April 16, 2008

EXECUTIVE SUMMARY

FDA's February 20, 2008, draft guidance, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved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," sets forth FDA's proposed recommendations for manufacturers who would like to give health care practitioners reprints of medical journal articles and medical or scientific reference texts that contain statements about "off-label" uses of FDA-approved drugs and approved or cleared medical devices.

The Medical Information Working Group (MIWG) is an informal group of ten drug, biotechnology, and medical device manufacturers. They have a common interest in asking the Food and Drug Administration (FDA) to clarify its policies on the dissemination of truthful scientific information concerning off-label uses of approved or cleared drugs and medical devices. The following is a summary of MIWG's comments on the draft guidance:

- Off-label uses of drugs and medical devices are a foreseeable aspect of medical care, because scientists discover possible new uses for medical products more rapidly than the FDA can review them. Physicians may legally prescribe drugs and medical devices off-label, and indeed off-label prescribing plays a critical role in patient care, especially for rare or difficult-to-treat diseases and disorders such as cancer and cystic fibrosis. MIWG believes that appropriate off-label uses—i.e., those that benefit patient care—are fostered by more, rather than less, communication of truthful, non-misleading scientific information.

- In 1997, the Food and Drug Administration Modernization Act (FDAMA) established a specific process for manufacturers to provide reprints of peer-reviewed journal articles discussing off-label uses to physicians. The law sunset in 2006, and since then there has been confusion about how manufacturers may legally distribute peer-reviewed off-label reprints to health care professionals. The draft guidance is intended to dispel the current confusion by recognizing the value of this practice and setting forth recommendations for reprint and reference text distribution.

- Under the draft guidance, as under earlier FDA policy and consistent with the 1997 law, manufacturers would be allowed to distribute reprints of peer-reviewed articles and reference texts to physicians under carefully limited circumstances. For example, the reprints would have to have been published in reputable journals with adequate peer-review mechanisms, and the information in them could not be false or misleading. In addition, the reprint would have to be unabridged, be accompanied by the approved labeling and a comprehensive bibliography, and prominently display a disclaimer that the uses discussed in the article have not been approved or cleared by FDA.

- The medical community supports manufacturer distribution of journal article reprints and reference texts. Both the American Medical Association and the American Heart Association have longstanding policies that support manufacturer dissemination of off-label use information to physicians by, among other things, distribution of reprints and textbooks.

- The guidance does not permit dissemination of off-label promotional material such as "detail aids," and does not broaden the scope of permissible direct-to-consumer promotion. It is limited to third-party, peer-reviewed journal articles and reference texts that are otherwise

widely available; indeed, courts have recognized that this sort of material is entitled to constitutional protection.

- MIWG strongly supports the intent of the draft guidance because it advances the public health. It will help physicians receive accurate and reliable off-label information, which directly enhances patient care and saves lives. We urge FDA to move quickly to evaluate the comments and issue a final guidance.

- Our comments ask FDA to clarify a few technical issues and affirm in the final guidance that pre-existing safe harbors continue to be available to manufacturers wishing to provide information about off-label uses. In our view, it is obvious that the safe harbor recognized in the draft guidance is in addition to these other safe harbors.

Timeline of FDA Policy Concerning Reprints and Reference Texts

Early '90s	FDA establishes the Division of Drug Marketing, Advertising, and Communications ("DDMAC"); DDMAC increases letters and telephone calls to drug manufacturers advising that the unsolicited distribution of reprints of peer-reviewed journal articles and independent medical textbooks in which off-label uses of their products are discussed exposes the manufacturers to potential agency enforcement actions.
1994	The Washington Legal Foundation ("WLF") files suit against FDA, arguing that FDA's policies on reprints and medical textbooks have the effect of chilling speech that is protected by the First Amendment and that is outside the purview of FDA's jurisdiction.
1996	As the WLF case is pending, FDA issues guidance describing the circumstances under which FDA "intends to allow" manufacturer dissemination of journal article reprints and reference texts that contain off-label information.[1] Under that guidance, reprint dissemination is limited to those instances where the product's pivotal, phase III trials are "the principle subject" of the article, or where the studies discussed were submitted to FDA as evidence of a device's safety or efficacy. For reference texts, FDA permits dissemination of those texts that are not written, edited, or significantly influenced by manufacturers, are available in ordinary distribution channels, and do not focus primarily on any one product.
1997	As the WLF case is pending, Congress passes the Food and Drug Administration Modernization Act ("FDAMA"). Section 401 of FDAMA and FDA's implementing regulations for that section establish a number of conditions governing manufacturer distribution of reprints and reference texts that contain off-label information.[2]
1998	The district court in the WLF case concludes that FDA's outright ban on the dissemination of scientific information is unconstitutional because it is not the least restrictive method for advancing the government's stated interests. The court therefore enjoined FDA from prohibiting any manufacturer from disseminating scientific information. The only restrictions the court allows FDA to impose on a manufacturer are that the information not be false or misleading and that the manufacturer disclose the fact that the discussed use is not approved by FDA.[3]
1999	FDA asks the court to exclude Section 401 of FDAMA from the injunction, but the court refuses. The court states that the injunction applies to the underlying policies of FDA, not just the express provisions of the guidance and Section 401

[1] 61 Fed. Reg. 52800 (Oct. 8, 1996).

[2] *See* FDAMA, Pub. L. No. 105-115, 111 Stat. 2296 (1997); codified in pertinent part at 21 U.S.C. §§ 360aaa *et seq.*

[3] *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998).

of FDAMA.[4]

2000 FDA appeals the district court decision and states that Section 401 of FDAMA is meant to be a "safe harbor" and imposes no independent obligations on manufacturers. In light of this clarification, the appellate court dismissed the appeal, as there was no constitutional issue that was ripe for judicial review.[5] Nevertheless, the appellate court did intimate that it agreed with the district court's decision, stating in a footnote that, "in disposing of the case in this manner, we certainly do not criticize the reasoning or conclusions of the district court."[6]

2000 As a result of the appellate court decision, the district court vacates the injunction it had entered against FDA, lamenting that after six years' worth of briefs, opinions, and Congressional acts, the issue whether FDA violates the First Amendment by penalizing manufacturers for distributing scientific literature to physicians regarding off-label uses "remains 100% unresolved."[7]

2000 FDA issues a Federal Register notice reaffirming its position that Section 401 of FDAMA represents a safe harbor and that a manufacturer's failure to abide by its provisions does not, by itself, constitute an independent violation of law.[8]

2002 FDA rejects a petition from WLF requesting that FDA withdraw the 2000 Federal Register notice and replace it with a statement adopting the position of the district court. FDA largely reiterates the "safe harbor" position, conceding only that it is "unlikely to initiate an enforcement action where the only evidence of an unapproved intended use is the distribution of enduring materials."[9]

2006 Section 401 of FDAMA and its implementing regulations expire.

2008 FDA issues 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.*

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[4] *Washington Legal Found. v. Henney*, 36 F. Supp. 2d 16 (D.D.C. 1999).

[5] *Washington Legal Found. v. Henney*, 202 F.3d 331 (D.C.Cir. 2000).

[6] *Id.* at 337 n.7.

[7] *Washington Legal Found. v. Henney*, 128 F. Supp. 2d 11 (D.D.C. 2000).

[8] *Decision in Washington Legal Foundation v. Henney*, 65 Fed. Reg. 14286 (Mar. 16, 2000).

[9] FDA Docket No. 01P-0250; Letter from Margaret Dotzel, Associate Commissioner for Policy, FDA to Daniel Popeo and Richard Samp, WLF (Jan. 28, 2002).