

Unapproved New Uses: FDA Revisits Policies on Distributing Scientific Publications

In new Draft Guidance, FDA revises requirements for manufacturers' distribution of publications about off-label uses for approved drugs or devices.

On March 3, 2014, the Food and Drug Administration (FDA) released a draft guidance document, "Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices"¹ (2014 Draft Guidance), which is intended to revise FDA's 2009 Guidance on this topic.² The 2014 Draft Guidance uses the terms "unapproved new use," "unapproved use," and "off-label use" interchangeably to refer to any use of an approved or cleared drug or medical device that is not included in that product's approved labelling or cleared indications for use. FDA published the 2014 Draft Guidance in response to citizen petitions and industry requests for clarification of the 2009 Guidance and its application to medical reference texts and clinical practice guidelines (CPGs) that report on unapproved new uses of a manufacturer's products.³ The Draft Guidance recommends drug and medical device manufacturers and their representatives provide additional detailed information when distributing to health care professionals or entities (i) scientific or medical journal articles; (ii) scientific or medical reference texts; or (iii) CPGs that discuss unapproved new uses for approved drugs or devices marketed in the US. Interested parties may submit comments to the FDA about the 2014 Draft Guidance until May 2, 2014.

Background on FDA Regulation of the Distribution of Scientific Information on Unapproved New Uses

FDA estimates that approximately 400 companies distribute scientific and medical publications that discuss unapproved new uses for FDA-approved or FDA-cleared products.⁴ While physicians may exercise their professional judgment to recommend that individual patients make off-label use of a drug or device, those recommendations should not rest on anecdotal or untested scientific information. Thus, access to reliable scientific publications regarding alternate uses of such products is essential to physicians' decision-making process. However, to protect the public health, FDA generally requires premarket review and approval or clearance for each new indication and intended use of a drug or device, and prohibits drug and device manufacturers from promoting their products for unapproved or uncleared new uses. In this way, FDA ensures that appropriate scientific evidence supports each use and that this scientific information is used to develop labelling for the safe and effective use of products.

In 1997 Congress passed the Food and Drug Administration Modernization Act (FDAMA). Section 401 of FDAMA and FDA's implementing regulations at 21 C.F.R. part 99 described conditions under which manufacturers may disseminate medical and scientific information that discusses unapproved uses of approved drugs or devices to specified health care providers and entities — disseminations which the FDA would not consider to be evidence of the manufacturer's intent to promote the product for an unapproved new use.⁵ Section 401 of FDAMA required manufacturers to submit to the Secretary of FDA,

60 days prior to dissemination, a copy of the information to be disseminated and any clinical trial information that the manufacturer possessed relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use and a summary of such information. Additionally, Section 401 required manufacturers to submit a supplemental application for new use or a request for exemption from the application requirement.

Following the sunset of FDA's regulations at 21 C.F.R. Part 99, on September 30, 2006, FDA issued the 2009 Guidance on good reprint practices. Consistent with the provisions in Section 401, among other things, the 2009 Guidance provided FDA's recommendations on the type of articles or publications that were appropriate for dissemination and the manner in which the information was to be disseminated. This narrow "safe harbor" reflected FDA's recognition of the public health benefit of distributing truthful and non-misleading scientific or medical information on unapproved new uses to support a practitioner's decision to prescribe an approved product for off-label use. While FDA recognized the utility of allowing the dissemination of such information, the Agency then believed and continues to believe that this information is no substitute for FDA premarket review and approval of drugs and devices.

FDA's 2014 Draft Guidance revises the 2009 Guidance in response to stakeholder questions about its application to scientific and medical reference texts and CPGs. The 2014 Draft Guidance includes recommendations in three separate sections for the distribution of scientific and medical publications that discuss unapproved uses; one each for scientific or medical journal articles, scientific or medical references texts, and CPGs. Similar to Section 401 of FDAMA, FDA regulations and the 2009 Guidance, the new 2014 Draft Guidance balances FDA's dual interests in permitting the dissemination of reliable scientific and medical information on the off-label use of approved drugs and devices and in ensuring premarket review and approval of new indications and uses for approved drugs and devices. Consistent with longstanding FDA policy and practice, if manufacturers distribute scientific or medical publications as recommended in the guidance, FDA does not intend to use such distribution as evidence of the manufacturer's intent to promote the product for an unapproved new use.

Recommended Practices for Distributing Scientific and Medical Publications on Unapproved New Uses

The 2014 Draft Guidance describes the types of scientific and medical publications appropriate for distribution. These include publications from independent sources that meet criteria for professional/peer review; publications based on specified types of scientific evidence; and publications that are up-to-date, complete, unabridged, and which the manufacturer has not highlighted or characterized. The 2014 Draft Guidance also includes restrictions on the distribution of scientific or medical publications: the publications must not be false or misleading; and they must not contain information that recommends or suggests the use of a product that renders the product dangerous to health.

While the 2014 Draft Guidance includes specific recommendations for journal articles, reference texts and CPGs in separate sections, several of the recommendations apply to all three types of publications, including that the publications *should be*:

- Distributed separately from the delivery of information that is promotional in nature and unattached to specific product information
- Disseminated with the approved labelling for each of the manufacturer's products addressed in the publication, or in the case of a medical device reviewed under section 510(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act),⁶ labelling for the indications in the product's cleared indications for use statement

The scientific or medical publication *should not be*:

- Part of a publication funded in whole or in part by the manufacturer(s) of the product that is the subject of the article
- Primarily distributed by a manufacturer, but rather should be generally available through independent distribution channels
- Written, edited, excerpted or published specifically for, or at the request of, a manufacturer
- Edited or significantly influenced by a manufacturer or any individual with a financial relationship with the manufacturer

The scientific or medical publication, or any portion of it disseminated independently from the complete publication, *should be accompanied by* a prominently displayed and permanently affixed statement disclosing:

- Any drug or device included in the publication in which the manufacturer has an interest
- That some or all uses of the manufacturer's products described in the publication have not been approved by FDA
- Any author known to the manufacturer as having a financial interest in the manufacturer or in any of the manufacturer's products that are included in the publication or receiving any compensation from the manufacturer, and the nature and amount of any such financial relationship
- Any person known to the manufacturer who has provided funding to the study
- All significant risks or safety concerns associated with the unapproved use(s) of the manufacturer's products discussed in the publication

Scientific or Medical Journal Articles

The 2014 Draft Guidance recommends that manufacturers distribute only those scientific or medical journal articles that have been published by an organization with an editorial board that consists of independent and objective experts with demonstrated expertise in the subject of the article. The organization should also adhere to a publicly stated policy of full disclosure of any conflict of interest or biases for all associated authors, contributors and editors. Journal reprints that *do not* meet the recommended practices outlined in the draft guidance include letters to the editor, abstracts of a publication, reports of healthy volunteer studies, and publications containing conclusory statements without the evidence upon which they are based.

In addition to the recommended practices detailed above, the scientific or medical journal article *should* also meet the following criteria:

- The article should describe well-controlled clinical investigations considered scientifically sound by experts with adequate training and experience to evaluate the safety and effectiveness of the drug or device. With regard to devices, meta-analyses testing specific clinical hypotheses and articles discussing significant non-clinical research may be appropriate.

- Where available, the article should be disseminated with a comprehensive bibliography of publications discussing clinical studies published in other scientific or medical publications about the use of the drug or device covered by the information disseminated.

Scientific or Medical Reference Texts

Scientific and medical reference texts discuss a wide range of topics in a format considerably longer than journal articles. Therefore, FDA included additional recommended practices that apply specifically to scientific and medical reference texts. The reference text *should be*:

- Based on a systematic review of existing evidence
- Authored, edited, and/or contributed to by experts who have demonstrated expertise in the subject area
- Be sold through usual and customary independent distribution channels (*e.g.* booksellers, subscription, Internet) for medical and scientific education content directed at health care professionals and students

If a manufacturer distributes an individual chapter or portion of a scientific or medical text, the portion *should*:

- Come from a scientific or medical publication that follows the recommendations in the 2014 Draft Guidance for complete scientific or medical publications
- Be unaltered/unabridged and extracted directly from the scientific or medical reference text in which it appears
- When necessary to provide context, be disseminated with other unaltered/unabridged chapters extracted directly from the same publication, such as chapters that provide related or supportive information

Clinical Practice Guidelines

Clinical Practice Guidelines assist clinicians in making decisions for individual patient care, including in situations where there are few or no approved drugs or devices indicated for a patient's condition or where approved therapies have not proven successful for the individual. Similar to reference texts, CPGs are generally longer and more detailed than journal articles. FDA therefore included recommended practices specific to CPGs. These include additional recommendations that incorporate the Institute of Medicine's (IOM's) standards for CPG "trustworthiness."⁷ These "trustworthiness" standards ensure that CPGs reflect a systematic review of evidence and an assessment of the benefits and harms of care options.

In order to disseminate CPGs that are "trustworthy," manufacturers *should* distribute only those CPGs that:

- Are based on a systematic review of existing evidence
- Are developed by multidisciplinary experts and representatives from key affected groups, and through an explicit and transparent process that minimizes distortions, biases, and conflicts of interest.
- Consider important patient subgroups and preferences

- Provide (i) a clear explanation of the logical relationships between alternative care options and health outcomes; (ii) clearly articulated recommendations in standardized form; and (iii) quality ratings and evidence of the strength of recommendations
- Are reconsidered and revised when new evidence warrants modification

Comments and Industry Response

Thus far, the reaction to the draft guidance has been mixed. Some stakeholders have lauded FDA's attempt to offer clarity, arguing that the 2014 Draft Guidance empowers manufacturers to distribute truthful and useful information.⁸ Supporters have also noted that the guidance enables more efficient communication between regulated companies and health care professionals, leading to more effective patient care.⁹ However, others wonder whether the burden imposed as a result of FDA's recommended practices would make distribution of scientific or medical publications on unapproved new uses worth the risk of noncompliance.¹⁰ This skepticism arises from the fact that, to comply with the recommended practices, manufacturers must provide a significant amount of information with the publications they are distributing. As a result, physicians must wade through these details to arrive at the relevant information on off-label uses. Whether or not industry will take substantial advantage of the 2014 Draft Guidance or, despite asking for clarity, opt out of distributing publications on unapproved new uses of drugs and devices remains to be seen.

FDA has requested that comments regarding the 2014 Draft Guidance be submitted by May 2, 2014 to ensure the Agency can consider them before beginning work on the final guidance.¹¹ As part of its ongoing effort to address questions related to the 2014 Draft Guidance, the Agency also requested comments on several additional issues, including (1) further explaining the concept of "scientific exchange"; (2) developing guidance on how manufacturers should respond to unsolicited requests for information relating to unapproved or uncleared uses of drugs or devices; and (3) providing draft guidance on industry interactions with formulary committees, payors and similar entities.

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Endnotes

- ¹ FDA, "Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices" (Revised Draft Feb. 2014), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf>.
- ² FDA, "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" (Jan. 2009), *available at* <http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm>.
- ³ The citizen petitions requested clarification on FDA's approach to the distribution of scientific and medical information reflecting unapproved or unapproved uses. The petitions also included specific requests for action from FDA, such as issuance or revision of regulations. FDA has not yet reached a final determination on the petitions. 79 Fed. Reg. 11793.
- ⁴ 79 Fed. Reg. 11796.
- ⁵ 21 U.S.C. § 360aaa.
- ⁶ 21 U.S.C. § 360(k).
- ⁷ Robin Graham, et al., "Clinical Practice Guidelines We Can Trust," Institute of Medicine of the National Academies, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines (2011), *available at* http://www.awmf.org/fileadmin/user_upload/Leitlinien/International/IOM_CPG_lang_2011.pdf.
- ⁸ David Pittman, "Off-Label Use? FDA Has a Plan for Spreading that Word," MedPage Today Public Health & Policy (Mar. 4, 2014), *available at* <http://www.medpagetoday.com/PublicHealthPolicy/FDAGeneral/44602>.
- ⁹ Thomas Sullivan, "FDA Draft Guidance: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices," Policy and Medicine (Mar. 4, 2014), *available at* <http://www.policymed.com/2014/03/fda-draft-guidance-distributing-scientific-and-medical-publications-on-unapproved-new-uses-recommended-practices.html>.
- ¹⁰ Jeannie Baumann, "FDA Draft May Replace 2009 Guidance On Printed Materials for Off-Label Uses," Bloomberg BNA Life Sciences Law & Industry Report (Mar. 3, 2014).
- ¹¹ 79 Fed. Reg. 11793.