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## Review Of Final FDA Guidance On Off-Label Use Publications

On Jan. 13, 2009, eleven months after the Food and Drug Administration (FDA) issued a draft guidance document, and 2 1/2 years after the sunset of the statute[1] intended to permit the dissemination of medical literature about unapproved uses of drugs and medical devices, the FDA issued a final guideline for such dissemination. Often referred to as "the distribution of off-label use journal articles," FDA's final guidance is aptly named "Guidance For Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices."[2]

As with the 2008 draft guidance, the final version begins by succinctly discussing the historical attempts to regulate the distribution of literature about unapproved uses, including noting the need to balance the law's prohibition on distributing or promoting "unapproved uses of approved drugs and approved or cleared medical devices" with the "important public policy" of providing information that "may even constitute a medically recognized standard of care." FDA concludes that the touchstone for lawful dissemination of literature about unapproved uses is that the publications "are truthful and non-misleading."

To meet this standard, the FDA final guidance lists "principles of Good Reprint Practices" that include criteria for determining the type of publication, and the manner in which the publication can be distributed. Although the final guidance closely tracks the draft guidance, it has some important clarifications.

The following discussion highlights these clarifications and provides an overview of the final guidance.

### *Important Clarification In The Final Guidance*

Although the final guidance clarifies a number of issues, including lessening the burden of needing to provide accompanying documentation with a reprint, it does not significantly deviate from the 2008 draft. The following bullets list the significant editorial differences between the final and draft versions. Specifically, the final version:

- Explains that the type of "adequate and well-controlled clinical investigations" addressed in a reprint that are considered scientifically sound include controlled studies, pharmacokinetic and pharmacodynamic studies, and meta-analyses (if testing a specific clinical hypothesis).
- Clarifies that a reprint should not be "characterized as definitive or representative" of the weight of credible evidence derived from adequate and well-controlled clinical investigations if it is inconsistent with that weight of credible evidence, or if a significant number of other studies contradict the article or reference text's conclusions.
- Clarifies that reprints may only be marked, highlighted, summarized, or characterized to provide disclosures that are required by the guidance.
- Removes the obligation for a manufacturer to always provide a comprehensive bibliography with each reprint. A bibliography is only required "when such information exists."
- Clarifies that articles reaching contrary or different conclusions only need to be provided "when such information exists," and only when such information is disseminated in a representative publication.
- Clarifies that when affixing a disclosure to the reprint of an author that has a financial interest in the product, a financial interest in the manufacturer, or who is receiving compensation from the manufacturer, the disclosure must also list the author's affiliation (to the extent known) and the nature and amount of any such financial interest or compensation received by the author from the manufacturer.

***Review Of Final Guidance***

**I. Criteria For Types Of Publications**

There are four criteria for qualifying a journal article for dissemination by a manufacture (which includes any person licensed to distribute or market the product):

1. The publishing organization should have an editorial board that:
   - Uses experts in the subject of the article who are independent of the organization
   - Has a publicly stated policy that it follows of full disclosure of any conflicts of interest or biases for all authors, contributors and editors
2. The article should be peer-reviewed and published in accord with peer-reviewed procedures
3. The article should not be in the form of a special supplement or publication that is funded in any way by the manufacturer(s)
4. The article should be based on scientifically sound research:
   - For a drug product, the article should discuss adequate and well-controlled clinical investigations that are considered scientifically sound by experts qualified by training and experience to evaluate the safety or effectiveness of the drug.
   - For a device, the article should discuss either: (1) adequate and well-controlled clinical investigations that are considered scientifically sound by experts qualified by training and experience to evaluate the safety or effectiveness of the device, or (2) significant non-clinical research.

In addition, the article should:

- Not be distributed primarily by the manufacturer
- Generally be available through independent distribution channels (e.g., bookstores selling medical texts or journals, the Internet, or subscription services)
- Not be written, edited, excerpted, or published specifically for the manufacturer, or at the request of the manufacturer
- Not be edited or "significantly influenced" by a manufacturer or any individual having a financial relationship with the manufacturer. It appears here that a manufacturer may fund an article so long as it does not "significantly influence" the writing of the article. The guideline does not appear to bar a person with a financial interest from having any influence over the article, but only significant influence.

In the final document, FDA also reminds the reader that, if relied upon, the article must not pose a significant risk to public health or be false or misleading. In other words, these prohibitions are not recommendations but rather requirements. FDA defines false or misleading by giving three examples:

- The article is contradicted by the weight of evidence derived from other adequate and well-controlled clinical investigations
- The article has been withdrawn by the journal or disclaimed by the author
- The article discusses an investigation in which FDA has previously informed the manufacturer that the investigation is not adequate or well-controlled

Certain types of articles are not appropriate for distribution by a manufacturer, regardless of content and even if the content is truthful and not misleading: These include: (1) letters to the editor; (2) abstracts of a publication; (3) reports of Phase I trials in healthy subjects; (4) reference publications that contain little or no substantive discussion of the relevant investigation or data.

***II. How Publications Can Be Disseminated***

The second major section of the final guidance describes what FDA would consider to be an acceptable manner of dissemination, and recommends that a disclosure statement be prominent and permanently affixed.

As to the form of the publication, the basic criteria are that the article be: (1) distributed as published, (2) not abridged, and (3) without marking, highlights, or summaries (except to provide the accompanying disclosures discussed in the final guidance).

The publication must also be accompanied by:

- The approved product labeling
- A comprehensive bibliography of publications, when such information exists, discussing adequate and well-controlled clinical studies published in a medical journal, or medical or scientific texts, about the use of the drug or medical device covered by the information disseminated (unless the information already includes such a bibliography)
- A representative publication, when such information exists, that reaches contrary or different conclusions, or that specifically calls the disseminated article into question.

These criteria are less burdensome than the draft guidance, which did not include the "when such information exists" clarification language. This clarification suggests that only contrary articles from representative publications (i.e., from similarly credible, peer-reviewed journals or texts that are published by an organization with an editorial board) need accompany the article. In addition, such contrary articles should be based on adequate and well-controlled studies.

To further ensure that the publication is not used to promote the product, FDA expects that a manufacturer provide it independently from any other promotional material for the product. In addition, FDA expects that articles generally not "be distributed in promotional exhibit halls or during promotional speakers' programs." This is consistent with FDA's expectation that promotional material be kept separate from educational and scientific materials. Interestingly, implicit in this guideline, it would be appropriate, therefore, for a manufacturer to set up a booth solely for the dissemination of qualifying articles inside conference areas, rather than in separated scientific exhibition halls.

Finally, FDA expects a manufacturer to provide a "prominently displayed and permanently affixed" disclosure statement. The disclosure should include all of the following information:

- A statement that the use discussed in the article has not been approved or cleared by FDA
- A description of the manufacturer's interest in the subject product
- Identify any author with a financial interest in the product or the manufacturer. The disclosure should also include the author's affiliation (to the extent known) and the "nature and amount" of the financial interest or compensation received by the author from the manufacturer.
- Identify any known funders of the study discussed in the article
- Identify "[a]ny significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed" in the publication

Here, FDA's disclosure statement provides an unnecessary redundancy and is unnecessarily burdensome. For example, any financial interest of the authors would have already been disclosed or addressed by the disclosure policy of the editorial board of the publishing organization, as FDA specifies in the first part of the guidance.

As with all FDA guidance documents, this guidance describes FDA's current thinking on the topic and should be viewed only as a recommendation. That being said, the document specifically states that when articles are disseminated in accordance with FDA's recommendations, FDA "does not intend" to consider the distribution of such information as establishing an intent that a product be used for an unapproved new use.

Rep. Henry A. Waxman (D-Cal.), a strong critic of the final and draft guidance, has already asked the incoming Obama administration to re-examine the final version, arguing it is too lenient and gives manufacturers the ability to promote their products off-label.

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***Endnotes***

1 Section 401 of the Food and Drug Administration Modernization Act (FDAMA (21 U.S.C. § 3600aaa, § 551, Federal Food, Drug, and Cosmetic Act (FD&C Act)

2 http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf. The Federal Register Notice can be found at http://edocket.access.gpo.gov/2009/pdf/E9-452.pdf.

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