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FDA Issues Draft Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses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

On February 20, 2008, the U.S. Food and Drug Administration ("**FDA**") made available for comment draft guidance titled "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of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 "**Draft Reprint Guidance**").[1] As stated in the Draft Reprint Guidance, the intent of the document is to describe the FDA's "current thinking regarding 'Good Reprint Practices' with regard to the distribution of medical journal articles and scientific or medical reference publications... that discuss unapproved new uses for approved drugs or approved or cleared medical devices marketed in the United States to healthcare professionals and healthcare entities."[2] The FDA is seeking comments and suggestions on the Draft Reprint Guidance. ***Any such comments or suggestions must be submitted to FDA by April 21, 2008 at Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852***.[3]

Background

Until September 30, 2006, section 401 of the Food and Drug Administration Modernization Act of 1997 and the regulations promulgated thereunder ("FDAMA") provided certain parameters to drug and medical device manufacturers for the dissemination of scientific information describing unapproved uses of an approved drug or approved or cleared medical device to healthcare providers and other potential referral sources.[4] Pursuant to FDAMA, a manufacturer's distribution of scientific information regarding an unapproved new use in compliance with the FDAMA requirements would not be deemed an expression of the manufacturer's intent to market the product for the unapproved use.[5]

Following litigation by the Washington Legal Foundation,[6] the FDA interpreted FDAMA and its implementing regulations to offer a "safe harbor" under which manufacturers could disseminate certain scientific reprints or reference publications without risk that the FDA would use such dissemination as evidence that the manufacturer intended for the product to be prescribed for an unapproved use.[7] However, in the absence of compliance with the FDAMA safe harbor, the dissemination of information regarding an unapproved use could

be used as evidence that a drug was promoted for an unapproved use, but would not constitute an independent violation of law.

Specifically, the FDAMA safe harbor permitted the dissemination of certain medical or scientific information describing an unapproved use to healthcare providers, pharmacy benefit managers, health insurance issuers, group health plans and state or federal government agencies, subject to the following conditions:

- the drug or device was subject to an approved application for marketing or, in the case of certain medical devices, a marketing clearance;[8]
- the information disseminated was either an unabridged reprint of a peer-reviewed article that was published in a scientific or medical journal meeting the standards of reliability under FDAMA, including an effective conflict of interest disclosure policy, or a reference publication;[9]
- the information was not false, misleading or a public health risk;[10]
- the information was not derived from clinical research conducted by another manufacturer unless used with permission of the manufacturer that conducted the clinical trial;[11]
- the manufacturer submitted to the FDA at least 60 days before dissemination of the information, the information to be disseminated, clinical trial data or information based on clinical experience related to the safety or effectiveness of the new use, and a summary of such information;[12]
- the manufacturer submitted and diligently pursued a supplemental application for the new use of the drug or device, submitted a plan for timely submitting such an application, or demonstrated to the FDA that it met the requirements for an exemption from the requirement to submit a supplemental application;[13] and
- the information included: (1) a disclosure that it concerned an unapproved use; (2) a statement that the information was being disseminated at the expense of the manufacturer; (3) the names of any authors of the information who were compensated or had a significant financial interest in the manufacturer; (4) the approved labeling of the drug or device; (5) a statement that there were other products approved for the unapproved use described in the information; (6) identification of persons or entities that provided funding for the study of the new use; and (7) a bibliography.[14]

Manufacturers who disseminated scientific information pursuant to FDAMA were required to submit biannual reports to the FDA detailing the information disseminated by the manufacturer in the preceding six (6) months and identification of the categories of healthcare providers and other entities to whom such dissemination was made.[15] A manufacturer also was required to submit clinical research data or other information concerning safety or efficacy of the new use.

As a practical matter, the FDAMA safe harbor was rarely used by manufacturers. However, it provided useful insight as to the FDA's frame of reference in evaluating the dissemination of reprints and reference materials. After FDAMA sunset on September 30, 2006, the FDA announced its intent to issue guidance concerning permissible means of disseminating scientific information regarding unapproved uses of approved drugs and approved or cleared medical devices.

On November 30, 2007, Representative Henry Waxman, Chair of the House Committee on Oversight and Government Reform, released a copy of the internal draft guidance on good reprint practices under development by the FDA, prior to the FDA's formal issuance of the Draft Reprint Guidance. In a letter to

the FDA voicing his concerns, Representative Waxman objected to the FDA's plan to permit dissemination of scientific information regarding unapproved uses and sought information regarding the development of the draft guidance and plans for its implementation. Representative Waxman asserted that permitting even limited dissemination of off-label information would "short-circuit FDA review and approval… [which] undercuts the prohibition on marketing of unapproved uses of drugs and devices and puts the public at risk for ineffective and dangerous uses of drugs."[16]

FDA Draft Reprint Guidance

Although it does not carry the legal weight of FDAMA and does not completely mirror FDAMA or its implementing regulations, the Draft Reprint Guidance includes several of the same themes. The Draft Reprint Guidance addresses five specific areas: (1) publishing organizations; (2) channels of distribution; (3) manufacturer influence; (4) content of the information disseminated; and (5) the manner in which the information is disseminated. Notably, the Draft Reprint Guidance does not require manufacturers to submit to the FDA certain reprints intended for distribution or supplemental applications concerning the unapproved uses described in a reprint.

Specifically, the Draft Reprint Guidance establishes the following criteria:[17]

- Publishing Organizations. The organization publishing a journal article must: (1) utilize an independent editorial review board composed of members with demonstrated expertise in the subject matter of the article under review who are free to objectively review submissions and to select, reject, or comment on proposed articles as it deems appropriate; and (2) have a publicly stated policy regarding full disclosure of any conflicts of interest or biases of the authors, contributors, or editors. The editorial board also must follow the organization's established peer-review procedures and publish journal articles in accordance with those procedures.[18]
- Channels of Distribution. A reference publication may not be primarily distributed by the manufacturer, and must be generally available, for example, in bookstores or other locations where medical textbooks are sold.[19]
- Influence of the Manufacturer. To ensure objectivity, reference publications written, edited, excerpted, or published for, or at the request of, a product manufacturer may not be disseminated. In addition, a disseminated reference publication must not have been edited or significantly influenced by the product manufacturer, or any party in a financial relationship with the manufacturer. Similarly, manufacturers may not disseminate special supplements or publications that a manufacturer funded in whole or in part.[20]
- Content of Disseminated Information. The information disseminated in a journal article or reference publication must not pose a significant risk to the public health. The information must address adequate, well-controlled, scientifically sound clinical investigations conducted by experts in the field. Also, the information disseminated must be truthful and not misleading. The FDA clarifies this standard using the following guidelines:
  - the information must not be inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical studies;
  - disseminating a withdrawn journal article or disclaimed reference publication would be considered false and misleading;

- disseminating information on clinical studies where a company had knowledge that the FDA deemed the studies to be inadequate or not well-controlled would be considered false and misleading.

Finally, the information must be disseminated in its original state (i.e., an unabridged reprint or a copy of an article or reference publication). The reprint or copy may not be edited by the manufacturer in any way, including marking, highlighting, summarizing or characterizing.

Examples of publications inappropriate for distribution include the following: letters to the editor, abstracts, reports of Phase I trials in healthy subjects, or reference publications with little or no substantive analysis of the clinical investigation and resulting data.[21]

♦ Manner of Dissemination. Particular considerations apply to how and when a journal article or reference publication may be disseminated. The information must be accompanied by a copy of the approved product labeling and, unless already contained in the body of the distributed material, a comprehensive bibliography of articles or texts discussing adequate and well-controlled studies of the relevant unapproved use. In addition, the information must be accompanied by a publication representative of any articles or texts reaching contrary or different conclusions.

The disseminated information must bear a permanently affixed and prominently displayed disclaimer, stating that the subject use of the product has not been approved or cleared by the FDA. The disclaimer must also disclose the following: the manufacturer's interest in the product; any author known to the manufacturer with a financial interest in the product or manufacturer; any author known to the manufacturer as having received any compensation from the manufacturer; any person known to the manufacturer as having provided funding for the study; and any significant safety risks regarding the unapproved use of the product that are known to the manufacturer and not discussed in the disseminated publication.

Finally, dissemination of reprints for educational purposes must take place separate and apart from promotional activities. Guidelines for establishing this separation include the following:

- a reprint may not be physically attached to any promotional materials distributed to a healthcare provider by a sales representative;
- sales representatives may not discuss the content of a reprint with a healthcare provider;
- a reprint may be distributed at medical or scientific conferences occurring in an academic setting, but not at promotional exhibitions or speaker programs.[22]

Consistent with its status as regulatory guidance, the Draft Reprint Guidance, if finalized, will represent recommendations for industry based upon the FDA's current thinking regarding the distribution of scientific and medical information regarding unapproved uses. However, there is no statutory assurance for the FDA's position on reprint dissemination as there was under the FDAMA safe harbor, and the FDA states on its website that "guidance documents… do not create or confer any rights for or on any person and do not operate to bind FDA or the public."[23] Accordingly, a manufacturer's failure to comply with the recommendations set forth in the Draft Reprint Guidance does not constitute a *per se* violation of law, and a manufacturer's compliance with the Draft Reprint Guidance does not confer an absolute assurance that the dissemination will not result in an enforcement action. Rather, in the Draft Reprint Guidance, the FDA

asserts its continuing regulatory authority to determine "whether distribution of medical or scientific information constitutes promotion of an unapproved 'new use,' or whether such activities cause a product to be misbranded or adulterated."[24] The FDA expresses its intent to exercise its enforcement discretion, such that, "if a manufacturer follows the recommendations described in…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."[25] In any event, until finalized, the Draft Reprint Guidance is subject to change.

Compliance Considerations

Although the Draft Reprint Guidance is not yet final, it presents a useful, albeit preliminary, reference for manufacturers assessing their current compliance efforts with respect to where the FDA may ultimately exercise its discretion regarding reprint or reference material dissemination. Manufacturers should carefully review the Draft Reprint Guidance with respect to their current practices, policies and procedures in this regard, and determine whether to take advantage of the comment period to provide comments and suggestions to the FDA, as applicable. Concurrent with evaluating the Draft Reprint Guidance for purposes of comment submission, manufacturers should also consider the following issues in evaluating their current reprint and reference material dissemination policies:

- Do the SOPs applicable to the review and approval of reprints and accompanying materials intended for distribution currently address, or can they be modified to address, and create an infrastructure to support key issues such as:
  - Whether a journal article was published by an appropriate organization, comprised of experts in a relevant field, after undergoing an established peer-reviewed process;
  - Whether such an organization's editorial board maintains adequate policies and procedures for disclosing potential conflicts of interest of authors, contributors or editors; and
  - Whether a reference publication is generally available through independent distribution channels and is free from manufacturer involvement with respect to funding, writing, editing or data analysis?
- Does the manufacturer's review committee have expertise to properly evaluate the scientific integrity of clinical investigations described in a reprint according to the criteria specified in FDA's Draft Reprint Guidance, including:
  - Whether a trial referenced in the reprint is adequately designed and conducted and well-controlled;
  - Whether trial outcomes are consistent with those of a majority of similar recognized studies;
  - Whether trial findings have been widely supported or contradicted by experts in a relevant field; and
  - Whether a trial yields information that could pose a significant risk to public health?
- Are SOPs applicable to practices for distribution of reprints by sales representatives designed to, or can they be modified to, create an infrastructure for addressing issues such as:
  - The appropriate form of a reprint;

- The materials and information that must accompany a reprint (e.g., disclosures, labeling, bibliography, representative contradictory articles, etc.);
- Requirements for distributing reprints separately from promotional materials, and prohibitions on discussing reprint content;
- Appropriate recipients and venues for reprint distribution; and
- Limitations on the frequency of distribution and categories of recipients?

♦ Does the manufacturer's audit agenda ensure the following:
- Regular audits of all SOPs relevant to reprint practices to ensure continued compliance with FDA guidance;
- Regular and periodic review of all reprints and accompanying materials being distributed to ensure that all distributed information is current and accurate?

♦ Does the manufacturer maintain records of all reprints and accompanying materials distributed, as well as distribution dates and the names and addresses of recipients?

* * *

[1] 73 Fed. Reg. 9,342 (Feb. 20, 2008).
[2] U.S. Food & Drug Admin., 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 (Feb. 2008) (hereinafter "Draft Reprint Guidance"), *available at* http://www.fda.gov/oc/op/goodreprint.html (last visited Mar. 4, 2008).
[3] *See id*.
[4] 21 U.S.C. § 360aaa (the FDA's implementing regulations were codified at 21 C.F.R. pt. 99).
[5] *See id.* § 360aaa-6.
[6] *Washington Legal Foundation v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999).
[7] 65 Fed. Reg. 14,286 (Mar. 16, 2000).
[8] 21 U.S.C. § 360aaa.
[9] *See id.* § 360aaa-1(a).
[10] *See id.*§ 360aaa-1(a)(2).
[11] *See id* .§360aaa(b)(3).
[12] *See id.* §360aaa(b)(4).
[13] *See id.* § 360aaa(b).
[14] *See id*.
[15] *See id.* § 360 aaa-2.
[16] Letter from H. Waxman, Chairman, House Committee on Oversight and Government Reform, to A. von Eschenbach, Commissioner, U.S. Food & Drug Admin. (Nov. 30, 2007), *available at* http://www.oversight.house.gov/documents/20071130102744.pdf (last visited Mar. 4, 2008).
[17] *See* Draft Reprint Guidance, *supra* note 2.
[18] *See id.* at 4.
[19] *See id.* at 5.
[20] *See id.*
[21] *See id.*
[22] *See i*d. at 5-6.
[23] *See* U.S Food & Drug Admin., Ctr. For Drug Evaluation & Res., Guidance Page, http://www.fda.gov/cder/guidance (last visited Mar. 4, 2008).
[24] *Id*. at 4.
[25] *Id*. at 6-7.

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