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# Review of Proposed FDA Guidance on Off-Label Use Publications

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On February 15, 2008, a year-and-a-half after the sunset of the statute[1] intended to permit the dissemination of medical literature about unapproved uses of drugs and medical devices, the Food and Drug Administration ("FDA") proposed a draft guideline for such dissemination. Often referred to as "the distribution of off-label use journal articles," FDA has saddled the proposed guidelines with a much heftier title: "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]

FDA has invited comments—which must be submitted no later than April 14, 2008—on the draft guidance. Only after consideration of any comments will FDA move to finalize the draft guidance.

The draft succinctly details the background of efforts to regulate distribution of literature about unapproved uses, 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, FDA proposes "principles of Good Reprint Practices" that include criteria for determining the type of publication, and the manner in which the publication can be distributed.

## Criteria for Types of Publications

FDA proposes four criteria for qualifying a journal article for dissemination by a manufacturer (which includes any person licensed to distribute or market the product):

- The publishing organization should have an editorial board that:
  - Uses experts in the subject of the article who are independent of the organization, and
  - Has a publicly stated policy that it follows full disclosure of any conflicts of interest or biases for all authors, contributors and editors
- The article should be peer-reviewed and published in accord with peer-reviewed procedures
- The article should not be in the form of a special supplement or publication that is funded in any way by the manufacturer(s)

- 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.

FDA also proposes distribution and publication guidelines to ensure that drug and device manufacturers (without recognizing any distinction between the commercialization practices of a drug and device manufacturer) do not improperly promote an off-label use. 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
- 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 guidelines would also not bar a person with a financial interest from having any influence over the article, but only significant influence.

In the draft, FDA also reminds the reader that 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; or
- The article discusses an investigation that FDA has previously informed the manufacturer that the investigation is not adequate or well-controlled.

If this draft guidance is implemented as written, FDA would consider certain types of articles not appropriate for distribution by a manufacturer, regardless of content, and even if the content is truthful and not misleading. These include:

- Letters to the editor
- Abstracts of a publication
- Reports of Phase I trials in healthy subjects
- Reference publications that contain little or no substantive discussion of the relevant investigation or data

### How Publications Can Be Disseminated

The second major section of the draft 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:

- Distributed "as published"
- Not abridged
- Without marking, highlights or summaries

The publication must also be "accompanied by":

- The approved product labeling
- A comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in a medical journal or medical or scientific text that have been previously published 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" of articles, if any, that reach contrary or different conclusions or that specifically call the disseminated article into question

These criteria appear particularly burdensome for manufacturers and fail to include the same criteria FDA proposes above for qualifying articles for dissemination. FDA does not appear to expect that any contrary articles be credible, subject to peer-review, be published by an organization with an editorial board, and based on adequate and well-controlled studies. Under this draft guidance, it is conceivable that a letter to the editor or an article funded by a competitor might need to accompany an article distributed by a manufacturer.

In addition, these criteria do not acknowledge differences between devices and drugs. For example, an instruction of use ("IFU") manual for a medical device might already be in the possession of the physician who uses the device and, because of its length and size, may be burdensome to provide with each reprint. It is also not clear whether the term "accompany" would require any physical attachment to the article or how closely the labeling should be to the qualified article. The same term is used in the definition of labeling ("all labels and any written, printed or graphic matter *accompanying* a container or wrapper"). In that context, the Supreme Court ruled that "labeling" did not need to be physically attached to the product so long as its content supplements or explains the use of the product, and the textual relationship is significant. *Kordel v. U.S.*, 335 U.S. 345 (1948). Consistent with this definition of accompanying, FDA's expectation could be met if the labeling (including an IFU), along with relevant bibliographies, would be provided at least once before the article is provided.

To further ensure that the publication is not used to "promote" the product, FDA would expect that a manufacturer provide it "independently" from any other promotional material for the product. In addition, FDA would expect that articles generally not "be distributed in promotional exhibit halls or during promotional speakers' programs." 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 exhibition halls. This would be consistent with FDA's expectation that promotional material be kept separate from educational and scientific materials.

Finally, notwithstanding that FDA expects an article not to be marked or highlighted, FDA proposes that the manufacturer provide a disclosure statement that is "prominently displayed and permanently affixed." 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
- Identity of any author with a financial interest in the product or the manufacturer, including the receipt of any compensation from the manufacturer
- Identity of any known funders of the study discussed in the article
- Identity of "[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 proposed 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.

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[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] *www.fda.gov/oc/op/goodreprint.html*; The Federal Register Notice can be found at *http://www.fda.gov/oc/op/goodreprint.html*.