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COMMENTS OF THE MEDICAL INFORMATION WORKING GROUP ON FDA'S "GOOD REPRINT PRACTICES" DRAFT GUIDANCE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Working Group (MIWG) appreciates the opportunity to provide the Food and Drug Administration (FDA) with comments on the draft guidance, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved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Although the MIWG supports the intent and thrust of the draft guidance, we also believe that the draft raises important issues that should be addressed in the final version. The most important issue concerns the relationship of the draft guidance to the other "safe harbors" that FDA has crafted over many years to encourage manufacturers to distribute off-label use information in specific situations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 Although we understand that the safe harbor recognized in the draft guidance is in addition to these other safe harbors, to help assure clarity in the regulatory environment, we respectfully request that FDA expressly affirm—ideally, in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 Part II sets forth our comments on specific aspects of the draft guidance.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As FDA notes in the draft guidance (p. 3), there are "important public policy reasons for allowing manufacturers to disseminate truthful and non-misleading medical journal articles and medical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. . . .
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> 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

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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

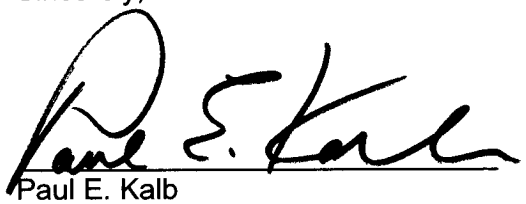
The reference to "Good Reprint Practices" (p. 1, lines 3-6; p. 2, lines 4-6; p. 2, lines 19-21) is awkward. This phrase implies that the focus of the document is on articles originally appearing in other publications. In fact, the document addresses not only "medical journal articles" but also "scientific 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,



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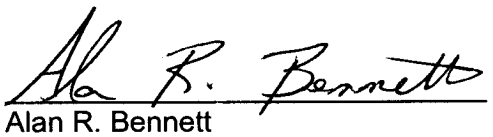

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