FDA issues draft guidance pertaining to good reprint practices for off-label uses

Guidance will replace the safe harbor that was provided under the FDA Modernization Act.

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In February, the Food and Drug Administration issued a draft guidance document titled, *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, better known as the "draft guidance."


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The draft guidance provides recommendations to drug or device manufacturers regarding proper practices for reprinting medical literature that discusses unapproved or off-label uses for approved drugs or cleared medical devices that are sold to health care providers and entities. Here is some of the regulatory history giving rise to the draft guidance and an overview of the recommendations contained with it.

Under the Food, Drug and Cosmetic Act (FD&C Act) manufacturers are required to obtain approval of new drugs and devices prior to selling them in interstate commerce. In addition, a manufacturer must obtain approval for a specific use of such drug or device. The approved use of a product is referred to as the product's approved labeling. Increasingly, providers are discovering that drugs or devices have health treatment benefits that may not be included on their approved labeling. This does not, however, prevent a health care provider from using the drug or device for an off-label use that is part of an effective treatment regimen.

Scientific value

Manufacturers have recognized the financial benefits associated with promoting their products for off-label uses. The FDA, however, considers a product misbranded if a manufacturer promotes or markets the product for an off-label use. Accordingly, the FDA has an interest in regulating the distribution of medical literature that promotes an off-label use.

Medical literature that discusses the effectiveness of a drug or device for an off-label use clearly has scientific and literary value. Recognizing the potential benefits that may be derived from distribution of such scientific or medical literature, the FDA created a safe harbor, found at section 401 of the FDA Modernization Act ("FDAMA"), that set forth conditions under which a manufacturer could reprint literature that discussed the benefits of an off-label use. If the manufacturer satisfied the conditions the safe harbor, the FDA would not consider the reprinting of those materials as evidence of the manufacturers' intent that the product be used for an unapproved new use in violation of the FD&C Act.

In 2000, an association challenged the constitutionality of Section 401 of the FDAMA in the U.S. Court of Appeals for the District of Columbia Circuit. In that case, *Washington Legal Foundation v. Henney*, the FDA conceded that, under the First Amendment, the FDA could not prohibit a manufacturer from distributing reprints of medical or scientific publications where the manufacturer did not satisfy the safe harbor. This case left the relevance of the safe harbor in question. The safe harbor expired on Sept. 30, 2006.

"Ill advised"

With the sun setting on the safe harbor, the FDA issued the draft guidance to provide much-needed recommendations to drug and device manufacturers regarding reprinting of medical literature relating to the benefits of off-label uses; however, it was not received well by all. Shortly after its publication, Rep. Henry A. Waxman (D-Calif.), chairman of the House Oversight and Government Reform Committee, described the guidance as "ill advised" and catering to the drug industry's desire to market their products without adequate testing or review. Waxman asked FDA Commissioner Andrew C. von Eschenbach to "refrain from going forward" with the document.

Consumer advocacy groups also have opined on the guidance document. Public Citizen, a constant watchdog of the FDA, characterized the draft guidance as yet another example of the FDA's reckless and dangerous attitude toward

the protection of the public health. According to Public Citizen, the guidance document encourages drug manufacturers to promote their drugs for uses that have not been proven to be safe and effective.

Recommendations

In the draft guidance, the FDA provided recommendations on both the types of reprints and the preferred manner of dissemination.

The draft guidance indicates that any reprint of a scientific or medical journal discussing an off-label use should be published by an organization that incorporates an editorial board of experts in the relevant field who are truly independent, and who disclose any conflict of interest. In addition, the article should be peer-reviewed and not be funded by a manufacturer of a product that is the subject of the article.

Manufacturers should ensure that reprinted articles are generally available in book stores and not distributed or made available primarily by manufacturers. Moreover, the article should not be drafted for or at the request of a manufacturer, and the manufacturer should not edit or have any influence over the content of the article. The reprinted article should contain information that is based on controlled clinical investigations, and the content of the article must not be false or misleading or pose a significant risk to public health.

Manner of dissemination

In addition to providing guidance on the preferred type of reprint, the draft guidance includes recommendations on the proper manner of distribution of the information. The draft guidance provides that the reprint should: be an unabridged copy; not be summarized or emphasized by the manufacturer; include information regarding the approved labeling for the drug or device; include a bibliography; include representative publications that reach contrary conclusions; be distributed separately from promotional material; and not be distributed at promotional exhibit halls or during promotional presentations at conferences.

The draft guidance also describes several disclosures that manufacturers must make when reprinting scientific or medical journals that discuss the benefits of an off-label use. First, the reprint must include a statement that indicates that the uses discussed in the reprint are off-label. Second, the disclosure must include a statement that indicates that the manufacturer has an interest in the subject drug or device. Third, the manufacturer must state whether the author has a relevant financial interest in the subject product or the manufacturer and whether the manufacturer provided funding for the study. Fourth, the statement must disclose any person of whom the manufacturer is aware, who has provided funding for the study. Finally, the statement must indicate whether there are any relevant safety concerns that are not addressed in the reprinted article.

The draft guidance clearly fills a void left by the expiration of the safe harbor, but the question remains: Will Congress intervene with legislation or sufficient pressure to compel the FDA to withdraw the draft guidance? Physicians who author articles or participate in trials that involve off-label uses of devices or drugs should ensure that any reprint of any such article or study is at least compliant with the recommendations set forth in the draft guidance.

Comments to the draft guidance are due on April 21.

For more information:

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Reference:

- To view the draft guidance, go to www.fda.gov/oc/op/goodreprint.html.