ROPES & GRAY

SIDLEY AUSTIN LLP
SIDLEY

July 16, 2013

Via Electronic Submission

Division of Dockets Management (HFA-301)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: CDER Medical Policy Council; Request for Comments (Docket No. FDA-2013-N-0206)

These comments are submitted on behalf of the Medical Information Working Group (MIWG), in response to the Federal Register notice published by the Food and Drug Administration (FDA) on March 18, 2013 (78 FR 16679).[1] The MIWG is a coalition of medical product manufacturers focused on improving the regulatory and enforcement environment affecting manufacturer communications about new uses of approved drugs and medical devices. For more than five years, the MIWG and its members have repeatedly asked FDA to address an issue that is of major public health significance: the need for additional clarity in those aspects of the Agency's regulatory scheme for drugs and medical devices that govern manufacturer dissemination of information about new uses of approved and cleared products.[2]

In response to FDA's March 18 notice, which asked interested parties to identify medical policy issues that the CDER Medical Policy Council could clarify through "notice and comment procedures," we ask that the Council: (1) commence notice-and-comment rulemaking to bring much-needed clarity to the policies and rules applicable to manufacturer communications about new uses of approved products, as described in a citizen petition submitted on July 5, 2011, on behalf of MIWG members (FDA-2011-P-0512); and (2) consider more fundamental changes to FDA's approach to regulating such communications, as described in comments submitted by the MIWG on March 1, 2013, to assure that manufacturers are permitted to provide truthful and non-misleading information to support clinical and economic decision making and protect and promote the public health.

---

[1] The members of the MIWG are: Allergan, Amgen, Bayer, Boehringer-Ingelheim, Eli Lilly & Company, Genentech, GlaxoSmithKline, Johnson & Johnson, Novartis, Novo Nordisk, Pfizer, Purdue Pharma, and Sanofi US.

[2] The MIWG has also submitted the following documents to FDA since 2008: (1) Comments, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices," FDA-2008-D-0053 (Apr. 18, 2008); (2) Comments, Transparency Task Force, FDA-2009-N-0247 (Apr. 15, 2010); (3) Citizen Petition, FDA-2011-P-0512 (filed July 5, 2011, on behalf of a subset of MIWG members); (4) Comments, FDA-2011-N-0912 (Mar. 27, 2012); and (5) Comments, FDA-2011-P-0512 (Mar. 1, 2013).

Each of these requests is addressed further below.

1. The Council should clarify FDA policies on manufacturer dissemination of information about off-label uses as part of scientific exchange, in response to unsolicited requests, through distribution of clinical practice guidelines, and in communications to payors and related entities.

In July 2011, members of the MIWG filed a citizen petition asking FDA to clarify four of the Agency's policies on manufacturer communications about off-label uses: (1) "scientific exchange"; (2) responses to unsolicited requests; (3) distribution of clinical practice guidelines; and (4) communications with payors and similar entities. The petition identified specific changes that should be made in each of those four areas, to provide much-needed clarity to manufacturers interested in engaging in appropriate communications regarding investigational products and new uses of approved products. The petition also stated that the changes should be effected through notice-and-comment rulemaking, rather than in guidance documents.

In December 2011, FDA published a Federal Register notice soliciting comments from the public on scientific exchange.[3] Two days later, the Agency published a notice announcing the availability of a draft guidance document on responses to unsolicited requests.[4] In the scientific exchange notice, FDA stated that it was "considering" the citizen petition's two remaining requests, on clinical practice guidelines and payor communications.[5] Although eighteen months have passed since then, to our knowledge no further action has been taken by FDA to address the petition's requests for clarification of agency policies respecting distribution of clinical practice guidelines or communications with payors and related entities. Moreover, we are aware of no effort to address the public comments that have been submitted to the Agency on scientific exchange or unsolicited requests.

We believe that FDA should take action to address fully the requests set forth in the July 2011 citizen petition, and respectfully ask that the Medical Policy Council consider the citizen petition in the context of the broad medical policy issues that we believe are presented by FDA's current approach to manufacturer communications about new uses of approved products. Our perspective on the policy implications of the current FDA approach is set forth in detail in our prior submissions, and we do not reiterate it here.[6] We do wish to address one specific policy question that we believe is inextricably linked with the July 2011 citizen petition: To what extent does the current regulatory scheme inappropriately disable manufacturers from providing accurate information to payors and similar entities to support their coverage and reimbursement decisions? The answer to this question is vitally important, as those decisions can affect the delivery of patient care and therefore the public health.

Formulary committees, payors, and similar entities[7] play a unique and increasingly important role in the healthcare delivery system. These entities must make

[3] 76 Fed. Reg. 81,508 (Dec. 28, 2011).
[4] 76 Fed. Reg. 82,303 (Dec. 30, 2011).
[5] Id.
[6] See supra n.2.
[7] These entities may include population health decision-makers such as integrated delivery networks (IDNs), treatment guideline and pathway developers, and compendium publishers.

coverage and reimbursement decisions based on a heterogeneous mix of information. They must take into account comparative, outcomes, and price information, as well as early information about investigational products. In many cases, this information arguably constitutes "off-label" information because it concerns clinical endpoints, dosing regimens, or patient populations other than those for which the drug or device was investigated for registration purposes. In addition, information of interest to payors often is derived from meta-analyses, uncontrolled observational studies, and other sources that would not necessarily qualify as "valid scientific evidence" or "substantial evidence" comprising "adequate and well-controlled" clinical investigations if evaluated by FDA in the context of premarket review. Nevertheless, organizations such as AHRQ, PCORI, and ISPOR are developing standards for the conduct of real world evidence studies and other non-RCT study designs.[8] These non-registration-type studies provide a more complete picture of a product's performance in actual clinical practice, and are frequently relied upon to inform coverage and reimbursement decisions that can affect patient care and health outcomes.

Currently, manufacturers cannot communicate adequately about their products or otherwise provide information relevant to coverage and reimbursement decisions, for at least two reasons.

First, FDA simply has not yet adequately addressed the issue. For several years starting in the 1990s, the Agency seemed poised to develop policies on manufacturer communications to payors and related entities in the managed care environment.[9] FDA abandoned further efforts, perhaps because Congress enacted the FDA Modernization Act of 1997 (FDAMA), Section 114 of which enabled drug manufacturers to provide health care economic information to payors and related entities even if the information was not completely on-label or derived from studies of the type ordinarily required for approval and promotional claims.[10] Since then, FDA has not addressed important interpretive questions in regulations or guidance. As a result, manufacturers often have not sought to rely on Section 114.[11]

[8] In 2010, Congress enacted the Patient Protection and Affordable Care Act, which established the Patient-Centered Outcomes Research Institute (PCORI), a new public-private entity that will fund and promote comparative effectiveness research, including "[s]ystematic reviews" and "observational data." See 42 U.S.C. § 1320e(d)(6)(C), (2)(A). It also authorized the Agency for Healthcare Research and Quality (AHRQ) to "disseminate the research findings . . . relevant to comparative clinical effectiveness research." Id. § 299b-37(a)(1). Pursuant to these provisions, PCORI has begun developing a research agenda to support the development of new data and analysis comparing treatment options, and AHRQ recently began disseminating comparative effectiveness research through the "academic detailing" of a comparative effectiveness and safety report on oral diabetes medications.

[9] DDMAC, Guidance: Principles for the Review of Pharmacoeconomic Promotion (Mar. 1995); FDA Public Hearing: Pharmaceutical Marketing and Information Exchange in Managed Care Environments (Oct. 19, 1995).. In 2001, FDA announced plans to develop guidance on pharmacoeconomic claims, but then almost immediately suspended the effort on the ground that "research . . . 'has not been adequately developed for FDA to begin setting . . . standards.'" The Pink Sheet, Mar. 19, 2001.

[10] 21 U.S.C. § 352(a).

[11] More recently, FDA officials have publicly rejected the notion that FDAMA § 114 entitles manufacturers to provide payors with "competent and reliable" HCEI based on unlabeled clinical endpoints. See, e.g., Robert Temple, "Communication of CER Findings" (Feb. 9, 2012) (http://npcdev.npcnow.org/App_Themes/Public/pdf/events/2012asymmetry/rtemple_asym12.pdf).

Second, existing FDA policies on manufacturer dissemination of information about investigational products and off-label uses are not adequate. FDA's 2009 guidance on reprints of journal articles and reference texts discussing off-label uses does not apply to the types of data sources (e.g., observational studies) that are often of greatest need in the coverage and reimbursement context. Moreover, FDA has not addressed whether the regulatory "safe harbor" for scientific exchange (21 C.F.R. § 312.7(a)) applies to payor communications. A manufacturer can provide information about off-label uses in response to an unsolicited request from a payor, but this option has its own risks and limitations. For example, payors and related entities often are unaware of the criteria set forth in FDA's policy on responses to unsolicited requests, and therefore do not have sufficient knowledge to enable them to craft a request of the type that would enable a manufacturer to provide a response. Where a payor posts a general request for manufacturer submissions, manufacturers cannot determine whether that request is sufficiently specific to permit them to respond.[12] Further, in some cases, a manufacturer may learn that a payor has premised a coverage decision on an error, but cannot proactively correct the mistake because doing so could be regarded by FDA as "promotion."

The payor dimension of the broader off-label communication problem illustrates the immediate need for concerted action by senior CDER leadership in this area. We ask the Medical Policy Council to consider the consequences of the current regulatory scheme for payors' ability to make coverage and reimbursement decisions based on the full range of appropriate information and analysis. Because manufacturers have unique access to, and wherewithal to provide, so much product-related information, their inability to communicate adequately means that this information is simply not used in payors' decision-making. As a result, in the current environment, payors are almost certainly reaching coverage and reimbursement decisions based on inadequate information, with uncertain and potentially far-reaching clinical implications. We believe FDA's efforts to make regulatory decisions to protect and promote the public health can be undermined in practice if payers and similar entities make determinations on the basis of inadequate information.

2. The Council should consider a comprehensive review of the entire regulatory scheme governing manufacturer communications about new uses of approved drugs and medical devices.

We also request that the CDER Medical Policy Council go beyond the four specific requests set forth in the July 2011 citizen petition, the policy implications of which are illustrated by the payor issue highlighted above. In addition to clarifying the four policy areas described above, the Agency should move quickly to solicit public comment on, and implement, fundamental changes to its approach to regulating manufacturer speech about new uses. Such changes are necessary to bring the current regulatory and enforcement environment into line with relevant statutory and constitutional limitations, and to assure that the regulatory scheme supports enforcement of the Federal Food, Drug, and Cosmetic Act, while also enabling manufacturers to engage with prescribers and payors, to contribute to informed clinical and economic decision making and thereby promote the public health.

[12] DDMAC said in 1994 that requests must be "specific." DDMAC, Current Issues & Procedures (Apr. 1994).

We have submitted comments to FDA explaining in greater detail the developments in the external environment that should lead the Agency to review comprehensively its existing approach to manufacturer speech about off-label uses.[13] The MIWG respectfully submits that the Council should immediately consider these comments, in addition to the specific requests for clarity set forth in the July 2011 petition. In our view, it is time for FDA to consider modifications to the current regulatory scheme, to align it more fully with applicable legal limitations. We believe that a modified scheme would better enable the Agency to fulfill the public health need for manufacturers to engage in appropriate communications, to payors as well as others, about new uses of approved drugs and medical devices.

On behalf of the MIWG, we ask that the Council both act on the July 2011 citizen petition and make fundamental changes to FDA's approach to regulating manufacturer communications about new uses of approved drugs and medical devices. The actions requested in the July 2011 citizen petition could be taken without extensive additional process, though we believe that notice-and-comment rulemaking should be used rather than guidance development procedures because only the former can produce legally binding rules. The more fundamental review of the entire regulatory scheme that we ask the Medical Policy Council to commence should, we believe, first include an open process of soliciting stakeholder views from patients, health care practitioners, payors, and related entities. In all events, immediate action is necessary to assure that manufacturers are permitted to provide truthful and non-misleading information to support clinical and economic decision making and protect and promote the public health.

We appreciate the opportunity to comment. Copies of other submissions made by the MIWG and its members are being submitted to this docket for convenient reference.

[13] MIWG Comments, FDA-2011-P-0512 (Mar. 1, 2013).

Respectfully submitted,

Colleen Klasmeier
Sidley Austin LLP
1501 K Street NW
Washington DC 20005
(202) 736-8132
cklasmeier@sidley.com

Alan Bennett
Ropes & Gray
One Metro Center
700 12th Street, NW
Suite 900
Washington, DC 20005-3948
(202) 508-4604
alan.bennett@ropesgray.com

Paul E. Kalb
Sidley Austin LLP
1501 K Street NW
Washington DC 20005
(202) 736-8050
pkalb@sidley.com

Joan McPhee
Ropes & Gray
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
(617) 951-7535
joan.mcphee@ropesgray.com

Counsel to the Medical Information Working Group

Enclosures

April 18, 2008

COMMENTS OF THE MEDICAL INFORMATION WORKING GROUP ON FDA'S "GOOD REPRINT PRACTICES" DRAFT GUIDANCE

The Medical Information Working Group (MIWG) appreciates the opportunity to provide the Food and Drug Administration (FDA) with comments on the draft guidance, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices," the notice of availability (NOA) for which was published in the Federal Register on February 20, 2008 (73 Fed. Reg. 9,342). The MIWG is an informal working group of major manufacturers of prescription drugs and medical devices (including biological products). The MIWG was formed to consider issues relating to the federal government's regulation of truthful, non-misleading, scientifically substantiated manufacturer communications about new (or "off-label") uses of approved drugs and approved/cleared medical devices.[1]

Although the MIWG supports the intent and thrust of the draft guidance, we also believe that the draft raises important issues that should be addressed in the final version. The most important issue concerns the relationship of the draft guidance to the other "safe harbors" that FDA has crafted over many years to encourage manufacturers to distribute off-label use information in specific situations (discussed below) while also assuring effective enforcement of the Federal Food, Drug, and Cosmetic Act (FDCA). Although we understand that the safe harbor recognized in the draft guidance is in addition to these other safe harbors, to help assure clarity in the regulatory environment, we respectfully request that FDA expressly affirm—ideally, in both the NOA accompanying the final guidance and in the final guidance itself—that these pre-existing safe harbors continue to be available to manufacturers wishing to provide information about off-label uses. The MIWG believes that, absent such clarification, manufacturers might be reluctant to employ these safe harbors, with attendant adverse public health consequences.

Part I of our comments addresses the safe harbor issue in view of the critical public health importance of off-label use information. Part II sets forth our comments on specific aspects of the draft guidance.

I. OFF-LABEL USE INFORMATION IS OF PARAMOUNT PUBLIC HEALTH IMPORTANCE.

As FDA notes in the draft guidance (p. 3), there are "important public policy reasons for allowing manufacturers to disseminate truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities." In view of these "important public policy" considerations, the MIWG asks that FDA affirm that the safe harbors the agency had previously established before issuing the draft guidance remain in full force and effect, allowing manufacturers to provide information about off-label uses under the carefully limited conditions the agency has established for those safe harbors. Such

[1] Members of the MIWG include: Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bayer Corporation; Cephalon, Inc.; Eli Lilly and Company; Eisai Inc.; Genentech, Inc.; Johnson & Johnson; Pfizer Inc; and Schering-Plough Corporation. In this document, we use "medical product approval" to include device approval and clearance and drug approval. "Approved product" refers to all medical products in commercial distribution pursuant to appropriate marketing authorization from FDA, including approved and cleared products.

affirmation would encourage appropriate dissemination of off-label use information, with corresponding benefits for health care practitioners and entities and their patients.

A. Patients Benefit from The Distribution of Reliable Information About Off-Label Use.

The MIWG fully concurs with FDA's statement in the draft guidance regarding the important public policy considerations supporting the appropriate dissemination of off-label use information. As discussed below, off-label use is a legitimate aspect of medical and surgical practice. Indeed, in some areas, off-label use is extremely common, and may even represent the standard of care. Because off-label use that benefits patients is encouraged by the dissemination of reliable information about such use, FDA has established a number of policies—supported by the American Medical Association and the American Society of Clinical Oncology, among others—expressly recognizing that manufacturers may provide off-label use information to health care practitioners in carefully limited circumstances. To help ensure that nothing in the draft guidance will be interpreted to limit these policies, the MIWG requests that FDA include a clarifying statement to that effect in the final guidance and accompanying NOA.

1. Off-Label Use Is A Legitimate Aspect of Sound Medical Practice.

As a general matter under the FDCA, to obtain approval, a manufacturer must submit information necessary to demonstrate the safety and effectiveness (or, in the case of class I and II devices, the substantial equivalence) of the product. 21 U.S.C. § 355(b), (j) (new drugs); id. § 360e(c) (class III devices); id. § 360(k) (class I and II devices); id. § 360c(a)(1)(B) (class II devices that do not require a Premarket Approval Application (PMA)). To obtain such information, the manufacturer ordinarily must sponsor clinical investigations of the product pursuant to a statutory exemption from the prohibition against distribution of unapproved or uncleared products in interstate commerce. See 21 C.F.R. Part 312 (clinical trials of unapproved new drugs), Part 812 (investigational devices). The same clinical study requirements apply to new uses of lawfully marketed products. See, e.g., id. § 312.2. By definition, therefore, data respecting the clinical utility of a new use for a marketed product emerge before FDA has officially determined that the new use should be approved and included in the labeling.

FDA has for many years distinguished between the approved uses of a product, which are set forth in the official labeling, and the known uses of that product. FDA regulations require that the approved labeling for a new drug, for example, "contain a summary of the essential scientific information needed for the safe and effective use of the drug." Id. § 201.56(a)(1). Elsewhere, FDA has stated that approved labeling must provide "a full, complete, honest, and accurate appraisal of the important facts that have reliably been provided about the drug." 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972). The labeling cannot simultaneously fulfill both requirements by providing a fully substantiated set of clinically relevant facts about use of the product and also setting forth all that might be known in the medical community about potentially beneficial uses. In other words, labeling "cannot be both authoritative and avant-garde." Robert Temple, Legal Implications of the Package Insert, 58 Med. Clinics of N. Am. 1151, 1155 (1974); see also 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."). FDA has therefore recognized that health care practitioners appropriately make prescribing decisions based on both the information set forth in approved labeling and "other adequate scientific data available" to them. 37 Fed. Reg. at 16,504.

Health care practitioners become aware of emerging data through a variety of mechanisms. Frequently, principal investigators conducting new-use studies publish their findings in peer-reviewed journals and reference publications. In 1956, Congress established the National Library of Medicine (NLM) to "aid the dissemination and exchange of scientific and other information important to the progress of medicine and to the public health." See The Public Health and Welfare Act, Pub. L. No. 84-941, 70 Stat. 960 (1956) (codified as amended at 42 U.S.C. § 286(a)). PubMed, one of the many services of the NLM, includes over 17 million citations from life science journals for biomedical articles, many of which contain extensive information on off-label uses. In oncology, data from clinical investigations of new uses may also be provided to health care practitioners by the National Cancer Institute. NCI frequently recommends drug regimens that include off-label uses through its web site. See National Cancer Institute website, www.cancer.gov.

FDA regulations also describe several mechanisms through which information from clinical investigations of new uses must or may be publicized. Sponsors of such investigations must provide information relating to prospective new uses of approved products to all investigators involved in the conduct of a clinical study, for example. See 21 C.F.R. §§ 312.55, 812.45. Information about these new uses must also be provided to prospective subjects as a condition of their agreeing to participate in the study. Id. § 50.25. Sponsors and investigators may choose to share the results of their studies of new uses in medical meetings, through press releases directed at the scientific and/or lay media, or through other forms of scientific exchange. See, e.g., id. § 312.7(a). To do this, they need not await FDA approval of the new use. Where emerging data demonstrate that a new use holds promise in the prevention or treatment of a medical condition, it is not only foreseeable but also desirable that health care practitioners will evaluate those data and employ the product for that new use where appropriate without first awaiting FDA's official imprimatur.

In oncology, off-label use is a mainstay and satisfies critical, unmet patient needs. Because of the high morbidity and mortality observed in many cancer patients due to the lack of effective approved treatments, oncologists quickly incorporate emerging data regarding new uses into clinical practice. In making decisions about new uses, oncologists consult the scientific literature and other sources because those materials often contain the most current information. As FDA has observed: "In their daily practice, many oncologists treat cancer patients with regimens that include off-label use of drugs. They evaluate the published data and past clinical experience to assess the risk of such treatments." See FDA, Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer (Jan. 2004), at 4, available at http://www.fda.gov/cber/gdlns/indcancer.pdf. As the American Society of Clinical Oncology (ASCO) 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." Letter from Joseph S. Bailes, M.D., Chair, Clin. Practice Comm., ASCO to Dockets Management Branch 1 (Sept. 13, 2002) (emphasis added), available at http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/091602/80027d3d.pdf.

It has long been recognized that off-label use in oncology is widespread. As early as 1991, the General Accounting Office (GAO) reported: "A third of all drug administrations to cancer patients were off-label, and . . . 56 percent of . . . cancer patients were given at least one drug off-label . . . ." GAO, Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies 3-4 (1991). More recently, ASCO reported that "[a]pproximately 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." ASCO, Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications, 24 J. Clin. Onc.

3206 (2006). As the National Cancer Institute has observed: "Frequently the standard of care for a particular type or stage of cancer involves the off-label use of one or more drugs." See National Cancer Institute, Understanding the Approval Process for New Cancer Treatments (Updated Jan. 6, 2004), available at http://www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page5.

Off-label use is also common in other areas of medical practice. A 2002 study, for example, determined that drugs were used off-label for every evaluated diagnosis in dermatologic disease. Joel Sugarman, et al., Off-Label Prescribing in the Treatment of Dermatologic Disease, 47 J. Am. Acad. Dermatol. 217 (2002). For some diseases, such as non-small cell lung cancer and cystic fibrosis, off-label uses either are the only therapies available, or are the therapies of choice. Susan G. Poole & Michael J. Dooley, Off-Label Prescribing in Oncology, 12 Support Care Cancer 302 (2004). Approximately 90 percent of patients with rare diseases are prescribed at least one drug for an off-label use. James O'Reilly & Amy Dalal, Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA Approved Drugs, 12 Ann. Health Law 295 (2003). Off-label use is such a well-accepted part of medical care that clinicians can be subject to malpractice claims for denying patients the potentially best treatment solely because the uses are not on-label. MS Cardwell, Preventing Perinatal Early-Onset Group B Streptococcal Infections: The New Standard of Care, 18 J. Legal Med. 511 (1997).

Given these realities, FDA has repeatedly affirmed that health care practitioners may lawfully prescribe, administer, and use approved products for any purpose in reliance on the full range of information available to them. In 1972, the agency described its policy of non-interference in the practice of medicine as follows:

> Throughout the debate leading to enactment, there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient. . . .
>
> As the law now stands, therefore, the Food and Drug Administration is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.

37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972). FDA therefore specifically affirmed that, once a new drug "is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration." Id. at 16,503. More broadly, FDA has recognized that off-label use of a product can constitute the standard of good medical care. See, e.g., 63 Fed. Reg. 31,143, 31,153 (June 8, 1998) ("FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice.").[2]

[2] FDA has reaffirmed the practice-of-medicine policy for drugs in at least two relatively recent documents. See FDA, Guidance for Industry: Development and Use of Risk Minimization Action Plans § IV.D (Mar.

The courts, too, have made clear that FDA lacks authority to control off-label use. "When FDA approves a drug, it approves the drug only for the particular use for which it was tested, but after the drug is approved for a particular use, the FDCA does not regulate how the drug may be prescribed" by health care practitioners. Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 206 (D.D.C. 2002); see also Sigma-Tau Pharms., Inc. v. Schwetz, 288 F.3d 141, 147 (4th Cir. 2002) (recognizing "the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses") (citing Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1496 (D.C. Cir. 1996)). The same is true for medical devices, as the Supreme Court has recognized. See Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350, 351 n.5 (2001) (Off-label use of medical devices "is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine. . . . Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care . . . which medical ethics, FDA, and most courts recognize.").[3]

B. The Public Health Benefits From Increased Distribution of Off-Label Use Information.

If drugs and medical devices are going to be prescribed for off-label uses, it necessarily follows that the benefits and risks of such uses will be optimized by the distribution of more, rather than less, truthful and non-misleading information about those uses. FDA itself has often recognized that, in providing state-of-the-art treatment to patients, health care practitioners must supplement agency-approved labeling. The agency has, in fact, repeatedly emphasized the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information" about off-label uses. See 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998); see also 63 Fed. Reg. 31,143, 31,153 (June 8, 1998) (same).[4]

Manufacturers are uniquely suited to provide reliable information on off-label uses. As noted by the Director of Medical Specialty Services at the Children's National Medical Center: "Pharmaceutical and biotechnology companies . . . happen to be in the best position to share information with the physician community at the earliest possible time, when it may really

---

2005), available at http://www.fda.gov/cder/guidance/6358fnl.pdf (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)). For medical devices, the prohibition on FDA interference in off-label use is set forth in the FDCA itself. 21 U.S.C. § 396 ("Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.").

[3] Indeed, even under the Food and Drug Administration Amendments Act of 2007, which expanded FDA's authority to address the risks posed by approved drugs, the agency is not authorized to regulate off-label use. FDCA §§ 505(p), 505-1; 21 U.S.C. §§ 355(p), 355-1.

[4] In some specialties, like oncology, FDA-approved labeling is but one of many sources to which health care practitioners turn for information. See, e.g., Off-Label Use of Anticancer Therapies: Physician Prescribing Trends and the Impact of Payer Coverage Policy, Covance Market Access Services (Sept. 2005) (survey showing that oncologists rely on the following sources, in decreasing order of importance, for patient care information: peer-reviewed literature, drug compendia, manufacturer hotlines, and case reports); see also Letter from John R. Durant, M.D., Exec. V.P., ASCO to Michael A. Friedman, M.D., Act'g Comm'r, FDA (July 21, 1998), available at http://www.fda.gov/ohrms/dockets/dockets/98n0222/c000039.pdf ("Instead of relying on the approved labeling, we look to peer-reviewed medical literature, continuing medical education programs, medical textbooks, and other reliable sources for information on cancer therapies.").

make a difference in treatment options." More Information for Better Patient Care: Hearing of the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of Dr. Gregory H. Reaman, Director, Medical Specialty Services, Children's National Medical Center). FDA has therefore acknowledged "the need for industry-supported dissemination of current scientific information." See 57 Fed. Reg. 56,412, 56,412 (Nov. 27, 1992) (emphasis added); see also 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994) ("Scientific departments within regulated companies generally maintain a large body of information on their products."). FDA policies reflect the singular role of manufacturers in advising health care practitioners about off-label uses.[5]

FDA allows manufacturers to disseminate new-use information in a number of carefully circumscribed situations. In addition to the clinical trial regulations described above (p. 3), FDA has developed policies allowing specific types of manufacturer communication regarding new uses of approved/cleared products. In devising its policies in this area, FDA has balanced enforcement of the FDCA with the need for health care practitioners to receive critically important new-use information. See, e.g., 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996) (noting that agency policies should "strike the proper balance between the need for an exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses."). In the exercise of its considered judgment over the course of many years, FDA has established at least three "safe harbors" allowing manufacturers to provide new-use information.[6]

- First, as part of "scientific exchange," manufacturers are expressly permitted to provide scientific information concerning an investigational product or a new use for an approved or cleared product, subject to the limitation that the manufacturer may not go further and represent in a promotional context that the product is safe and effective for its investigational use. See, e.g., 21 C.F.R. § 312.7(a).

- Second, in response to unsolicited requests, manufacturers are expressly permitted to provide responsive, non-promotional, and balanced scientific information, which may include information on off-label uses. See, e.g., 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

- Third, according to an FDA guidance document issued on December 3, 1997 (62 Fed. Reg. 64,074), manufacturers are expressly permitted to provide content and financial support for continuing medical education (CME) and other "scientific and educational activities," provided that these activities are independent from the substantive influence of the supporting manufacturers and the supporting

[5] Some have argued that allowing industry-supported dissemination of off-label use information creates disincentives for manufacturers to seek approval for unlabeled uses. This argument ignores that manufacturers will continue to have powerful legal and economic incentives to seek supplemental approvals. For example, when an innovative use is incorporated into FDA-approved labeling, it receives FDA's official imprimatur and thus encourages more widespread prescribing by health care practitioners. In addition, manufacturers may be granted three years of exclusivity for labeling changes approved in supplemental new drug applications. 21 U.S.C. § 355(j)(5)(D)(i)-(v).

[6] This discussion does not address statements about off-label uses of a product that are not subject to FDA regulation under the FDCA. See, e.g., United States v. An Undetermined Number of Cases . . . Balanced Foods, Inc., 338 F.2d 157, 158-59 (2d Cir. 1964) ("[L]abeling does not include every writing which bears some relation to the product. There is a line to be drawn, and, if the statutory purpose is to be served, it must be drawn in terms of the function served by the writing."). Such statements would include, for example, statements in patent applications, judicial proceedings, and SEC filings.

manufacturers do not effectively convert the activities into promotional vehicles for particular products.

These safe harbors are necessitated not only by the practice-of-medicine policy, but also by the First Amendment.[7]

As important as FDA's existing safe harbors are, they are insufficient to ensure the full and effective distribution to health care practitioners of the essential information on off-label uses contained in reprints and reference texts. The "scientific exchange" regulation is broad, covering "the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media," but it does not specifically address the dissemination of reprints and reference texts in the manner described in the draft guidance. Similarly, the unsolicited requests policy is limited to the reactive provision of information, and therefore does not provide a sufficient mechanism for manufacturers to distribute state-of-the-art off-label use information proactively. The CME guidance also is inadequate because it applies only to programs conducted by third parties, and does not provide a pathway for manufacturers to communicate directly with health care practitioners about new uses.

Indeed, when FDA was considering the types of policies to establish for off-label use information in the 1990s, it determined that not only the CME guidance but also two guidances on "enduring materials," including reprints and reference texts, should be established. FDA therefore clearly believed that specific safe harbors for reprints and reference texts were necessary to encourage manufacturers to disseminate appropriate off-label use information. See 62 Fed. Reg. 64,093 (Dec. 3, 1997) (CME guidance document); 61 Fed. Reg. 52,800 (Oct. 8, 1996) (enduring materials guidance documents). Similarly, in establishing the statutory safe harbor for reprints in 1997, Congress expressly recognized that that provision was distinct from the safe harbor for responses to unsolicited requests. 21 U.S.C. § 360aaa-6(a) (2006). No FDA safe harbor of which we are aware clearly and expressly allows manufacturers to provide journal article reprints or reference texts addressing off-label uses directly to health care practitioners.[8]

The medical community supports manufacturer distribution of journal article reprints and reference texts. The American Medical Association (AMA) recently reaffirmed its longstanding support for manufacturer dissemination of off-label use information to physicians by, among other things, distribution of reprints and textbooks See AMA, Resolution 819, I-07 (Oct. 10, 2007), available at http://www.ama-assn.org/ama1/pub/upload/mm/469/i07918.doc (reaffirming Policy H-120.988, Patient Access to Treatments Prescribed by Their Physicians). For more than a dozen years, the American Heart Association (AHA) has recognized the importance of manufacturer distribution of off-label use information in reprints and reference texts. See, e.g., More Information for Better Patient Care: Hearing of the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of Bernard Gersh, Chairman

[7] FDA has acknowledged the constitutional principles supporting manufacturer dissemination of off-label use information. See, e.g., Letter from Margaret M. Dotzel, Assoc. Comm'r for Policy, FDA to Daniel J. Popeo & Richard A Samp, WLF 1 (Jan. 28, 2002), available at http://www.fda.gov/ohrms/dockets/dailys/02/Jan02/013002/01p-0250_pdn0001_01_vol2.pdf; 65 Fed. Reg. 14,286, 14,287 (Mar. 16, 2000).

[8] The "enduring materials" guidance, issued at 61 Fed. Reg. 52,800 (Oct. 8, 1996) and included in the Washington Legal Foundation litigation, established safe harbors for reprints and reference texts but was apparently superseded by the FDAMA reprints provision. See 65 Fed. Reg. at 14,287. To the extent that FDA determines there is confusion within the regulated industry regarding the continued viability of these guidance documents, the agency may wish to address that issue in the final guidance or in its accompanying NOA.

of the Council on Clinical Cardiology of the American Heart Association) ("Physicians require better access to current, scientifically reliable and balanced information about drugs in order to make informed decisions for optimal treatment of their patients. Pharmaceutical and device companies should be permitted to disseminate copies of peer-reviewed scientific articles that report controlled clinical trials for off-label indications for their products."). As discussed above, oncologists concur. See, e.g., Letter from John R. Durant, M.D., Exec. V.P., ASCO to Michael A. Friedman, M.D., Act'g Comm'r, FDA (July 21, 1998), available at http://www.fda.gov/ohrms/dockets/dockets/98n0222/c000039.pdf (encouraging FDA to adopt policies that "seek to maximize the free flow of information to oncologists and other physicians who rely on published material"). Such broad support is not surprising, as there can be no doubt that peer-reviewed journal articles and reference publications—even those that contain data from studies that fall short of FDA's adequate and well-controlled "gold standard"—are better sources of information than hearsay, rumor, and anecdotal evidence.[9]

II. COMMENTS AND PROPOSED REVISIONS

A. Affirmation of Other Safe Harbors and First Amendment Principles

The NOA accompanying the final guidance and the "Purpose" section of the final guidance (p.3) should affirm that: (1) the safe harbor recognized in the draft guidance is in addition to those currently in effect (e.g., the safe harbors for scientific exchange, responses to unsolicited requests, and support for CME-type activities); and (2) because the First Amendment provides an independent basis for manufacturers to engage in truthful and non-misleading speech relating to off-label uses, the draft guidance merely recognizes a safe harbor. It cannot, and should not be interpreted to, establish the exclusive means for manufacturers to provide off-label use journal article reprints and reference texts or otherwise to distribute off-label use information without violating the FDCA.

The MIWG asks FDA to make clear that the existing safe harbors continue to be available to manufacturers wishing to provide off-label use information. Absent such clarification, manufacturers might well be far less inclined to engage in the very kinds of information dissemination that FDA regulation and policy are intended to facilitate. The agency's carefully calibrated program allowing off-label use information to be provided in controlled circumstances would thereby be undermined, to the detriment of the public's health.

The MIWG proposes that the following be included in the NOA accompanying the draft guidance and added at the end of the second paragraph of the "Purpose" section of the final guidance (p. 3, lines 38-43/p. 4, lines 1-6): "Given that the public health is advanced by truthful and non-misleading information on unlabeled uses, the guidance recognizes a safe harbor for the distribution of medical and scientific journal articles or reference publications that discuss unlabeled uses of approved drugs and approved/cleared medical devices. This safe harbor is intended to supplement and not supersede those already in effect, including the safe harbors for scientific exchange, responses to unsolicited requests, and support for continuing medical education activities."

[9] This is not to suggest that every journal article reprint and reference text will have clinical implications for all patients. However, because health care professionals are not naïve consumers of scientific and medical literature, they have the ability to review and make reasoned, informed judgments concerning whether to act on the data reported in such literature.

B. Assuring the Genuine Availability of the Safe Harbor

The phrase, "and there is no unlawful promotion of the product," in the final sentence of the guidance (p. 6, line 38) undermines the creation of a bona fide safe harbor. The final sentence of the guidance states: "if a manufacturer follows the recommendations described in Section IV of this draft guidance and there is no unlawful promotion of the product, FDA does not intend to use the distribution of such medical and scientific information as evidence of an intent by the manufacturer that the product be used for an unapproved use."

The MIWG recognizes the importance of enforcement in the promotion area, but is concerned that a manufacturer engaged in the distribution of reprints in full adherence to the recommendations in the draft guidance could, according to one reading of this language, find its lawful conduct effectively converted into unlawful conduct based on wholly unrelated promotional activity, including potentially on-label promotional conduct (e.g., a fair balance violation). Under this approach, manufacturers could rationally determine that the distribution of reprints, even in strict conformity with the recommendations in the guidance, is unduly risky given the difficulty in ensuring perfect compliance with FDA's expectations for promotional materials, many of which are created on an ad-hoc basis in DDMAC warning and untitled letters. That reading would effectively nullify the guidance, undermining the creation of a genuine safe harbor. Indeed, Section 401 of FDAMA, which established a limited but nevertheless important pathway for manufacturer distribution of certain types of off-label use information, included no such disqualifying language. Rather, Congress expressly provided that dissemination of information in accordance with the provision's safe harbor "shall not be considered by [FDA] as labeling, adulteration, or misbranding of the drug or device."

For these reasons, the MIWG requests that FDA delete the text, "and there is no unlawful promotion of the product," from the final sentence of the draft guidance.

C. Adequate and Well-Controlled Clinical Investigations

The draft guidance's recommendation that reprints "address adequate and well-controlled clinical investigations" (p. 5, lines 14-17) threatens to deprive health care practitioners of accurate, clinically relevant information and presents substantial questions under the First Amendment.

Under the FDCA, FDA cannot approve a new drug if "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d). The statute defines "substantial evidence" to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." Id.[10] FDA has imported this concept into the draft guidance, taking the position that the same type

[10] FDA by regulation has defined "adequate and well-controlled investigation" to mean a study having the following characteristics: (1) a protocol containing a clear statement of the study's objectives and methods of analysis; (2) a design that permits a valid comparison with a control; (3) a method of selecting subjects that assures they actually have the disease being studied; (4) a method of assigning subjects to treatment and control groups that minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables, such as severity of disease, duration of disease, and use of other therapies; (5) adequate measures to minimize bias, such as blinding; (6) well-defined and reliable methods for assessing subject response; and (7) analysis of results that is adequate to assess the effects of the drug. 21 C.F.R. § 314.126.

and quantity of proof required for approval is necessary for off-label use reprint/reference text dissemination.

This restrictive policy would harm the public health by denying credible and reliable scientific information to health care practitioners, and it would do so on the insubstantial ground that the information comes from clinical investigations that might not be deemed sufficient in the context of premarket review. Clinical investigations can provide information highly relevant to the use of a drug, even if the investigation is not designed as rigorously in FDA's view as trials intended to demonstrate that the product should be allowed onto the market. FDA acknowledged this point in the preamble to 21 C.F.R. Part 99, the regulations implementing Section 401 of FDAMA, by asserting that "clinical investigations" for purposes of FDAMA § 401 would include "historically controlled studies, retrospective analyses, open label studies, and metanalyses if they are testing a specific hypothesis." 63 Fed. Reg. 64,556, 64559 (Nov. 20, 1998). Indeed, in the medical device context, FDA's standard for approval/clearance includes both "well-controlled investigations" and "other valid scientific evidence . . . even in the absence of well-controlled investigations." 21 C.F.R. § 860.7(e)(2).

The draft guidance's current approach assumes that health care practitioners are both incapable of understanding that information pertinent to clinical decisions can come from a variety of sources, including observational studies, and unable to properly differentiate among and assess such sources. The draft therefore interferes with the dissemination of truthful, non-misleading, scientifically substantiated scientific information to health care practitioners. Scientific viewpoints may differ as to the usefulness of any particular study in clinical practice. The only course that adequately respects both the reality of the practice of medicine and First Amendment values would be for FDA to allow dissemination of truthful and non-misleading reprints/reference texts about a clinical study, whether or not it is deemed an acceptable study by the agency for purposes of marketing authorization. The draft guidance's recommendation against dissemination of reprints based on studies that FDA does not believe meet the "substantial evidence" standard deprives health care practitioners of useful information in contravention of First Amendment principles. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 67 (D.D.C. 1998) ("'[T]he FDA is not a peer review mechanism for the scientific community.'") (citing Lars Noah & Barbara A. Noah, Liberating Commercial Speech: Product Labeling Controls and the First Amendment, 47 Fla. L. Rev. 63, 96 (1995)), vacated, Washington Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

We request that FDA revise the draft guidance to make clear that information disseminated under the guidance need not concern a clinical investigation that meets the "adequate and well-controlled" standard and propose instead the following language: "The information contained in the above scientific or medical journal article or reference publications should address ~~adequate and well-controlled~~ clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device. Such clinical investigations may include historically controlled studies, retrospective analyses, open-label studies, observational studies, and metanalyses."

D. "Unapproved New Use/Unapproved Use" Constructions

The "unapproved new use" and "unapproved use" constructions (p. 1, lines 3-6; p. 2, lines 4-6; p. 2, lines 22-23; p. 3, lines 1-2; p. 3, line 6; p. 3, lines 16-17; p. 3, lines 23-24; p. 3, line 34; p. 3, lines 39-41; p. 4, lines 4-6; p. 4, lines 8-9; p. 4, lines 13-14; p. 4, lines 20-21; p. 6, line 8; p. 6, lines 29-30; p. 6, lines 36-37; p. 7, line 2) improperly imply that "uses" are approved by FDA. In fact, FDA approves (or clears) products and their labeling. Actual use is,

according to long-standing FDA policy, not the subject of FDA's regulatory focus and not within the agency's statutory authority. See 21 U.S.C. § 396. In the past, FDA has referred to "new use," "off-label use," and "unlabeled" use. See, e.g., 59 Fed. Reg. 59,820, 59,820 (Nov. 18, 1994).

Consistent with prior FDA constructions and statutory and regulatory policies, the MIWG recommends that all references to "unapproved new uses" and "unapproved uses" be replaced with "new uses," or "unlabeled uses."

E. Elucidation of "False or Misleading" Standard

The description of the conditions under which information in reprints would be considered "false or misleading" and the "significant risk" terminology (p. 5, lines 17-24) raise concerns. Under the draft guidance, for example, a reprint would be "false or misleading" and thus ineligible for the safe harbor if "a significant number of other studies contradict[ed] the [conclusions of the] article." The document's approach to the false or misleading standard is inappropriate. As to the "significant risk" terminology in line 24, it would raise First Amendment issues for FDA to finalize the draft guidance without affirming that the government bears the burden of demonstrating that information provided under the guidance is false or misleading—rather than the forcing the manufacturer to demonstrate that its speech is truthful and non-misleading. Moreover, we believe that FDA should clarify that, even if a particular clinical investigation might be contradicted by a number of other studies, that investigation would not necessarily be false or misleading.

The MIWG therefore proposes that the guidance simply state: "The information must not: be false or misleading, ~~such as a journal article or reference text that is inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical investigations (e.g., where a significant number of other studies contradict the article or reference text's conclusions), that has been withdrawn by the journal or disclaimed by the author, or that discusses a clinical investigation where FDA has previously informed the company that the clinical investigation is not adequate and well-controlled; or pose a significant risk.~~"

F. Disclosure of Financial Interests

The recommendation that reference publications not be edited or significantly influenced by a manufacturer or any individuals having a financial relationship with the manufacturer (p. 5, lines 5, 11-12) is too broad. A ban on essentially any financial relationship between textbook editors and manufacturers could effectively eliminate the distribution of textbooks. Similar language (p. 4, line 29/p. 5, lines 1-3) poses the same problem with respect to special supplements.

Such recommendations conflict with FDA's prior acknowledgment "that there are some useful reference texts that are written, edited, or published by a sponsor or agent of the sponsor." 61 Fed. Reg. 52,800, 52,801 (Oct. 8, 1996). In fact, previous agency policy provided that: "In those instances, where the authorship, editing, and publishing of the reference text results in a balanced presentation of the subject matter, FDA intends to allow the distribution of a reference text under [certain] circumstances." Id. Such recommendations also are inconsistent with the disclosure regime established elsewhere in the draft guidance. Page 6 (lines 19-20, 25-28), for example, provides that a journal reprint or reference publication bear a "permanently affixed statement" disclosing "any author known to the manufacturer as having a financial interest in the product or manufacturer or receiving compensation from the

manufacturer" and "any person known to the manufacturer who has provided funding for the study." On page 4 (lines 33-35), the draft guidance recommends that scientific or medical journal articles be published by "an organization . . . that has a publicly stated policy . . . of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization."

Thus, the MIWG recommends that the language effectively banning reference texts (p. 5, lines 5, 11-12) and special supplements (p. 4, line 29/p. 5, lines 1-3) be struck from the guidance and that the following language be added to the other disclosure requirements enumerated on page 6, lines 21-30: "whether the reprint or reference text was edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturers" and "if the reprint is in the form of a special supplement or publication, whether it has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article."

G. Potential Recipients of Information

The draft guidance discusses the provision of unlabeled use information to "healthcare professionals and healthcare entities" (p. 2, lines 19-24) but fails to address any other potential recipients of this information or to define "healthcare professionals" or "healthcare entities." It should make clear, for example, that "healthcare entities" include those to which manufacturers are permitted under Section 502(a) of the FDCA, as amended by FDAMA § 114, to provide promotional labeling containing health care economic information (e.g., formulary committees).

The MIWG proposes that the draft guidance include a footnote after the last sentence of the first paragraph in the "Introduction" section (p. 1, line 24) that states: "As used in this guidance, the term 'healthcare professional' includes licensed healthcare practitioners (including pharmacists) or individuals acting at the direction and under the supervision of licensed health care practitioners. The term 'healthcare entity' includes hospitals (and other organizations that provide healthcare services), professional medical organizations, and medical formulary committees and health plans."

H. Distribution of Reprints/Reference Texts and Post-Market Reporting

The discussion of the relationship of reprints/reference texts to promotional communications and promotional contexts (p. 5, line 36/p. 6, lines 10-17/p. 6, n.5) raises a question that, we respectfully submit, should be addressed in the final guidance. It is not clear whether the draft guidance is intended to convey FDA's view that reprints disseminated consistent with the agency's recommendations constitute promotional communications that are required to be submitted in accordance with various post-approval reporting regulations (21 C.F.R. §§ 314.81(b)(3)(i), 314.550, 601.45).

The MIWG requests that FDA state in the final guidance: "With respect to reprints and reference texts distributed in a promotional context, manufacturers are not required to submit these materials to FDA pursuant to 21 C.F.R. §§ 314.81.(b)(3)(i), 314.550, or 601.45, or under any other requirement or request for the submission of promotional materials."

I. Off-Label Theory

The draft guidance (p. 3, lines 29-35) should more precisely set forth the grounds available to FDA to proceed against products promoted off-label. The document states that the

FDCA and FDA implementing regulations "generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective or cleared through a substantial equivalence determination." The document cites the statutory "new drug" provisions but not FDCA § 502(f)(1), 21 U.S.C. § 352(f)(1). The document goes on to state, without citation, that "An approved new drug that is marketed for an unapproved use becomes misbranded and an unapproved new drug with respect to that use."

This explication of FDA's authorities is problematic because it fails to acknowledge the limitation inherent in proceeding under a "new drug" theory (FDCA §§ 505 and 301(d), 21 U.S.C. §§ 355(a) and 331(d)), i.e., that the theory applies only where the off-label use information at issue constitutes "labeling" under the FDCA. To proceed against a manufacturer pursuant to the new drug provisions, the government has to show that something in the "labeling" of the drug causes the drug to become an unapproved new drug. This is because the definition of "new drug" in FDCA § 201(p)(1), 21 U.S.C. § 321(p)(1), depends on what is prescribed, recommended, or suggested in the drug's labeling. Section 502(f)(1), by contrast, requires the government to show only some kind of promotional claim that creates a new intended use for which adequate directions are not provided, and that claim need not appear in labeling. In Alberty Food Prods. Co. v. United States, 185 F.2d 321 (9th Cir. 1950), for example, the claims were in advertising. The draft guidance's lack of precision in setting forth the theories available to FDA to proceed against products promoted off-label incorrectly implies that the agency can proceed under the "new drug" provisions if the only off-label claim is an oral statement or an advertisement. This is not correct.

We therefore request that FDA revise the draft guidance to provide better clarity regarding the scope of the agency's statutory authority to proceed against off-label promotion and propose the following: "~~As explained in FDA's March 16, 2000 Notice, t~~The FD&C Act and FDA's implementing regulations generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective or cleared through a substantial equivalence determination. (E.g., FD&C Act §§ 505(a), 502(f)(1), 502(o), 501(f)(1)(B), 301(a) and (d); 21 U.S.C. §§ 355, 352(f)(1), 352(o), 351(f)(1)(B), 331(a) and (d)). FDA takes the position that an approved new drug that is marketed in 'labeling' under the FD&C Act) for an unapproved use becomes misbranded and an unapproved new drug with respect to that use. FD&C Act § 505(a), 201(p) and (m); 21 U.S.C. §§ 355(a), 321(p) and 321(m))."

J. "Good Reprint Practices" Construction

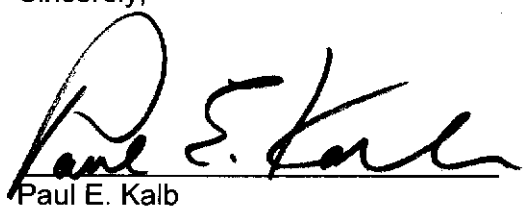
The reference to "Good Reprint Practices" (p. 1, lines 3-6; p. 2, lines 4-6; p. 2, lines 19-21) is awkward. This phrase implies that the focus of the document is on articles originally appearing in other publications. In fact, the document addresses not only "medical journal articles" but also "scientific or medical reference publications." According to page 2, these materials—presumably, collectively, although that is not clear—are "referred to generally as medical and scientific information." It is not clear why, in the first paragraph, the document refers to "scientific or medical reference publications" but omits "scientific" from the phrase, "medical journal articles." Scientific journal articles, in addition to medical journal articles, can provide useful, clinically relevant off-label use information to health care practitioners.

To address these issues, the MIWG proposes that the guidance be entitled, "Good Practices for the Distribution of Medical and Scientific Information."

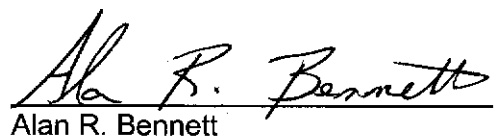
Page 2, lines 19-21 should be revised to state: "This draft guidance is intended to describe the Food and Drug Administration's (FDA or Agency) current thinking regarding good practices with regard to the distribution of scientific or medical journal articles and scientific or medical reference publications . . ."

We appreciate the opportunity to comment on the draft guidance. If there are questions about these comments, please contact us.

Sincerely,



Paul E. Kalb
Daniel E. Troy
Coleen Klasmeier
SIDLEY AUSTIN LLP
1501 K Street, NW
Washington, DC 20005
Telephone: (202) 736-8000
Facsimile: (202) 736-8711



Alan R. Bennett
ROPES & GRAY LLP
One Metro Center
700 12th Street, NW, Suite 900
Washington, DC 20005
Telephone: (202) 508-4604
Facsimile: (202) 383-8327

Joan McPhee
ROPES & GRAY LLP
One International Place
Boston, MA 02110
Telephone: (617) 951-7535
Facsimile: (617) 235-0412

Counsel for the Medical Information Working Group

April 15, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

Re: Amended Comments of the Medical Information Working Group for the Food and Drug Administration Transparency Task Force, Docket No. FDA-2009-N-0247, 75 Fed. Reg. 11893 (Mar. 12, 2010)

Dear Sir/Madam:

On April 12, 2010, the Medical Information Working Group submitted a response to FDA's request for comments on ways to increase transparency between FDA and the regulated industry, published in the Federal Register on March 12, 2010, 75 Fed. Reg. 11893. Please find attached our amended comments, which are substantively unchanged but include Eli Lilly and Company among the manufacturers in support.

Sincerely,

/s/Alan R. Bennett

Alan R. Bennett
ROPES & GRAY LLP
One Metro Center
700 12th Street, NW, Suite 900
Washington, DC 20005-3948
(202) 508-4600

Paul E. Kalb
Coleen Klasmeier
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000

Joan McPhee
ROPES & GRAY LLP
One International Place
Boston, MA 02110
(617) 951-7000

Attorneys for the Medical Information Working Group

April 15, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

Re: Amended Comments of the Medical Information Working Group for the Food and Drug Administration Transparency Task Force, Docket No. FDA-2009-N-0247, 75 Fed. Reg. 11893 (Mar. 12, 2010)

Dear Sir/Madam:

The following comments and recommendations are being submitted on behalf of The Medical Information Working Group (MIWG),[1] in response to FDA's request for comments on ways to increase transparency between FDA and the regulated industry, published in the Federal Register on March 12, 2010, 75 Fed. Reg. 11893. In that document, FDA specifically asked for comments on how it can make improvements in "[p]roviding useful and timely answers to industry questions about specific regulatory issues." Id. at 11894. As discussed in more detail below, we respectfully request that FDA implement an advisory opinion process that would provide timely binding advice[2] in response to a specific request on proposed promotional and scientific exchange practices. We believe that doing so would not only encourage greater industry compliance but also lead to the improved communication of important health information.

Once a product is approved for a particular use, the law permits health care professionals to prescribe or use the product in ways that are different than those approved by FDA. Indeed, the legal recognition of off-label use is an accepted and necessary corollary of the FDA's public health mission to regulate products without directly interfering in the practice of medicine, and it is generally recognized that off-label use can result in significant benefit to patients so long as it is appropriate and informed. While physicians may prescribe or use products in a manner different from that approved by the FDA, the Agency restricts how manufacturers can communicate information about unapproved uses and prohibits manufacturers from promoting those uses. Unfortunately, statutes, regulations, FDA guidance documents, and other agency policies are frequently unclear in this regard and may become even more difficult to interpret as technology and business practices evolve. Deciding whether a particular activity

[1] The MIWG is an informal working group of prescription drug and medical device manufacturers that was formed to consider issues relating to the federal government's regulation of truthful, non-misleading, scientifically substantiated manufacturer communications about products subject to FDA jurisdiction. The members of the MIWG in support of these comments include: Allergan, Inc., Amgen Inc.; Bayer Healthcare Pharmaceuticals; Eisai, Inc.; Eli Lilly and Company; GlaxoSmithKline; Genentech Inc.; Johnson & Johnson; Novo Nordisk, Inc.; Pfizer Inc.; and Sanofi-Aventis U.S. LLC. The group has previously submitted comments to FDA on Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices.

[2] Although the opinions themselves would be binding, we recognize that the Agency will occasionally need to amend opinions in light of changed circumstances. In such a case, we suggest that amendment occur only after appropriate public notice.

is violative or permissible in light of FDA regulation and policy requires companies to maintain large regulatory staffs, and even then there is often disagreement within a company.[3] Although companies seek to achieve compliance, rules can be both vague and evolving.[4] The lack of clarity surrounding regulation of these issues, as well as an understanding that FDA cannot possibly anticipate every scenario when developing regulations or guidance, can result in unnecessary self-censorship by manufacturers. We believe that implementation of an advisory opinion process would help facilitate the effective communication of useful scientific information to the public while at the same time maintaining appropriate regulatory controls.

Advisory opinions encourage compliance with the law by permitting parties to "double-check" their legal interpretations before acting "at-risk" to commit time and resources to activities that might later be alleged to be illegal. At the same time, the issuance of advisory opinions allows agencies to develop a robust, publicly available set of fact-dependent recommendations without engaging in the labor-intensive and time-consuming task of formal rulemaking or guidance development. Complementing, rather than replacing, broad-based legal guidance, advisory opinions afford parties the unique opportunity to seek detailed agency input on issues relevant to their business practices. While regulations and formal guidance generally set forth the legal rules to be followed, advisory opinions can provide a specific roadmap to compliance for requestors and can serve as helpful examples for the public at large about "real-world" activities. Agencies with advisory opinion processes include, among others, the Office of Inspector General (OIG) at the Department of Health and Human Services, the Centers for Medicare and Medicaid Services (CMS), the Securities and Exchange Commission (SEC), the Federal Election Commission (FEC), and the Federal Trade Commission (FTC).

Although FDA currently has a regulation that provides for an advisory opinion process, it is seldom used. We believe, moreover, that the existing process is not conducive to the issuance of opinions on many promotional issues. Among the problems with the existing regulation, it requires that requests relate to issues of "general applicability" rather than specific proposed business practices, does not require FDA to respond to the request in a timely manner, and does not distinguish between the legal effect of opinions for the requestors and the general public. 21 C.F.R. § 10.85(a). At the same time, FDA regulations regarding presubmission and preapproval of promotional materials (e.g., 21 C.F.R. § 202.1(j)) are similarly inadequate because they allow for FDA input on individual advertising or labeling pieces, as opposed to business practices. Companies and individuals seeking advice on a course of action requiring prompt attention in the context of promotion therefore have no avenue by which to seek advice. We therefore request that FDA implement a special advisory opinion process through which individuals or companies can seek guidance with respect to specific proposed business practices relating to promotional and scientific exchange activities that adheres to the parameters discussed below.

Scope. We recommend the implementation of an advisory opinion process that would focus on issues relating to promotional and scientific exchange practices concerning drugs

[3] See Wayne L. Pines, Regulation of Promotion and Distribution, in A Practical Guide to Food and Drug Law and Regulation (Kenneth R. Pina & Wayne L. Pines, eds., 3rd ed. 2008) 321.

[4] See id.

and medical devices. In our view, providing an advisory opinion process focused on promotional and scientific exchange practices would more closely mirror the advisory opinion processes administered by agencies such as the OIG and others, and it would fulfill an unmet need with regard to the current state of FDA guidance on these issues. In an ever-vigilant enforcement environment governed by vague statutes and regulations, the development of robust recommendations—even if nonbinding except as to the requestor—promises to serve the public interest and enhance compliance.

In addition, we believe that, for the advisory opinion process to hold the greatest public benefit and to ensure the most effective use of FDA resources, individuals and companies should outline a specific, proposed course of action in their requests. The more details provided in the request, the more helpful FDA's advice will be to the requestor. For example, a company could seek the Agency's opinion on whether specific types of communications with payors are "non-promotional," or whether a company's recordkeeping system for unsolicited requests is appropriate. As with the advisory opinion processes of other agencies, however, we believe that individuals and companies should refrain from submitting requests regarding questions of general legal interpretation, actions undertaken by parties other than the requestor, or conduct by the requestor that has already occurred or is occurring on an ongoing basis.

Requesting Parties and Legal Effect. Because advisory opinions are inherently fact-bound, moreover, they should be legally binding only with respect to the requestors. For other parties, advisory opinions may serve as nonbinding recommendations.

Public involvement and availability of opinions. As with the advisory opinion processes of other federal agencies, the mechanism for advisory opinions on promotional issues should allow for public comment. Specifically, we recommend that, upon receiving a request, FDA publish a notice in the Federal Register briefly summarizing the issues raised in the request and solicit public comment, to be taken under advisement during the preparation of the advisory opinion. Further, we suggest that, once FDA issues an opinion, it post both the request and the opinion on its website in an easily searchable format similar to that available for FDA guidance documents.

Timeframe. FDA's general regulation on advisory opinions, 21 C.F.R. § 10.85, does not provide a deadline by which requests must be answered by FDA. To encourage companies and individuals to seek FDA's advice before engaging in activities about which they are unsure, FDA should provide comprehensive and substantive responses to such requests in a timely manner. A review of the advisory opinion processes of other federal agencies indicates that the timeframe between the request and issuance of the opinion ranges from 60 to 120 days. Cognizant of the labor required in considering the issues and drafting the opinion, as well as the desirability of public input, we suggest that FDA issue an advisory opinion within 90 days of accepting the request for filing.

Reasonable fee. We believe that this process—including FDA's timely response to detailed industry questions, the availability of robust public guidance regarding business practices, and the ability to rely on the expertise of agency staff— has significant advantages for all parties. However, we recognize that the implementation of a special advisory opinion process would require the expenditure of limited agency resources. The MIWG would be willing to

discuss a system that charged a reasonable fee for the review of advisory opinion requests and the development and issuance of advisory opinions in response to those requests.[5]

As described, we believe that the establishment of an advisory opinion process focused on advertising and promotion issues would be of great benefit to the public health, to industry, and to FDA itself. We therefore respectfully request that FDA adopt a process consistent with the considerations outlined above.

Respectfully submitted,

/s/Alan R. Bennett

Alan R. Bennett
ROPES & GRAY LLP
One Metro Center
700 12th Street, NW, Suite 900
Washington, DC 20005-3948
(202) 508-4600

Paul E. Kalb
Coleen Klasmeier
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, DC 20005
(202) 736-8000

Joan McPhee
ROPES & GRAY LLP
One International Place
Boston, MA 02110
(617) 951-7000

Attorneys for the Medical Information Working Group

[5] We recognize that Congress likely would need to authorize the imposition of such a fee. Such an authorization could be discussed as part of the reauthorization of the Prescription Drug User Fee Act, which expires September 30, 2011.

ROPES & GRAY

SIDLEY AUSTIN LLP
SIDLEY

July 5, 2011

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This petition is submitted on behalf of seven medical product manufacturers[1] pursuant to 21 C.F.R. § 10.30 to ask the Commissioner of Food and Drugs to clarify FDA regulations and policies with respect to manufacturer dissemination of information relating to new uses of marketed drugs and medical devices.

I. ACTIONS REQUESTED

We request that the Commissioner clarify FDA regulations and policies governing certain communications and activities relating to new uses of marketed products. The specific actions requested are discussed further below.

II. STATEMENT OF GROUNDS

A. THE PUBLIC HEALTH CONTEXT

FDA is the expert federal agency designated by Congress to assure the safety, effectiveness, and proper labeling of new drugs and medical devices. According to FDA's statutory mission statement, which was added to the FDCA in 1997:

> [FDA] shall—
> (1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;
> (2) with respect to such products, protect the public health by ensuring that—
> . . . (B) human and veterinary drugs are safe and effective;

[1] This petition is submitted on behalf of the following companies: Allergan, Inc.; Eli Lilly and Company; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Novo Nordisk, Inc.; Pfizer, Inc.; and sanofi-aventis U.S. LLC.

(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;

. . .

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with . . . manufacturers, . . . of regulated products.

21 U.S.C. § 393. As this provision emphasizes, FDA must not only safeguard the public health by managing the risks of medical product use, but also promote the health of the public by facilitating the appropriate availability of new drugs and medical devices. The agency must perform these functions through appropriate expert consultation and cooperation with important stakeholders, including specifically drug and medical device manufacturers.

Consistent with FDA's mission statement, a cornerstone of the agency's activities is the review of new drugs and medical devices before marketing in accordance with the new drug and medical device clearance and approval provisions of the FDCA. Under those provisions, subject to certain limited exceptions, careful premarket review is required before a manufacturer is legally entitled to introduce onto the United States market any "new drug" or any medical device. Once a drug or medical device has been authorized for marketing, it must be accompanied by labeling containing information adequate for the safe and effective use of the product. 21 C.F.R. §§ 201.100(c), 801.109(c).

Such labeling is not intended to be, and indeed cannot be, comprehensive. In developing a new medical product, the manufacturer in the first instance determines the use for which the product will be investigated, in the laboratory and then in human subjects through clinical trials. See, e.g., 21 C.F.R. pts. 312, 812 (describing regulatory procedures for clinical trials of new drugs and medical devices). Decisions relating to the use under investigation reflect a variety of considerations, including the likelihood that the product has an appropriate risk/benefit profile for that use, the unmet medical need 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 authorized for marketing by FDA, its labeling contains a summary of the essential scientific information relating to the investigated use(s) of the product. Uses not set forth in labeling are often referred to as "new" or "off-label" uses.[2]

[2] "The uses that are approved by the agency are sometimes referred to as 'labeled' uses because they appear in the product's approved or cleared 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." Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices: Request for Comments, 59 Fed. Reg. 59,820, 59,820 n.1 (Nov. 18, 1994).

Off-label use is lawful, and it is axiomatic that physicians may prescribe both drugs and devices for uses not included in the product labeling.[3] In addition to being lawful, off-label prescribing is "common, can be a source of innovation, and in some settings may represent the standard of care."[4] For many diseases, off-label uses are the only therapies available,[5] and for others, "a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease."[6] Indeed, as the American Medical Association (AMA) has noted, "[u]p to date, clinically appropriate medical practice at times requires the use of pharmaceuticals for 'off-label' indications."[7]

Congress has recognized that off-label uses are appropriate for quality patient care; in a number of situations, it has mandated that payors in federal health care programs must provide reimbursement for off-label uses that are "medically accepted" and may reimburse for other off-label treatments. E.g., 42 U.S.C. §§ 1396r-8(d)(1)(B)(i), (k)(6), (g)(1)(B)(i).

The public health necessity of off-label use has also long been recognized by FDA.[8] Accordingly, the agency has emphasized the value of physicians having as

---

[3] See 21 U.S.C. § 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."); 21 C.F.R. § 312.2(d) (exemption from FDA regulations for "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by the agency); Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,733 (June 9, 1983) ("Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling."); Legal Status of Approved Labeling for Prescription Drugs, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972) ("[T]he physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.").

[4] Donna T. Chen et al., U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey, 18 Pharmacoepidemiology & Drug Safety 1094 (2009) (footnotes omitted).

[5] See Bryan A. Liang and Tim Mackey, Reforming Off-Label Promotion to Enhance Orphan Disease Treatment, Science (Jan. 15, 2010), at 3.

[6] Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. on Government Reform and Oversight, 104th Cong. 12 (1996) (statement of Sarah F. Jaggar, Dir. of Health Services Quality and Public Health Issues, Health, Education, and Human Services Division, GAO). Off-label use has particular importance in the oncology field, where doctors depend on off-label uses because they "are regularly faced with few approved treatment options, especially if the first treatment didn't work." See Am. Cancer Soc., Off-Label Drug Use, http://tinyurl.com/ygxobso (last visited June 22, 2011). Indeed, the National Comprehensive Cancer Network estimated in 2005 that "50% to 75% of all uses of drugs and biologics in cancer care in the United States are off-label." Michael Soares, Off-Label Indications for Oncology Drug Use and Drug Compendia: History and Current Status, 1 J. of Oncology Prac. 102, 104 (2005).

[7] Memorandum of the AMA House of Delegates, Resolution 820, Off-Label Use of Pharmaceuticals (Sept. 21, 2005), available at http://tinyurl.com/yfpwmyo (emphasis added).

[8] In 1998, FDA provided guidance to institutional review boards regarding off-label use, stating that "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement [sic]." FDA, "Off-Label"

much truthful, accurate, and non-misleading new use information as possible, noting the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products."[9] The dissemination of up-to-date medical information about a product—irrespective of the product's labeled indications—helps to guide physicians in their treatment decisions and ensures that patients receive care based on current, sound, scientific and clinical information.[10] Manufacturers are uniquely positioned to provide such information,[11] and as a result, the agency's policy is to seek a "balance" between two objectives: limiting off-label "promotion" on the one hand, while allowing manufacturer communication of reliable scientific information regarding off-label uses on the other.[12]

B. THE NEED FOR CLEARER REGULATION

FDA has repeatedly opined on the importance of off-label use and manufacturer dissemination of information relating to such use, and indeed, has

---

and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet, available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (emphasis added). More recent guidance from FDA states that "off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care." FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved or Cleared Medical Devices (Jan. 2009), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm. In certain drug shortage situations, FDA has even gone so far as to recommend to physicians that they use a substitute drug product off-label until the shortage has been resolved. See, e.g., FDA, Current Drug Shortages, www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm (last visited June 22, 2011) (describing current drug shortages and referring to alternatives, including off-label uses).

[9] See Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998) (emphasis added).

[10] The Associate Commissioner for Health Affairs at FDA wrote in 1992 that "the very latest information that can be of value to physicians . . . . must be made available as soon as possible. Frequently, unlabeled use information is extremely important." Stuart Nightingale, Unlabeled Uses of Approved Drugs, 26 Drug Info. J. 141, 145 (1992). See also Donna T. Chen et al., U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey, 18 Pharmacoepidemiology & Drug Safety 1094 (2009) (concluding that survey results point out "a pressing need for more effective methods to inform physicians about the evidence base, or lack thereof, for drugs they prescribe off label").

[11] For example, FDA has recognized that "[s]cientific departments within regulated companies generally maintain a large body of information on their products," Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices: Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994). This information relates to the risks, optimization strategies, and rewards of off-label uses and can help guide practitioners' decisions. See also 1997 Annual Meeting of the American Medical Association, supra; see also More Information for Better Patient Care: Hearing of the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of Dr. Gregory H. Reaman, Dir., Medical Specialty Services, Children's National Medical Center) ("Pharmaceutical and biotechnology companies obviously have an interest in supporting new uses of their products, but they also happen to be in the best position to share information with the physician community at the earliest possible time, when it may really make a difference in treatment options.").

[12] 59 Fed. Reg. at 59,823; see also Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996); Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56,412, 56,412 (Nov. 27, 1992).

explicitly recognized important mechanisms for the sharing of truthful and non-misleading scientific information.[13] While the agency has made clear that these mechanisms exist, there is a significant lack of clarity as to the practices they permit. Further complicating matters, FDA policies may be difficult to interpret due to the use of ambiguous language and undefined terms like "promotion" and "scientific exchange." Moreover, manufacturers have often pieced together the agency's positions over time from Federal Register documents, guidance, letters, and similar pronouncements. But these pronouncements are not only difficult to find, but also often nonbinding. This void creates significant obstacles for the stakeholders that must rely on FDA's legal interpretations.

The lack of clarity and vagueness surrounding the contours of permissible manufacturer speech has significant consequences to manufacturers, the government, physicians, and patients. Companies dedicate substantial resources to compliance, with many of them staffing entire departments for this purpose and engaging outside counsel solely to advise on compliance-related matters. The paucity of clear rules requires manufacturers, their lawyers, and prosecutors to infer operative law from FDA's letters and other agency materials, as well as the publicly available papers in settled criminal investigations, such as government press releases, informations, statements of factual bases for pleas, and related documents. Once manufacturers have discerned what they believe is the correct interpretation, they develop internal guidelines and policies governing the dissemination of off-label information and train their sales representatives, field medical personnel, and other relevant employees on the information that may appropriately be shared about their products. In the face of uncertainty, manufacturers may develop policies that do not align with the government's expectations. As a result, each individual manufacturer may either over- or under-communicate clinically relevant information, with significant attendant consequences for the public health.[14]

C. REQUESTED ACTIONS

We set forth below the publicly available sources of information embodying certain of FDA's policies on the dissemination of information on off-label uses. We request that FDA affirm and clarify the contours of these policies in regulations that are legally binding[15] and believe that the agency could offer comprehensive guidance consistent with its mission to protect the public health.

1. Manufacturer Responses to Unsolicited Requests

[13] See, e.g., the establishment of mechanisms for sharing off-label information in the context of scientific exchange and in response to an unsolicited request, discussed infra Part II.C.1-2.

[14] This petition is limited to the regulatory standards that govern the speech of medical product manufacturers. Important constitutional concerns arise out of the regulatory scheme. See Sorrell v. IMS Health, Inc., No. 10-779, __ S. Ct. __ (decided June 23, 2011); Reno v. American Civil Liberties Union, 521 U.S. 844, 871-72 (1997) (vagueness presents "special concern" when it has a "chilling effect on free speech" as well as where citizens are put at risk of criminal prosecution).

[15] We strongly prefer changes to FDA's regulations rather than guidance documents.

We have long understood that manufacturers may provide new use information in response to unsolicited requests, but no law or regulation states this rule or defines the boundaries of the safe harbor. Since 1982, FDA has expressly recognized the permissibility of manufacturers' communications about off-label uses in response to "any and all unsolicited requests received from outside the company for information about a drug manufactured, distributed or repacked by the company." The Division of Drug Advertising and Labeling (DDAL), the Division of Drug Marketing, Advertising, and Communications' (DDMAC's) predecessor entity, set forth this policy in a one-page document intended to provide "clarification and guidance" to industry.[16] The document explained that such responses did not constitute "labeling," but were rather "personal communication[s] between the requester and firm" under the FDCA. DDAL maintained that the exception only applied if a company did not expressly encourage the request, and recommended including the package insert in company responses. DDAL also said it would "reconsider" the policy if "problems or abuses [were] noted."

In 1994, DDMAC reiterated the unsolicited requests policy in a document entitled "Current Issues and Procedures," stating that "individual, nonpromotional responses by pharmaceutical companies to specific, unsolicited requests for information will not be considered as promotional labeling."[17] The restated policy withdrew the recommendation that responses include references to the indications and package insert. It also added two new criteria, that companies: (1) "maintain documentation concerning the nature of the request(s)," and (2) avoid a "pattern of repeated dissemination of materials." DDMAC explained that merely preparing material for routine dissemination could qualify as solicitation.

That same year, FDA articulated a further revised version of the policy in a notice published in the Federal Register. Acknowledging the "large body" of scientific information available within companies, the notice established that, "[w]hen health care professionals request such information, companies can provide responsive, non-promotional, balanced scientific information, which may include information on unapproved uses, without subjecting their products to regulation."[18] The notice did not identify conduct that could constitute solicitation, and it implied that responses would not subject a company's drug to any kind of regulation. Unlike preceding statements, FDA's notice left open the possibility that corporate employees other than members of a medical affairs department could issue responses. Finally, the notice was for the first time officially binding on FDA, 21 C.F.R. § 10.85(d)(1), and by its terms covered not only drug products but also medical devices.

The passage of the Food and Drug Administration Modernization Act (FDAMA) of 1997 changed little about FDA's policy on responses to unsolicited requests. FDAMA, in Section 401, stated that any prohibition on off-label promotion

---

[16] See DDAL, Position on the Concept of Solicited and Unsolicited Requests (Apr. 22, 1982).
[17] DDMAC, "Current Issues and Procedures" (Apr. 1994).
[18] Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices: Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

should not "be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner." FDA affirmed this principle in subsequent regulations, which were codified in 21 C.F.R. part 99.[19]

The expiration of FDAMA Section 401 in 2006 led the agency to issue a draft guidance document on the distribution of reprints of journal articles and reference publications discussing off-label uses.[20] The reprints guidance made clear that responses to unsolicited requests were governed by FDA's 1994 Federal Register notice, discussed above. The reprints guidance also cited FDA's 1997 Guidance on Industry-Supported Scientific and Educational Activities, in connection with which FDA stated with respect to unsolicited requests: (1) manufacturers could provide "technical support" (e.g., "preparing slides or audiovisual materials") for a scientific or educational activity in response to an unsolicited request; and (2) whether a statement made in the context of a scientific or educational activity qualified as "promotional"—a relevant factor under the 1994 FDA statement on responses to unsolicited requests—could depend on whether it had been disseminated after an initial program.[21] Although the draft guidance confirmed that there is an "unsolicited requests" safe harbor, it did not codify that rule or adequately define its scope.

On behalf of the medical product manufacturers we represent, we ask FDA to promulgate binding regulations embodying FDA's current policy on responses to unsolicited requests. To assure that the policy affords manufacturers a meaningful "safe harbor" and therefore fulfills FDA's objective of attaining a "balance" between prohibiting off-label promotion and allowing appropriate dissemination of information relating to off-label uses, FDA should also clearly distinguish a non-promotional response to an unsolicited request from product promotion[22] and clarify that responses to unsolicited requests are excluded from the scope of materials that can create an intended use under 21 C.F.R. §§ 201.128 and 801.4 and do not constitute "advertising" or "labeling."

2. "Scientific Exchange"

We have also long understood that manufacturers may engage in "scientific exchange," but no law or regulation adequately defines the boundaries of "scientific exchange." This important and well-accepted concept is only mentioned in a regulation in the narrow context of 21 C.F.R. § 312.7, which prohibits a drug

---

[19] See Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556, 64,558 (Nov. 20, 1998) (formerly codified at 21 C.F.R. § 99.1(b)).

[20] Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 73 Fed. Reg. 9,342 (Feb. 20, 2008).

[21] Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,091 (Dec. 3, 1997).

[22] FDA has stated that speech about an off-label use creates an "intended use" if it "expressly or implicitly promote[s]" the safety or efficacy of that use, but that a manufacturer may disseminate non-promotional information without triggering penalties. See Decl. of Dr. Robert Temple ¶ 10, Allergan v. United States, No. 09-1879 (D.D.C. Dec. 11, 2009). But this definition does not provide adequate guidance as to what would constitute "implicit[]" promotion of safety or efficacy.

manufacturer from representing in a promotional manner that an investigational new drug is safe or effective. In recognition of the critical importance of scientific exchange in the advancement of medicine, FDA made sure to carve out an exception from this otherwise restrictive regulation for scientific exchange. The scientific exchange safe harbor, which FDA has repeatedly affirmed in various rulemaking and guidance development proceedings over the years, suggests that the agency was both cognizant of the First Amendment concerns attendant to § 312.7 and careful to limit the scope of the regulatory prohibition. Nonetheless, the agency has not issued a comprehensive, binding statement as to the contours of the safe harbor. There is also no regulation confirming that a similar safe harbor applies to "scientific exchange" about investigational medical devices.

Drugs. FDA's regulations governing investigational new drugs, 21 C.F.R. pt. 312, provide that the regulatory prohibition on the promotion of an investigational new drug as safe or effective should not be construed to prohibit "scientific exchange." The "scientific exchange" language dates back to 1963, when FDA first published the investigational new drug regulations following enactment of the Drug Amendments of 1962.[23]

Amendments to the "scientific exchange" rule were published on March 19, 1983.[24] These amendments "retain[ed], essentially unchanged, the current provisions prohibiting promotion and commercialization of investigational drugs."[25] On May 22, 1987, FDA published a separate final rule providing procedures under which investigational new drugs could be made available to "desperately ill patients" prior to general marketing.[26] In the preamble to that rule, 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. Id. at 19,475. 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." Id.

Medical Devices. In 1976, FDA proposed regulations prohibiting the promotion of investigational devices.[27] FDA finalized only the part of its proposal relating to intraocular lenses (IOLs).[28] For a time, this provision, codified at 21 C.F.R. § 813.50(a), expressly did "not restrict the full exchange of scientific information concerning" a device, "including dissemination of scientific findings." In 1997, FDA

---

[23] Procedural and Interpretative Regulations: Investigational Use, 28 Fed. Reg. 179 180 (Jan. 8, 1963).
[24] New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 8,798, 8,833 (Mar. 19, 1987).
[25] Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,734 (June 9, 1983).
[26] See Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 19,466 (May 22, 1987).
[27] Proposed Investigational Device Exemptions, 41 Fed. Reg. 35,282 (Aug. 20, 1976).
[28] See Investigational Device Exemption Requirements, 42 Fed. Reg. 58,874 (Nov. 11, 1977).

issued a final rule that removed and reserved 21 C.F.R. part 813, effective March 31, 1997.[29]

In a separate proposed rule in 1977, FDA affirmed manufacturers' entitlement to engage in scientific exchange.[30] Instead of issuing a final rule, however, FDA published a guideline on monitoring.[31]

Throughout the following decade, CDRH continued to recognize "scientific exchange" relating to medical devices. 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."[32]

We ask FDA to clarify its position on scientific exchange as set forth in the 1987 Federal Register notice and to bring appropriate parity to the rules for drugs and medical devices. Specifically, FDA should state that, in its view, to qualify as "scientific exchange," statements must: (1) make clear that a use or product is not FDA-approved or -cleared; (2) make no claims that a use or product has been proven to be safe or effective; and (3) be truthful and non-misleading when measured against available information on the use or product.

Because there is no principled reason to distinguish drugs from medical devices in this context, and FDA has in the past affirmed that scientific exchange is permissible for medical devices as well as drugs, we further request that FDA amend 21 C.F.R. § 812.7 to include analogous "scientific exchange" language, and to affirm that the principles in the 1987 Federal Register notice apply equally to medical devices. In addition, we ask that FDA promulgate regulations expressly providing that the "scientific exchange" concept applies not only with respect to investigational new drugs and medical devices, but also with respect to new uses of already approved drugs and medical devices.

---

[29] Investigational Device Exemptions, 62 Fed. Reg. 4,164 (Jan. 29, 1997).
[30] Proposed Establishment of Regulations, 42 Fed. Reg. 49,612 (Sep. 27, 1977) (proposed 21 C.F.R. § 52.118).
[31] See Monitoring of Clinical Investigations, 53 Fed. Reg. 4,723 (Feb. 17, 1988).
[32] FDA, Guidance for Industry and FDA Staff on Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects (Mar. 19, 1999), at 1, available at www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073585.pdf.

Finally, FDA should clarify that activities meeting the definition of scientific exchange are excluded from and cannot be used to establish an "intended use" within the meaning of 21 C.F.R. §§ 201.128 and 801.4. FDA also should clarify that activities meeting the definition of scientific exchange do not constitute "labeling" or "advertising."

3. Interactions with Formulary Committees, Payors, and Similar Entities

We have also long understood that manufacturers may engage in communications with formulary committees, payors, and similar entities regarding investigational products or off-label uses, but again the boundaries of permitted communications are unclear. Manufacturers must be able to provide (and often do provide) information to formulary committees, managed care organizations, and other third-party payors in order to obtain coverage of and reimbursement for their products. DDMAC has expressed the view that certain of these communications are within its regulatory jurisdiction and are generally expected to be on-label.[33] In order to ensure that an investigational product will be reimbursable immediately upon approval and launch, or that an off-label use is reimbursable, however, manufacturers may be interested in communicating information about off-label uses or investigational products pre-approval. Manufacturers may also be interested in communicating information concerning off-label uses of approved or cleared products to payors to address prior authorization or other utilization control issues.

We understand that FDA representatives have, in the past, worked with the Academy of Managed Care Pharmacy (AMCP)—a national professional organization for individual pharmacists, health care practitioners (non-pharmacists), and associates who practice in managed care settings—to develop a standard format for healthcare systems to use in asking drug manufacturers to submit comprehensive product information (including on- and off-label use information) to assist in coverage decisions. Unfortunately, FDA itself has not publicly stated that submissions of drug information that follow the AMCP format and are either submitted in response to an unsolicited request from a healthcare system or consistent with the principles of scientific exchange would be regarded by the agency as permissible. Moreover, nothing akin to the AMCP format exists specifically for medical devices, and the relevance of the AMCP approach to devices remains unclear.

As a result, the extent to which manufacturers can provide safety, efficacy, and health care economic information concerning pre-approval products or unapproved uses of approved products requires clarification. We briefly describe our understanding of these issues below.

---

[33] See, e.g., DDMAC, "Current Issues and Procedures," supra (stating that formulary kits and similar materials, such as those prepared for review by formulary committees, that discuss a regulated product and that are prepared for and disseminated to hospitals or managed care organizations constitute promotional labeling).

Communications Regarding Investigational Products or Off-Label Uses of Approved or Cleared Products Generally. FDA's regulations prohibit manufacturers from commercializing investigational medical products, 21 C.F.R. §§ 312.7(a) & 812.7, or otherwise representing "in a promotional context that an investigational new [product] is safe or effective for the purposes for which it is under investigation or otherwise promote the [product]." 21 C.F.R. § 312.7(a).

Although one intent of §§ 312.7 and 812.7 is to restrict manufacturers from making claims of safety or effectiveness regarding investigational products, the former provision is explicitly not intended to restrict "the full exchange of scientific information" concerning the investigational drug. Thus, we believe that communications to payors that focus on an investigational new drug are permissible so long as they do not commercialize the product and are made in the context of scientific exchange. We also believe that the same "scientific exchange" concept applies to investigational devices and off-label uses of previously approved drugs and devices. Unfortunately, as discussed above, FDA has not adequately explained what is meant by the terms "commercialization" or "exchange of scientific information," and no regulation explicitly states that "scientific exchange" is permitted for investigational devices or off-label uses.

Communication of Health Care Economic Data Concerning Unapproved Products or Unapproved Uses of Approved Products. The FDCA allows manufacturers to provide to payors "health care economic information" that "directly relates" to an approved indication, so long as the information is based on "competent and reliable scientific evidence." 21 U.S.C. § 352(a). Because Congress specifically limited communication of health care economic information to labeled uses, it could be inferred that communication of health care economic information about off-label uses would not be permitted in labeling, except in the context of scientific exchange or in response to an unsolicited request. FDA has not addressed this issue specifically, however.

To address the uncertainties highlighted above, we respectfully request that FDA address whether, and to what extent, health care economic and other product-related information may be shared with payors. Specifically, we recommend that FDA indicate that communication of truthful, non-misleading information by or on behalf of a manufacturer to payors, whether prior to or after approval or clearance of the manufacturer's product, will be considered scientific exchange when such communication is: (1) delivered by representatives of the manufacturer with appropriate medical, scientific, or health care economic or health outcomes expertise; (2) provided to payors who are carrying out their responsibilities for the selection of products and coverage of therapies and products for managed care or other similar organizations; and (3) limited to (a) health care economic information directly related to the indication for which the product is expected to be approved or cleared or (b) published scientific or health care economic information.

4. Dissemination of Third-Party Clinical Practice Guidelines

Leading associations of medical professionals, academic institutions, and government agencies often produce clinical practice guidelines, which are meant to

guide decisions concerning diagnosis, management, and treatment in specific areas of health care. Such clinical guidelines are most often based on a thorough examination of the most robust and most up-to-date evidence and data. The primary objective of such guidelines is to raise the quality of care and to optimize clinical outcomes. The recommended use of any particular drug or medical device in a clinical practice guideline may, however, vary from the approved or cleared labeling for that product (e.g., the guidelines may recommend an off-label use of the product). The tension between these concepts—dissemination of recognized practice guidelines to improve patient care and the prohibition on promotion of a product for off-label uses—is evident; what is less evident, however, is whether, or to what extent, a manufacturer can disseminate such guidelines.

There are no formal FDA policies specifically relating to manufacturer dissemination of clinical guidelines that may discuss off-label uses. We propose that FDA confirm the following: A manufacturer may disseminate clinical guidelines if they are: (1) developed or adopted by a nationally or internationally recognized scientific or medical organization or by a federal or state government agency, or are recognized by the National Guideline Clearinghouse or the National Quality Measures Clearinghouse; (2) reproduced in a manner that retains the same format, content, and configuration of the guidelines as published by the organization or agency with respect to all indications or categories for which the manufacturer's product is recommended; (3) reproduced by the manufacturer to include all guidelines or measures relating to products that have the same indication as the indication for which the manufacturer's product is recommended; and (4) accompanied by relevant disclaimers and disclosures.

D. CONCLUSION

The confusion surrounding the issues discussed above results in significant difficulties for companies in their day-to-day decision-making. Most companies, including the manufacturers on whose behalf we submit this petition, dedicate substantial time and resources to ensuring that their business practices are compliant with FDA rules and regulations. They rely heavily on FDA's statutory interpretations to guide them.

Unfortunately, the current state of regulatory guidance is not clear or comprehensive, or in some cases, even binding. That lack of clarity places manufacturers at risk of criminal and civil sanctions if they cannot correctly guess where the government would draw a line in the matters detailed above. Industry should not have to refer to the terms of DOJ settlements or informal statements of FDA officials to learn what is expected of them prospectively. FDA can, and should, take up its responsibility to interpret the FDCA with respect to the dissemination of new use information. We therefore urge FDA to establish comprehensive, clear and binding regulations to guide the industry in the critical matters discussed herein.

III. OTHER REQUIRED INFORMATION FOR FILING OF CITIZEN PETITION

A. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

B. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

C. CERTIFICATION

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

Alan R. Bennett
ROPES & GRAY LLP
One Metro Center
700 12th Street, NW
Washington, DC 20005
Telephone: (202) 508-4604
Facsimile: (202) 383-8327

Paul E. Kalb
SIDLEY AUSTIN LLP
1501 K Street, NW
Washington, DC 20005
Telephone: (202) 736-8000
Facsimile: (202) 736-8711

Joan McPhee
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
Telephone: (617) 951-7535
Facsimile: (617) 235-0412

Coleen Klasmeier
SIDLEY AUSTIN LLP
1501 K Street, NW
Washington, DC 20005
Telephone: (202) 736-8000
Facsimile: (202) 736-8711

cc: Janet Woodcock, M.D.
Rachel Behrman, M.D., M.P.H.
Thomas W. Abrams, R.Ph., MBA
Jeffrey E. Shuren, M.D., J.D.
Ralph Tyler, J.D.
Ann Witt, J.D.

ROPES
&GRAY

SIDLEY AUSTIN LLP
SIDLEY

March 27, 2012

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

COMMENTS OF THE MEDICAL INFORMATION WORKING GROUP ON SCIENTIFIC EXCHANGE (DOCKET NO. FDA-2011-N-0912) AND RESPONSES TO UNSOLICITED REQUESTS (DOCKET NO. FDA-2011-D-0868)

The Medical Information Working Group (MIWG) hereby submits these comments on (1) the notice published in the Federal Register on December 28, 2011 (76 Fed. Reg. 81,508), inviting comments on scientific exchange, and (2) the draft guidance on responses to unsolicited requests, published in the Federal Register on December 30, 2011 (76 Fed. Reg. 82,303). The MIWG is a coalition of prescription drug and medical device manufacturers seeking clarity in the federal regulatory paradigm for the dissemination of information relating to investigational products and new uses of lawfully marketed medical products.[1] We thank FDA for establishing the scientific exchange docket and proposing new guidance on unsolicited requests, and look forward to learning more about the other initiatives to which the December 28 notice refers to improve the rules applicable to manufacturer dissemination of information relating to new products and uses.

Several members of the MIWG submitted the July 5, 2011, citizen petition to which the December 28 notice refers. The petition asks FDA to clarify the rules governing manufacturer communication of information about new uses and unapproved, uncleared products by promulgating binding regulations with respect to four types of off-label communications—responses to unsolicited requests for medical information, scientific exchange, distribution of clinical practice guidelines, and communications with payers. With regard to responses to unsolicited requests, FDA's draft guidance creates a new definition of "solicited," and distinguishes "public" from "non-public" requests. On these points, we support the comments of Pharmaceutical Research and Manufacturers

[1] The following companies are currently members of the MIWG: Allergan, Inc.; Amgen Inc.; Bayer Healthcare Pharmaceuticals, Inc.; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline LLC; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Novo Nordisk, Inc.; Pfizer, Inc.; Purdue Pharma L.P.; and sanofi-aventis U.S. LLC.

of America (PhRMA), and respectfully request that the Agency abandon its "public" and "non-public" distinction and more narrowly define the concept of solicitation.

As to scientific exchange, the petition asks FDA to revise 21 C.F.R. § 312.7 to specify additional forms of permitted communication based on prior preamble language and to recognize scientific exchange in the medical device context. In response, FDA's December 28 notice sets forth thirteen questions and invites "detailed comment on all aspects of scientific exchange communications and activities related to off-label uses of marketed drugs, biologics, and devices and use of products that are not yet legally marketed."[2] Rather than respond to each of those questions, we focus our comments on the following key points:

- First, we renew the citizen petition's request for clarity to the extent that clarity can be provided without sacrificing critically important public health, constitutional, and statutory principles. Highly restrictive rules on scientific exchange would harm the public health, violate the First Amendment, and exceed the scope of FDA's statutory authority.

- Second, we believe that FDA should seek to clarify key definitions in the areas in which it has statutory authority rather than purporting to define the conduct over which it lacks such authority. Specifically, FDA should focus its efforts on clarifying the scope of key statutory provisions, such as the "labeling" and "advertising" definitions, that determine the extent of the agency's regulatory authority. We do, however, agree with the July 5 citizen petition that the 1987 preamble language set forth in the petition and reproduced in the December 28 notice represents a sound approach to defining scientific exchange.[3]

- Third, although we have reservations about a wholesale reconsideration of the scope of permissible scientific exchange, we have set forth in an accompanying appendix a non-exclusive list of activities and communications that we believe are properly regarded as scientific exchange in an effort to assist the Agency.

---

[2] 76 Fed. Reg. at 81,509 (emphasis added).

[3] 52 Fed. Reg. 19,466, 19,475 (May 22, 1987). The language recommends that manufacturers making statements about investigational new drugs (1) make clear that the drug is investigational, (2) make no claims that the drug has been proven to be safe or effective, and (3) assure that their statements are truthful and non-misleading "when measured against available information on the drug . . . as set forth in materials such as investigators' brochures . . . ." It would be necessary, in adopting the approach reflected in this language, to explain the meaning of "claims" in the second criterion, and extend the approach reflected in the language so that it also explicitly covers new uses (in addition to investigational products) and medical devices.

I. 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."[4] 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.[5]

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."[6] 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."[7]

"Physicians," in particular, "must make decisions in the face of uncertainty and without . . . [the] luxury of awaiting further information."[8] 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

---

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

[5] "[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).

[6] 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 Pharmaceuticals Inc., 509 U.S. 579 (1993).

[7] 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.

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

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 . . . ."[9] As the Director of the Center for Drug Evaluation and Research put it: "How do you generate knowledge that you can rely on? . . . I think there are very different opinions about that in different sectors. The regulators come down on pretty reliable data and inferences because we make decisions that are big regulatory decisions. If you are a payer or an individual practitioner, you make decisions . . . based on other considerations and that is reasonable."[10] Because medical practice requires making judgments beyond the clinical trials leading to regulatory approval, clinicians must often consider information from non-regulatory sources.

From FDA's perspective, approved labeling serves as the source of permissible statements in promotional labeling and advertising.[11] Yet labeling does not always contain the most up-to-date (or even the most accurate) information about the use of a medical product.[12] For physicians to use their "best knowledge and judgment" in the use of approved drugs,[13] they must have access to information that has not been reviewed by FDA or set forth in approved labeling. 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

---

[9] 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972).

[10] Drug Developers Facing "Unsettled" Period of 5 to 10 Years as CER Environment Evolves, FDA's Woodcock Says, The Pink Sheet (June 28, 2010) (quoting Janet Woodcock). Even the population-level judgments reached by FDA are the subject of disagreement, and indeed, "the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others." CDER & CBER, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998); see also SOPP 8006: Resolution of Differences in Scientific Judgement in the Review Process (Jan. 15, 2009) ("Differences in scientific opinion can occur regarding the interpretation and/or application of information pertinent to the regulatory process. . . . Differences in scientific opinion or perspective are an expected part of any scientific review or regulatory process."). Moreover, as FDA has long recognized, the regulatory assessment of risks and benefits often changes after approval, sometimes dramatically, based on information obtained from clinical use. 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) (Results of treatment obtained outside of adequate and well-controlled trials "may be helpful to patients and physicians as well as to" FDA, and can lead to warnings against dangerous unapproved uses or "acceptance of previously unknown uses.").

[11] 21 C.F.R. § 202.1(e)(4) ("An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the act after October 10, 1962 . . . shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application . . . .").

[12] Labeling "cannot be both authoritative and avant garde." Robert Temple, Legal Implications of the Package Insert, 58 Med. Clinics of N. Am. 1151, 1155 (1974).

[13] 44 Fed. Reg. 37,434, 37,435 (June 26, 1979).

exchange and investments in the processes of science themselves.[14] Scientific exchange therefore must not—and, as a constitutional matter, cannot—be restricted.

II. FIRST AMENDMENT PROTECTION OF SCIENTIFIC EXCHANGE REFLECTS ITS PUBLIC HEALTH IMPORTANCE

Robust scientific exchange about investigational products and new uses of lawfully marketed products is fully consistent both with FDA's vital public health mission and with First Amendment principles. This past Term, in Sorrell v. IMS Health Inc., the Supreme Court held that First Amendment protection is particularly vital "in the fields of medicine and public health, where information can save lives." 131 S. Ct. 2653, 2664 (2011).[15] By aligning its regulatory scheme with constitutional limitations, FDA can also assure an appropriate role for manufacturer speech in supporting sound medical practice.

It has, for many years, been beyond dispute that "core" scientific speech is entitled to robust protection under foundational First Amendment principles. "Scientific" speech "reside[s] at the core of the First Amendment." Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 62 (D.D.C. 1998); Bd. of Trs. 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"). Scientific exchange is precisely the type of expression that is entitled to the highest level of First Amendment protection. Miller, 413 U.S. at 34. Even if regulations governing scientific exchange were evaluated according to a more forgiving standard, however, Sorrell makes clear that regulatory regimes that disfavor certain speakers or viewpoints are subject to "heightened scrutiny."

Sorrell makes clear that, where a law restricts truthful, non-misleading speech on the basis of its content and the identity of the speaker, that law "must be subjected to heightened judicial scrutiny," even if the speech is characterized as "commercial." See 131 S. Ct. at 2664 (holding that "[c]ommercial speech is no exception" to the heightened judicial scrutiny applicable to speaker- and content-based speech restrictions); id. at 2667 (holding that if a law "imposes a speaker- and content-based burden" on commercial speech, "that circumstance is sufficient to justify application of heightened scrutiny"). Under Sorrell, content- and speaker-based

[14] Hearing on S. 1944 Before a Subcomm. of the S. Comm. on Commerce, 73d Cong. 10 (1933) ("There is no disposition to write anything into the bill to interfere with progress.") (statement of Commissioner Campbell).

[15] Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 73 (D.D.C. 1998) (truthful information about medical products "may be life saving information, or information than makes a life with a debilitating condition more comfortable.").

restrictions on commercial speech will fail heightened judicial scrutiny "[i]n the ordinary case." Id. at 2667.

The relevance of Sorrell to scientific exchange and responses to unsolicited requests is plain: the decision dispels any remaining notion that FDA is free to regulate manufacturer dissemination of information about investigational products and new uses without constitutional limitation. Although Sorrell itself did not deal with the FDCA, in his dissenting opinion Justice Breyer acknowledged that the majority opinion implicated FDA's regulatory framework because it, too, imposes "speaker-based" restrictions on speech. Id. at 2678 (Breyer, J. dissenting).

The First Amendment limits the government's power to suppress truthful, non-misleading speech relating to lawful activities such as off-label use. "If the First Amendment means anything," it means that suppressing such speech "must be a last—not first—resort." Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002). Society has a "strong interest in the free flow of commercial information." Va. St. Bd. of Pharm. v. Va. Cit. Cons. Council, 425 U.S. 748, 764 (1976). The First Amendment requires the government "to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them. . . . It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us." Id. at 770; see W. States, 535 U.S. at 374 ("We have previously 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."). "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." 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996) (plurality op.) (citation omitted). FDA, no less than any other government entity, must adhere to these constitutional principles. See R.J. Reynolds Tobacco Co. v. FDA, Civ. No. 11-1482, at 18 (RJL) (D.D.C. decided Feb. 29, 2012) ("Congress must pass laws, and the FDA must implement final rules, that are consistent with the requirements of the Constitution.").

FDA must assure the applicable rules are appropriately tailored and well-defined to avoid chilling manufacturer speech. "Because First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity." Keyishian v. Bd. of Regents of the U. of N.Y., 385 U.S. 589, 604 (1967); Reno v. ACLU, 521 U.S. 844, 874 (1997). The First Amendment requires speech restrictions to be clear and precise, because "[u]ncertain meanings inevitably lead citizens to 'steer far wider of the unlawful zone' than if the boundaries of the forbidden areas were clearly marked." Grayned v. City of Rockford, 408 U.S. 104, 109 (1972) (quoting Baggett v. Bullitt, 377 U.S. 360, 372 (1964)). The Government cannot ban

broad swathes of speech without specifying the limitations and the basis for doing so. "The test is whether the [restriction] affords the precision of regulation that must be the touchstone in an area so closely touching our most precious freedoms." Buckley v. Valeo, 424 U.S. 1, 41 (1976) (internal quotation marks omitted); see Nat'l Ass'n of Mfrs. v. Taylor, 582 F.3d 1, 22–23 (D.C. Cir. 2009).

A series of ongoing cases likely will further explicate the precise ways in which First Amendment principles affect FDA's regulation of manufacturer speech. In the meantime, however, FDA can help assure that its approach to the regulation of speech respects constitutional limitations and recognizes the high value of scientific exchange in medical practice. FDA does not have the option of simply implementing the FDCA despite obvious constitutional infirmities on the ground that the agency cannot "second-guess Congress."[16] Rather, "Congress must pass laws, and the FDA must implement final rules, that are consistent with the requirements of the Constitution."[17]

In recent First Amendment litigation, FDA has recognized[18] 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." Press releases are not subject to regulation as "labeling."

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."

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

---

[16] U.S. Opp. to Pl.'s Mot. for Prelim. Injunct., R.J. Reynolds Tobacco Co. v. FDA, No. 11-1482 at 32 (D.D.C. filed Sept. 9, 2011).

[17] R.J. Reynolds Tobacco Co. v. FDA, Civ. No. 11-1482, at 18 (RJL) (D.D.C. decided Feb. 29, 2012).

[18] Decl. of Dr. Rachel Sherman ¶ 14, Par Pharmaceutical v. United States, No. 11-1820 (D.D.C. Jan. 1, 2012); Transcript of Cross Examination of Sandeep Saini, United States v. Stevens, No. RWT-10-694, at 89 (D. Md. Apr. 27, 2011); Decl. of Dr. Robert Temple ¶¶ 9-10, Allergan v. United States, No. 09-1879 (D.D.C. Dec. 11, 2009); Allergan v. United States, Gov't Summ. J. Br. 9; Gov't Summ. J. Reply 6, 9; U.S. Opp. to Def's Mot. to Dismiss, United States v. Harkonen, No. 08-164 at 8, n.3 (N.D. Cal. Apr. 20, 2009).

be used "off-label"; or by the manufacturer's practice of teaching its representatives about potential off-label uses.

4. FDA's off-label promotion restrictions do not prohibit manufacturers from teaching paid speakers about potential off-label uses, and do not prevent those speakers from discussing off-label uses, so long as the information shared is in response to the unsolicited question of an audience member.

These statements should be incorporated directly into the relevant regulatory provisions to help align the regulatory scheme with constitutional limitations.

III. THE FDCA APPLIES TO PARTICULAR FORMS OF MANUFACTURER COMMUNICATION EXPRESSLY IDENTIFIED IN THE STATUTE

As discussed above, by its very nature, scientific exchange 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 exchange 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. Scientific exchange is also outside the scope of FDA's authority under the "labeling" and "advertising" provisions of the FDCA.[19]

The scope of the "labeling" definition in the FDCA is central to FDA's authority to regulate manufacturer speech because it is the touchstone of key statutory provisions, such as the "new drug" and "adequate directions" requirements.[20] The FDCA establishes specific requirements and specific prohibitions for the content of "labeling."

Section 502(a) provides that "A drug or device shall be deemed to be misbranded—. . . If its labeling is false or misleading in any particular." 21 U.S.C. § 352(a). 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

[19] Even remedial statutes cannot be interpreted without limitation. See, e.g., Brown & Williamson v. FDA, 529 U.S. 120, 161 (2000) ("[N]o matter how important . . . the issue, . . . an administrative agency's power to regulate in the public interest must always be grounded in a valid grant of authority from Congress.") (internal quotes and citation omitted); United States v. Article of Drug . . . Bacto-Unidisk, 394 U.S. 784, 800 (1969) ("'[I]n our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop.'") (quoting 62 Cases of Jam v. United States, 340 U.S. 593, 600 (1951)).

[20] 21 U.S.C. §§ 321(p), 355(a), 352(f)(1).

respect to such drug." Id. § 355(a). Whether a product is a "new drug" depends on the content—in particular the "conditions prescribed, recommended, or suggested"—of its labeling. Id. § 321(p)(1); see also id. §§ 360(k), 351(f)(1)(B), 352(o), 360e(a) (counterpart device provisions). 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." Id. § 352(f)(1).[21]

The FDCA defines "labeling" to mean "written, printed, or graphic matters" upon the article or "any of its containers or wrappers," or "accompanying such article." 21 U.S.C. § 321(m), (k). The Supreme Court in Kordel v. United States addressed whether written material could "accompany" a drug, and thus qualify as labeling, even when it was distributed separately from the package. 335 U.S. 345, 348 (1948). 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. Id. at 348, 350 (emphasis added). As subsequent decisions have explained, "labeling does not include every writing which bears some relation to the product. There is a line to be drawn, and, if the statutory purpose is to be served, it must be drawn in terms of the function served by the writing." United States v. An Undetermined Number of Cases . . . "Sterling Vinegar and Honey . . . ," 338 F.2d 157, 158-59 (2d Cir. 1964).

FDA has acknowledged that the list of items included in the regulation that is often cited as a definition of "labeling," 21 C.F.R. § 202.1(l)(2), is not a straightforward regulation of definition but rather operates to exclude certain forms of manufacturer communication from the scope of the advertising provisions of the FDCA and FDA regulations.[22] The only applicable legal definition of labeling therefore arises out of the statutory text itself (21 U.S.C. § 321(m)), a general regulatory definition of labeling in 21 C.F.R. Part 1 (§ 1.3(a)), and relevant case law. Properly construed, FDA's "labeling" authority does not reach manufacturer communications such as press releases, reprints (whether "on-label" or "off-label"), or indeed anything that does not (among other criteria) function as an essential supplement to the label for the product.

---

[21] The concept of "intended use" is closely related to the scope of FDA's authority under the "labeling" provisions. The two are linked by Section 502(f)(1) and FDA implementing regulations, 21 C.F.R. §§ 201.5, 801.5, 201.128, 801.4, which define "intended use" to reach "expressions." To assure appropriate latitude for scientific exchange, FDA must clarify the scope of its intended use regulation to reflect the authoritative legislative history and the relevant case law. See S. Rep. No. 361, 74th Cong., 1st Sess. 4 (1935) ("The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put."); Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) ("no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use") (citing Coyne Beahm v. FDA, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997)), aff'd on other grounds, 529 U.S. 120 (2000).

[22] Def.'s Summ. J. Reply at 22-23, Allergan v. United States, No. 09-1879 (D.D.C. filed Mar. 29, 2010).

The scope of the "advertising" definition is similarly limited. Although the statute itself does not include a definition, it is clear that "advertising" refers to forms of manufacturer speech that are "published" or "broadcast"—references that clearly reflect FDA's recognition of the need to truncate required disclosures because space for them may not be practicable in many media. 21 C.F.R. § 202.1(l)(1).[23]

The FDCA carefully limits the scope of manufacturer communications about regulated products and does not reach "communications and activities" generally (as stated in the December 28 notice) or any and every manufacturer statement that names a product, bears a "textual relationship" with a product, or "effectively promotes" a product.[24] FDA cannot regulate the content of any communication that falls outside the scope of the "labeling" and "advertising." Properly construed, the FDCA provisions delineating FDA's authority over manufacturer speech do not reach scientific exchange (such as the specific activities set forth in the accompanying appendix).[25]

---

[23] Nothing in the FDCA was intended to interfere with a manufacturer's ability to provide emerging efficacy information to physicians. Hearing on S. 2800 Before the S. Comm. on Commerce, 73d Cong. 114 (1934) ("Well, isn't it right that the medical profession should have this progressive thought as early as possible, even though it might not yet be thoroughly established on a scientific basis? . . . [T]he purpose of the original writer of the bill—this was in the original bill—was to make it possible for the medical profession to receive even those glimmerings of hope that are held out by the scientific research men, and I am inclined to think that it is right that they should have that information. . . . [Y]ou take some great research laboratory, that will do a lot of work in connection with one of these diseases—we will say goiter, or nephritis, or high blood pressure, or something like that—it develops what in the laboratory appears to be something worthwhile. It gives that information to the profession.") (remarks of Sen. Copeland). The Drug Amendments of 1962 were intended to require a modest disclosure—a "true statement" in "brief summary" of efficacy information—in drug advertising, not to "censor" it. E.g., Hearings on S. 1552 Before the S. Subcomm. at 192 (colloquy between Dr. May and Sen. Kefauver) ("Dr. May. . . . As I understand S. 1552, there are no censorial powers that would check many prevalent shortcomings in promotion. . . . . Sen. Kefauver. That is true. It does do this though—it requires that in advertisements . . . the claims as to what the drug will do and also the adverse side effects, in summary form at least, be sent to the doctors . . . but it does not undertake to set up a board of censors as to what the advertising should be.").

[24] These "rules of thumb" have been used to describe the range of communications over which FDA has authority. See, e.g., Regulating Prescription Drug Promotion, Statement of Janet Woodcock, M.D., Dir., CDER, Senate Special Committee on Aging (July 22, 2003) ("'Product-claim' ads are regulated by FDA and are those ads which generally include both the name of a product and its use, or make a claim or representation about a prescription drug."); FDA, Draft Guidance for Industry: "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms, at 8 (Jan. 2004) (referring to "textual relationship" standard); Letter from Christine Hemler Smith, Pharm. D., DDMAC to John R. Cutt, Ph.D., Novartis Pharmaceuticals Corp. (June 27, 2003) ("effectively promotes"). That FDA has used so many formulations in an effort to explain the scope of its power, and that these statements have changed over time, illustrates the need for clarity in this area.

[25] Other examples of manufacturer speech not subject to FDA regulation include public relations activities, patent applications, securities filings, statements to analysts, and testimony in government proceedings (including communications with regulators, legislators, and courts).

IV. CONCLUSION

Because of the societal importance of scientific exchange, FDA's policy development in this area should focus on providing clear definitions of key statutory and regulatory provisions that determine the extent of the agency's authority. FDA should not seek to "regulate," through the establishment of non-binding "guidance" or "recommendations" or otherwise, in areas in which it lacks statutory authority. Because scientific exchange is not within the labeling and advertising provisions of the FDCA and cannot provide "evidence of intended use," it is not subject to regulation by FDA, and FDA should not seek to engage in a comprehensive reevaluation of the extent to which the Agency might deign to permit it.

Assertions of sweeping FDA regulatory authority over manufacturer speech are not now and indeed have never been consistent with the FDCA. Nor have they adequately reflected First Amendment limitations. FDA should take the opportunity provided by important developments in the case law to revise its approach to the regulation of manufacturer speech.[26] In so doing, FDA must recognize that it cannot and should not regulate scientific exchange—because of limitations imposed by the First Amendment and by the statute, and in recognition of the need for the unfettered flow of information about scientific developments, in medicine as in other areas of scientific endeavor.

[26] In the past, FDA has advanced First Amendment positions that clearly need to be revisited, particularly in view of recent judicial decisions. See, e.g., 59 Fed. Reg. 395, 422 (Jan. 4, 1994) (asserting that agency regulations are valid "under the limited scrutiny that has been afforded restrictions on speech under extensive regulatory schemes involving areas of economic activity").

Comments of MIWG
Docket No. FDA-2011-N-0912 & FDA-2011-D-0868
March 27, 2012

Respectfully submitted,

Coleen Klasmeier
Sidley Austin LLP
1501 K Street NW
Washington DC 20005
(202) 736-8132
cklasmeier@sidley.com

Alan Bennett
Ropes & Gray
One Metro Center
700 12th Street, NW
Suite 900
Washington, DC 20005-3948
(202) 508-4604
alan.bennett@ropesgray.com

Paul E. Kalb
Sidley Austin LLP
1501 K Street NW
Washington DC 20005
(202) 736-8050
pkalb@sidley.com

Joan McPhee
Ropes & Gray
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
(617) 951-7535
joan.mcphee@ropesgray.com

Counsel to the Medical Information Working Group

APPENDIX
PRACTICES THAT CONSTITUTE SCIENTIFIC EXCHANGE

Below, we describe by way of example several practices that comprise neither labeling nor advertising and do not provide "evidence of intended use." These practices, along with those described in the Citizen Petition (i.e., dissemination of third-party clinical practice guidelines and communication with payers, formulary committees, and similar entities[27]) and a wide variety of others, have never been addressed by FDA in any binding or comprehensive fashion.[28] Consistent with the statutory and First Amendment analyses above, these practices are not subject to FDA regulation. For clarity's sake, however, we ask FDA to explicitly recognize in binding regulations that such communications and activities constitute permissible scientific exchange so long as: (1) the information is truthful and non-misleading;[29] (2) the manufacturer clearly states that the product or use that is the subject of the communication is not approved by FDA; and (3) the manufacturer makes no claims that the product or use has been proven safe or effective.[30]

1. Communication of Information About Risks Of New ("Off-Label") Use

Health care professionals, to make informed treatment decisions with their patients, must have access to up-to-date scientific information, particularly risk information, even if the information concerns an "off-label" use. Manufacturers are superior repositories of information about their products,[31] systematically collecting, organizing, analyzing, and retaining information that is often of a type and quality relied on by physicians in the exercise of their medical judgment, and in many cases, relates to unapproved as well as approved uses of the manufacturers' products.[32] Although

---

[27] Payer communications continue to be a critical area of concern for manufacturers. Included within this category would be the submission of dossiers to managed care organizations and the like, regardless of whether a "standing unsolicited request" was in effect.

[28] Indeed, the only activities explicitly characterized by FDA as scientific exchange are publishing results of "scientific studies, letters to the editor in defense of public challenges, [and] investigator conferences." See 52 Fed. Reg. at 19,475. We ask that FDA confirm in binding regulations the status of these communications as scientific exchange.

[29] As described in Section I, supra, the scientific process is dynamic and self-correcting, and hypotheses and conclusions initially deemed to be accurate may later be deemed incorrect. The possibility that a scientific statement may ultimately be disproven does not undermine its "truthfulness" so long as the statement is factual and is not promotional, and the underlying research being discussed was derived using appropriate scientific methodology.

[30] These criteria reflect the parameters previously outlined by FDA. See 52 Fed. Reg. at 19,475.

[31] See, e.g., Wyeth v. Levine, 129 S. Ct. 1187, 1202 (2009) ("[M]anufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.").

[32] Indeed, FDA requires a manufacturer to review and analyze all information it obtains regarding adverse events associated with its products, regardless of source and regardless of whether the events involved an off-label, as opposed to an on-label, use. See 21 C.F.R. § 314.80(b)–(c). FDA also requires manufacturers to analyze all information obtained about the safety of a drug from any source, regardless

product labeling may warn of adverse events associated with certain off-label uses or discourage the uses altogether, manufacturers are chilled from informing physicians about how to minimize or avoid risks associated with the off-label uses of their products (e.g., by altering the dose of the product) even when the off-label use represents the standard of care.[33] This chill arises from understandable concern on the part of manufacturers that FDA and DOJ prosecutors may treat any manufacturer-provided direction on how to use a drug or device safely off-label as impermissible promotion of an off-label use.[34] We ask that FDA, in recognition of the public health importance of such information, explicitly affirm that such communication constitutes scientific exchange.

2. Medical Science Liaisons

Manufacturers often bifurcate their field-based personnel into sales representatives and medical representatives. The role of the medical representative, often referred to as a medical science liaison (MSL), is to act as a scientific expert who can provide scientific information to prescribers, clinical investigators, and other health care professionals. Unlike sales representatives, MSLs are not tasked with selling product, are not compensated as sales representatives based on the sale of any particular products, and report to the scientific affairs, medical affairs, or clinical development arms of their companies.[35] As medical professionals, most of whom hold an advanced postgraduate degree, such as an MD, PhD, or PharmD.,[36] their tasks center around conveying complex medical and technical information to health care providers, keeping abreast of relevant scientific developments, representing the manufacturer at scientific symposia and meetings, supporting clinical trials by identifying

---

of whether it pertains to an on- or off-label use. See 21 C.F.R. § 314.50(d)(5)(iv); see also Ethan M. Basch, et al., Potential Pharmaceutical Manufacturer Sponsorship and Drug Information, 161 Arch. Internal Med. 2625, 2625-26 (2001).

[33] One circumstance where the problem is particularly evident is where a product is used off-label by physicians in a medical specialty other than the one associated with the labeled indication(s). In this circumstance, companies may risk a criminal investigation if their representatives so much as appear in the medical offices of the physicians who specialize in the off-label condition—even if only for the purpose of discussing a safety concern. The risk arises because the government may seize upon such presence alone to allege an intent on the manufacturer's part that the drug or medical device in question be used for the off-label condition (See Allergan v. United States, Gov't Summ. J. Br. at 36).

[34] Although FDA has stated that it does not construe the FDCA and accompanying regulations as prohibiting the communication of information regarding the risks associated with an off-label use of a product if that information is "non-promotional" (see id.), the meaning of "non-promotional" is unclear.

[35] See Bass et al., Surveys of Medical Liaison Practices Across the Pharmaceutical Industry: A Review, 43 Drug Info. J. 685, 686 (2009).

[36] Id.

sites, educating investigators, attending investigator meetings, and responding to unsolicited requests.[37]

FDA has repeatedly recognized the value that these professionals add to the communication of medical and scientific information; the Agency has, for example, required the use of MSLs to fulfill communication and physician training requirements associated with various products' Risk Evaluation and Mitigation Strategies (REMS). FDA has 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[38]), but it has never addressed more broadly the ability of MSLs to affirmatively communicate off-label information about their products. We ask the Agency to clarify that MSLs may share truthful and nonmisleading off-label information and that this activity constitutes scientific exchange.

3. Pipeline Information

Drug and device manufacturers must occasionally affirmatively 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 a successful clinical development program. The information, which may be directed to potential investors or clinical investigators, clinicians, researchers, and insurers (including government payers), may take various forms, but often includes references to specific product candidates and investigational uses of marketed products. Whether posted on company websites, discussed at conferences, or communicated through other fora, these pipeline presentations represent scientific exchange in its most classic form because they focus on the dissemination of data regarding development-stage products. We therefore request that FDA explicitly permit manufacturers to engage in pipeline discussions provided that the scientific exchange criteria are otherwise satisfied.

4. Investigator-Initiated Research Websites

Medical product manufacturers frequently provide grant monies for or products to be used in investigator-initiated research (IIR) that advances medical or scientific knowledge about the manufacturers' 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,

---

[37] See, e.g., Morgan et al., History and Evolution of Field-Based Medical Programs, 34 Drug Info. J. 1049, 1051 (2000); see also id. at 687 (noting that MSLs meet an "unmet medical information need").
[38] See FDA, Draft Guidance on Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices, at 5 (Dec. 2011).

data analysis, and communication of results.[39] To facilitate IIR, 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 IIR websites may contain information about new uses of marketed products as well as information about investigational products. While allegations of off-label promotion arising from sponsorship of IIR have been made by DOJ in the past,[40] FDA has never (to our knowledge) commented on manufacturer communication about IIR. We ask that the Agency recognize that manufacturers are permitted to engage in IIR discussions and to sponsor IIR websites so long as the information satisfies the criteria for scientific exchange as set forth above.

5. Rebuttal of Comparative Effectiveness Research Findings

Comparative effectiveness research (CER) purportedly aims to support clinical decision-making by providing recommendations on which products are safe, efficacious, and cost-effective.[41] Although CER has long been conducted and distributed by public health agencies and private health plans, it promises to gain even more prominence as a result of the creation of the Patient Centered Outcomes and Research Institute (PCORI), which was established in 2010 and has a mandate that includes the sponsorship and assessment of CER.[42] Through publication of the research findings, for example, so-called "academic detailing,"[43] a variety of information may be disseminated about a manufacturer's products by AHRQ and other government entities. Such information often includes analyses of products for unlabeled uses, and the findings may be based on observational studies, meta-analyses, or other

---

[39] See, e.g., FDA, Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs), available at http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm071098.htm (describing sponsor responsibilities and making clear that companies that provide study drug are not study sponsors).

[40] See DOJ, Press Release: Pharmaceutical Giant AstraZeneca to Pay $520 Million for Off-Label Drug Marketing (Apr. 27, 2010), available at http://www.justice.gov/opa/pr/2010/April/10-civ-487.html (alleging among other things that the company "engaged doctors . . . to conduct studies on unapproved uses of Seroquel").

[41] See, e.g., Institute of Medicine, Initial Priorities for Comparative Effectiveness Research, at 29 (2009).

[42] See PCORI Mission Statement, available at http://www.pcori.org/about/mission-statement-2/ (explaining that PCORI's aims include "producing and promoting" CER).

[43] It is expected that PCORI's findings will be shared with clinicians and payers through in-person visits and publicity campaigns by the Agency for Healthcare Research and Quality (AHRQ), which has awarded multi-million dollar contracts to various companies for that purpose. See Joshua D. Lenchus, A Federal Unsales Force?: "Academic Detailing" on Medical Treatments and the Oversight Imperative, The Washington Legal Foundation Legal Backgrounder (Apr. 22, 2011), available at http://www.cohealthcom.org/wp-content/uploads/2011/07/click-here.pdf.

information that may not constitute the "substantial evidence" typically required in the prescription drug context for comparative claims. What results is an asymmetrical scheme in which CER findings may be publicized without restriction by government entities, payers, or others, while manufacturers may not even respond to CER findings without risking government allegations of unlawful "promotion."[44] To the extent that manufacturers want to rebut CER (e.g., when it is based on faulty assumptions or methodological errors), the uncertainty in the regulatory scheme prevents them from doing so.

An FDA official recently stated that a manufacturer may "correct" or "dispute" a CER finding by a payer, researcher, or governmental entity,[45] but the contours of that position have not been clarified, nor has the position been adopted by in a binding manner by the Agency. The FDA official emphasized, moreover, that the manufacturer's response to CER may be appropriate only to the extent that it was "non-promotional" and consistent with the product labeling. Not only is there no way to determine what "non-promotional" means in this setting, but also for off-label CER in particular, manufacturers are left apparently unable to rebut CER findings, no matter how inaccurate. In recognition of the value of CER and the importance of the flow of truthful scientific information,[46] we ask that FDA explicitly recognize that manufacturers are entitled to respond to CER statements made by third parties, whether or not off-label, provided that the discussions comply with the scientific exchange parameters described above.

---

[44] See Scott Gottlieb & Coleen Klasmeier, Comparative Effectiveness Research: The Need for a Uniform Standard, AEI Outlook (June 2009), available at http://www.aei.org/files/2009/06/09/06%20HPO%20Gottlieb-g.pdf.

[45] See Gregory Twachtman, FDA Product Promotion Regs Shouldn't Stop Companies from Challenging CER Results, Official Says, The Pink Sheet (Feb. 10, 2012) (describing a presentation made by Bob Temple, Deputy Center Director for Clinical Science in FDA's Center for Drug Evaluation and Research, at the National Pharmaceutical Council conference on "Asymmetry in the Ability to Communicate CER Findings: Ethics and Issues for Informed Decision Making").

[46] As discussed above, manufacturers are superior repositories of information about their products and are thus uniquely positioned to communicate about them.

SIDLEY AUSTIN LLP
SIDLEY

ROPES
&GRAY

March 1, 2013

Via Electronic Submission

Dockets Management
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Docket Nos. FDA-2011-P-0512 and FDA-2011-D-0868

Dear Sir or Madam:

We write on behalf of the Medical Information Working Group (MIWG) regarding FCC v. Fox Television Stations, Inc., 132 S. Ct. 2307 (2012) ("Fox II"), and United States v. Caronia, 703 F.3d 149 (2d Cir. 2012). Because of their relevance to the subject matter of the above-captioned dockets, we enclose a copy of each decision and ask that these documents be made a part of the administrative records in both proceedings.

The decision of the United States Court of Appeals for the Second Circuit in Caronia points up the importance of prompt FDA clarification of the agency's current approach to the regulation of manufacturer speech concerning new uses of approved products. The majority "construe[d] the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns," 703 F.3d at 160, thereby reaching the conclusion presaged by the Supreme Court's decision in Sorrell v. IMS Health, Inc., 131 S. Ct. 2653, 2659, 2667 (2011) ("Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the . . . First Amendment."). The majority opinion has potentially sweeping implications for FDCA enforcement, for two reasons. First, it raises the question whether, in future cases involving speech both as actus reus and as "evidence of intent," a reviewing court might invalidate a conviction following the same logic as the Second Circuit. 703 F.3d at 161 (finding that the Government not only had used Caronia's speech as "evidence of intent" but also had "prosecuted Caronia for his promotion and marketing efforts"). Second, it identifies obstacles the Government would confront in misbranding cases in which speech is used solely for evidentiary purposes. Id. at 162 n.9 (raising questions concerning the "scope of the misbranding proscription"). As Caronia represents the first occasion on which an appeals court has vacated a misbranding conviction on FDCA grounds, it warrants careful review, and the agency should give careful consideration to both the decision's repercussions for future enforcement and its implications for the underlying regulatory scheme itself.[1]

[1] In Caronia, the Court of Appeals vacated a conspiracy conviction premised on an FDCA misbranding violation. Other cases have involved the invalidation of provisions of the FDCA itself. Thompson v.

While Caronia considered the First Amendment in the context of a criminal prosecution, it is clear that lack of specificity in a regulatory scheme also raises serious Fifth Amendment issues. In Fox II, the Supreme Court held, invoking Fifth Amendment Due Process principles, that the Federal Communications Commission (FCC) 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. 132 S. Ct. at 2317 (Due process principles require "first, 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 v. City of Rockford, 408 U.S. 104, 108-09 (1972)).

In Fox II, the Supreme Court reviewed the FCC's interpretation of 18 U.S.C. § 1464, prohibiting broadcasters from using "obscene, indecent, or profane language." 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. Id. 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, 8003). In 2004, the FCC adopted a new interpretation according to which even "fleeting" (non-repeated) expletives and nudity constituted prohibited material under § 1464. Id. at 2314. 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. Id. 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.'" Id. at 2318 (quoting United States v. Williams, 553 U.S. 285, 304 (2008)).

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. Since then, FDA has published a notice on scientific exchange, ostensibly intended to commence a regulatory proceeding to clarify the scope of that safe harbor. That notice has had the opposite effect, increasing the existing ambiguity by seeking comment on fundamental questions that were not raised in the petition. The lack of clarity in FDA's current approach to manufacturer speech about off-label uses has a constitutional dimension because, as the Fox II Court observed, the Due Process Clause requires federal agencies to provide fair notice of their interpretations of key statutory provisions prior to commencing regulatory action based on them.

Second, the Court emphasized that fair notice principles operate with greater force "when applied to . . . regulations that touch upon 'sensitive areas of basic First

---

Western States Med. Ctr., 535 U.S. 357 (2002) (invalidating a provision of FDAMA § 127, 21 U.S.C. § 353a(c)); Wash. Legal Found. v. Henney, 56 F. Supp. 2d 81, 88-89 (D.D.C. 1999) (declaring FDAMA § 401, 21 U.S.C. §§ 360aaa-360aaa-6, unenforceable), rev'd, 202 F.3d 331, 337 n.7 (D.C. Cir. 2000) (declining to "reach the merits of the district court's First Amendment holdings"). From these decisions and others it remains clear that a careful reconsideration of the scope of FDA's authority over manufacturer speech in this area is overdue.

Amendment freedoms.'" Id. at 2318 (quoting Baggett v. Bullitt, 377 U.S. 360, 372 (1964)). 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. Id. at 2317 ("When speech is involved, rigorous adherence to [fair notice] requirements is necessary to ensure that ambiguity does not chill protected speech."). Finally, the Court determined that the FCC's action was improper on the ground that its "findings of wrongdoing" caused "reputational injury" to the broadcasters. Id. at 2318-19. The decision indicates that the Due Process infirmity with the current regulatory framework applicable to manufacturer speech about off-label uses is not obviated by FDA's use of untitled and warning letters, because those letters purport to find FDCA violations and cause reputational injury.

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 (62 Fed. Reg. 14,912 (Mar. 28, 1997) (enclosed)) and to resolve questions created by First Amendment case law (67 Fed. Reg. 34,942 (Mar. 16, 2002) (enclosed)). 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. 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, e-mails, and advisory comments. No concise set of rules or guidelines exists, and key statutory terms—such as "promotion" and "scientific exchange"—have been left undefined. As a result, important questions remain regarding the rules applicable to manufacturer communications, both on- and off-label.

Moreover, manufacturers lack a mechanism to obtain FDA interpretations on key statutory issues in advance of undertaking specific promotional activities. The advisory comment process for prescription drug promotional materials (21 C.F.R. § 202.1(j)(4)) is deficient for the reasons set forth in prior comments. MIWG, Amended Comments dated April 15, 2010 re: Food and Drug Administration Transparency Task Force Request for Comments, Docket ID No. FDA-2009-N-0247. FDA's general procedural regulations (21 C.F.R. § 10.85) describe an advisory opinion process that theoretically could be invoked by manufacturers seeking binding agency advice, but the process has fallen into disuse. Members of the MIWG submitted comments to the transparency docket asking FDA to revive the advisory opinion process to ameliorate the lack of clarity in the regulatory environment. In January 2011, however, FDA declined that request on the ground that doing so "may place inappropriate restrictions on FDA's ability to respond to emerging issues to best protect and promote the public health." See Transparency Task Force, DHHS, FDA TRANSPARENCY INITIATIVE: IMPROVING TRANSPARENCY TO REGULATED INDUSTRY § V.A (2011). MIWG members, invoking another procedure available to manufacturers seeking clarity in the regulatory scheme, submitted a citizen petition in July 2011 asking FDA to clarify the scope of various safe harbors and to address other ambiguities in the current framework. Although FDA opened a docket and issued a draft guidance in response to the petition, it has not addressed the petition's fundamental request for binding regulations that will set forth avenues for manufacturers to communicate protected speech. The need for such specificity and clarity here is not simply a policy preference, it is a legal necessity. Both the Due Process Clause of the Fifth Amendment and the First Amendment require "precision" and "narrow specificity" in content regulation, and

these standards are more demanding where, as here, violations are punishable criminally. Reno v. ACLU, 521 U.S. 844, 874 (1997); Keyishian v. Board of Regents of the Univ. of the State of N.Y., 385 U.S. 589, 604 (1967); see also Buckley v. Valeo, 424 U.S. 1, 76-77 (1976).

The July 2011 citizen petition has been pending for nearly twenty months. The actions taken by FDA in response to the petition have not squarely addressed the issues presented by the regulatory scheme. Meanwhile, courts have continued to recognize the First Amendment constraints on FDA regulation. Interested parties will continue to look to the courts for answers in the absence of clear regulation by FDA, and many are certain to argue that the continued lack of clarity and the associated chilling effects by themselves create a reviewable controversy. This litigation risk aside, however, we cannot imagine that agency officials would prefer a regulatory scheme characterized by ambiguity, patchwork 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, we renew our request for precise, narrowly specific rules governing manufacturer speech.

Respectfully submitted,

Alan Bennett

Paul E. Kalb

Coleen Klasmeier

Joan McPhee

cc: Elizabeth H. Dickinson, Esq. (via mail)

Enclosures