2014 that FDA is "aware of the outside world," including recent court rulings and that "[t]here is a paradigm that has existed for quite a long time," but that "[c]ommunication has changed, attitudes have changed, health care has changed"); Remarks by Elizabeth Dickinson, Chief Counsel, FDA at the FDLI Annual Conference (Apr. 24, 2014) ("Industry challenges along with the agency's own evolving scientific and medical policy views and changes in how information is conveyed and healthcare is delivered are driving a new commitment at the highest levels of the agency . . . to realign FDA's regulatory posture" as it relates to speech about off-label uses of drugs and devices.").

[87] 52 Fed. Reg. 19,466, 19,475 (May 22, 1987).

[88] Id.

[89] 42 Fed. Reg. 49,612 (Sep. 27, 1977) (proposed 21 C.F.R. § 52.118).

[90] See Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices 5 (Dec. 2011).
[91] See, e.g., FDA, Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs), http://tinyurl.com/kmta62b (describing sponsor responsibilities and making clear that companies that provide study drug are not study sponsors).
[92] See DOJ, Press Release: Pharmaceutical Giant AstraZeneca to Pay $520 Million for Off-Label Drug Marketing (Apr. 27, 2010) (alleging among other things that the company "engaged doctors . . . to conduct studies on unapproved uses of Seroquel").
[93] See Joseph P. Griffin, Bryant M. Godfrey, and Rachel E. Sherman, Regulation Requirements Of The Food And Drug Administration Would Preclude Product Claims Based On Observational Research, 31 Health Affairs 2188, 2189 (2012) ("[A] manufacturer must be able to engage in scientific discussions of comparative effectiveness data that affect its products.").
[94] 21 U.S.C. § 352(a).
[95] Id. § 355(a).
[96] Id. § 321(p)(1); see also id. §§ 360(k), 351(f)(1)(B), 352(o), 360e(a) (counterpart device provisions).
[97] Id. § 352(f)(1).
[98] Id. § 321(m).
[99] See, e.g., S. Rep. No. 74-361, at 4-5 (1935) (stating that "differentiation between label and labeling is necessary because the declaration of certain facts . . . should . . . appear on the principal label or labels where they can be easily observed, rather than on side panels of the labeling or in circulars within the package where they may escape notice") (emphasis added).
[100] 7 Cases of Eckman's Alterative v. United States, 239 U.S. 510, 517 (1916).
[101] See 335 U.S. 345, 348-351 (1948) ("The question whether the separate shipment of the literature saved the drugs from being misbranded within the meaning of the Act presents the main issue in the case . . . . [W]e conclude that the phrase 'accompanying such article' is not restricted to labels that are on or in the article or package that is transported.").
[102] Id. at 350 (emphasis added).
[103] Id. at 348, 350.
[104] 21 C.F.R. § 201.100(d).
[105] See, e.g., Draft Guidance for Industry: Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices (June 2014); Draft Guidance for Industry: Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics (Jan. 2014); Draft Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion (May 2009).
[106] Def.'s Reply in Supp. of Mot. to Dismiss or Summ. J. at 22-23, Allergan, Inc. v. United States, No. 09-1879 (D.D.C. Mar. 29, 2010).
[107] 21 C.F.R. §§ 201.128, 801.4.
[108] See Letter from John L. Hammer, Jr., Vice President, Smith, Kline & French Laboratories to Hearing Clerk, Federal Security Agency (Mar. 4, 1952) (If a manufacturer's "market research department learns that 20% of the purchasers use the preparation as a sedative . . . [and] he inserts in his label directions for use as a sedative . . . he is forced into the position of recommending his product for a use of which he heartily disapproves and for which his drug may be largely ineffective.").
[109] See Ass'n of Am. Physicians & Surgeons v. FDA, 226 F. Supp. 2d 204, 217-18 (D.D.C. 2002) (stating that "even the FDA has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses").
[110] Mem. in Supp. of Mot. to Dismiss or for Summ. J. at 10, Allergan v. United States, No. 09-01879 (D.D.C. filed Dec. 11, 2009).
[111] See Defs.' Mem. In Supp. of Mot. To Dismiss or for Summ. J. at 8, 29, Par Pharm., Inc. v. United States, No. 11-01820 (D.D.C. filed Jan. 11, 2012) (emphasis added).
[112] Am. Health Prods. Co. v. Hayes, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983) (emphasis added) (citations omitted).
[113] See United States v. Articles of Drug for Veterinary Use, 50 F.3d 497, 500 (8th Cir. 1995) (holding that FDA must demonstrate that the materials in question are promotional in nature, actually distributed to customers, and relied on by those customers to establish an intended use).
[114] 655 F.2d 236, 239 (D.C. Cir.1980).

[115] See Letter from Leslie Kux, Assistant Commissioner for Policy, FDA to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP at 3, n.3, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014); see also Letter from Margaret M. Dotzel, Assoc. Commissioner for Policy, FDA to Daniel J. Popeo & Richard A. Samp, Wash. Legal Found., at 4 (Jan. 28, 2002).

[116] 417 F. Supp. 30 (D. Minn. 1976), aff'd, 540 F.2d 947 (8th Cir. 1976) (per curiam).

[117] See United States v. Article . . . "Sudden Change," 409 F.2d 734, 739 (2d Cir. 1969) (advertisements); United States v. Millpax, Inc., 313 F.2d 152 (7th Cir. 1963) (letters and oral representations), cert. denied, 373 U.S. 903 (1963); Nature Food Ctrs, Inc. v. United States, 310 F.2d 67 (1st Cir. 1962) (speeches at public lecture hall), cert. denied, 371 U.S. 968 (1963); V.E. Irons v. United States, 244 F.2d 34 (1st Cir. 1957).

[118] E.g., 63 Fed. Reg. 31,143, 31,145 (June 8, 1998).

[119] 63 Fed. Reg. 64,556, 64,559 (Nov. 20, 1998).

[120] See Gov't Summ. J. Br., Allergan v. United States, No. 09-1879, at 5-7, 9 (D.D.C. Dec. 11, 2009).

[121] U.S. Opp. to Def's Mot. to Dismiss the Indictment or, in the Alternative, Motion in Limine, United States v. Harkonen, No. 08-164 at 8, n.3 (N.D. Cal. Apr. 20, 2009).

[122] Decl. of Dr. Robert Temple ¶ 10, Allergan v. United States, No. 09-1879 (D.D.C. Dec. 11, 2009).

[123] Id. at ¶ 9; Decl. of Dr. Rachel Sherman ¶ 14, Par Pharmaceutical v. United States, No. 11-1820 (D.D.C. Jan. 1, 2012).

[124] Transcript of Cross Examination of Sandeep Saini, United States v. Stevens, No. RWT-10-694, at 89 (D. Md. Apr. 27, 2011).

[125] Femrite v. Abbott Nw. Hosp., 568 N.W.2d 535, 542 (Minn. Ct. App. 1997) ("'In general, a physician who engages in off-label uses has the responsibility to be well informed about the device, and to base the decision to use it on sound medical evidence and a firm, scientific rationale.'" (quoting FDA correspondence entitled "Update on the Regulatory Status of Pedicle Screws" (Feb. 17, 1994))).

[126] See, e.g., Bernard v. Block, 176 A.D.2d 843, 846 (N.Y. App. Div. 1991) (stressing that practitioners must use their "best judgment" and provide "reasonable care").

[127] Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices 9 (Dec. 2011).

[128] Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices 9 (Feb. 2014); see also id. at 12 & 16.

[129] See 21 U.S.C. § 352(f)(1) (requirement of adequate directions for use).