

FDA Seeks Public Comment on Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices

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March 2014

On March 3, 2014, the U.S. Food and Drug Administration (“FDA”) made available for comment a revised draft of its “Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices” (“Revised Draft Guidance”).¹ The Revised Draft Guidance explains FDA’s current thinking on the recommended practices that drug and device manufacturers should follow when distributing scientific or medical publications that discuss unapproved new uses for either approved drugs or approved or cleared medical devices to health care professionals and health care entities.² The Revised Draft Guidance clarifies and expands on FDA’s 2009 “Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific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and Approved or Cleared Medical Devices” (“2009 Guidance”).³ FDA is seeking comments and suggestions on the Revised Draft Guidance. **To ensure that FDA considers such comments and suggestions before it begins working on the final version of the guidance, all comments and suggestions must be submitted in either electronic or written form by May 2, 2014.**⁴

Notably, the Revised Draft Guidance responds to industry’s calls for a means by which manufacturers can distribute clinical practice guidelines that discuss off-label uses of their products without that distribution being deemed evidence of the manufacturers’ intent that the product be used for an unapproved indication. Additionally, the Revised Draft Guidance

¹ 79 Fed. Reg. 11793 (March 3, 2014).

² U.S. Food & Drug Admin., Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices (Feb. 2014) (hereinafter “Revised Draft Guidance”), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf> (last visited Mar. 4, 2014).

³ 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 (Jan. 2009) (hereinafter “2009 Guidance”), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> (last visited March 4, 2014).

⁴ See *id.* Electronic comments must be submitted to <http://www.regulations.gov>. Written comments must be submitted to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

reorganizes, clarifies, and, in some instances, provides more specific guidance on recommendations made in the 2009 Guidance. The Revised Draft Guidance also reiterates FDA's position that, despite a ruling by the U.S. Court of Appeals for the Second Circuit in *United States v. Caronia*,⁵ the First Amendment does not prohibit FDA from using even truthful, non-misleading, off-label speech by manufacturers as evidence in enforcement actions. Specifically, in *Caronia*, the Second Circuit "decline[d] to adopt [FDA's] construction of the [Federal Food, Drug, and Cosmetic Act's ("FD&C Act's")] misbranding provisions to prohibit manufacturer promotion alone" and instead held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the [FD&C Act] for speech promoting the lawful, off-label use of an FDA-approved drug."⁶

Background

Recognizing the value to the public health that results from the dissemination of medical journals and scientific and medical reference texts, FDA published the 2009 Guidance "to provide drug and medical device manufacturers . . . with recommendations on distributing scientific or medical information on unapproved uses to health care professionals and health care entities, without such dissemination being considered as evidence of the manufacturer's intent that the product be used for an unapproved new use."⁷ Following issuance of the 2009 Guidance, industry continued to request additional clarification from FDA, both formally and informally. In response to such requests, FDA issued the Revised Draft Guidance.⁸ Specifically, the Revised Draft Guidance:

- 1) clarifies its earlier recommendations with respect to the dissemination of scientific or medical journal articles and scientific or medical reference texts, and
- 2) expands the scope of scientific and medical publications to which its recommendations apply to include clinical practice guidelines ("CPGs").

Clarifications to Existing Guidance

The Revised Draft Guidance attempts to clarify existing guidance with respect to FDA's recommended practices. The Revised Draft Guidance also offers separate recommendations for disseminating scientific and medical journal articles and scientific and medical reference texts, and new recommendations with respect to each of these types of publications.

A. Scientific or Medical Journal Articles

In general, the Revised Draft Guidance reiterates FDA's recommendations for dissemination of scientific or medical journal articles that were included in the 2009 Guidance. However, a few notable exceptions are:

- Underlying Research. FDA clarifies that, with respect to medical devices, dissemination of journal articles discussing "significant investigations other than adequate and well-controlled studies and non-clinical research" may be consistent with FDA's

⁵ 703 F. 3d 149 (2d Cir. 2012).

⁶ *Caronia* at 168-69.

⁷ See Revised Draft Guidance, *supra* note 2 at 6.

⁸ See *id.*

recommendations.⁹ However, with respect to drugs, FDA did not state that the dissemination of articles discussing such studies would be consistent with the Revised Draft Guidance.

- Information Making the Product Dangerous. The 2009 Guidance stated that the disseminated articles must not include information that would “pose a significant risk to the public health, if relied upon.”¹⁰ However, the Revised Draft Guidance updates this such that it recommends that the scientific or medical journal article must not “[c]ontain information recommending or suggesting use of the product that makes the product dangerous to health when used in the manner suggested.”¹¹ The updated language mirrors Section 502(j) of the FD&C Act, pursuant to which a drug will be deemed to be misbranded “[i]f it is dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended or suggested in the labeling thereof.”¹² Mirroring the language used in the misbranding statute may be an acknowledgement by FDA that the First Amendment does impose certain limits on its authority. If it seeks to use speech as evidence of misbranding, FDA is more likely to withstand a First Amendment challenge if it is able to directly link the speech with an activity expressly prohibited by the FD&C Act.¹³

Marking, Highlighting, Summarizing, or Characterizing Scientific or Medical Journal Articles. The Revised Draft Guidance is more permissive with respect to marking, highlighting, summarizing, or characterizing scientific or medical journal articles, allowing such activities so long as they do not emphasize or promote an unapproved use (in writing or orally).¹⁴ Although this change appears to be an acknowledgement of certain of the limitations imposed by the *Caronia* decision on FDA’s ability to use truthful, non-misleading speech as a basis for enforcement of FD&C Act violations, manufacturers should still proceed with caution when highlighting, summarizing, or characterizing articles that discuss unapproved uses. FDA may still be able to use such activities as evidence in an enforcement action, even if, pursuant to *Caronia*, such activities alone cannot support an enforcement action. Additionally, such activities may be used to support civil actions brought under the federal False Claims Act, on the basis that such activities cause the submission of a false claim.

- Attachment to Specific Product Information. The Revised Draft Guidance adds a specific limitation that the articles should not be attached to specific product information, other than the approved product labeling or the cleared indications for use statement.¹⁵ This statement is consistent with other recommendations in both the 2009 Guidance and the Revised Draft Guidance that articles should not be distributed with promotional

⁹ See *id.* (stating, “In the case of *devices*, significant investigations other than adequate and well-controlled studies, such as meta-analyses, if they are testing a specific clinical hypothesis, and journal articles discussing significant non-clinical research (such as well-designed bench or animal studies) may be consistent with this guidance.” (emphasis added)); See 2009 Guidance, *supra* note 3 (stating, “These can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a specific clinical hypothesis.”)

¹⁰ See 2009 Guidance, *supra* note 3.

¹¹ See Revised Draft Guidance, *supra* note 2 at 8.

¹² FD&C Act §502(j).

¹³ This may be another example of FDA attempting to address some of the deficiencies that the Second Circuit noted in *Caronia*, primarily that the FD&C Act “and its accompanying regulations do not expressly prohibit or criminalize off-label promotion.” *Caronia* at 160.

¹⁴ See 2009 Guidance, *supra* note 3; see Revised Draft Guidance, *supra* note 2 at 9.

¹⁵ See Revised Draft Guidance, *supra* note 2 at 9.

materials. Notably, the example provided by FDA appears to reinforce the current practice of many manufacturers limiting the discussion of disseminated reprints by sales representatives to statements demonstrating “limited familiarity” with the article, such as the title, author, and journal in which it was published, and the hypotheses that were tested, and referring any substantive discussions of the reprint’s content to the manufacturer’s scientific or medical personnel.

B. Scientific or Medical Reference Texts

Recognizing the differences between scientific or medical reference texts and journal articles (i.e., generally reference texts are longer and address a wider range of topics),¹⁶ the Revised Draft Guidance provides separate recommendations with respect to scientific or medical reference texts. However, FDA recommendations for the dissemination of scientific or medical reference texts are substantially similar to the journal reprint recommendations, and many of the differences are not substantive.¹⁷

Nonetheless, there are a few substantive differences. This section of the Revised Draft Guidance includes new guidance permitting manufacturers to disseminate an individual chapter or chapters of a reference text, rather than calling for the distribution of the reference text in its entirety, as required by the 2009 Guidance. This new means of dissemination is subject to specific recommendations for the dissemination of an individual chapter or chapters, including the following:¹⁸

- If a manufacturer is disseminating an individual chapter or chapters, those chapters should be unaltered and/or unabridged and extracted directly from the scientific or medical reference text in which they appear.¹⁹ Additionally, the manufacturer should include other unaltered and/or unabridged chapters from the same text that provide context, such as related or supportive information.²⁰
- If a manufacturer is disseminating an individual chapter or chapters, the manufacturer would also need to disseminate the approved labeling or cleared indications for use for each product discussed in the individual chapter or chapters.

When disseminating either entire texts or individual chapters, the Revised Draft Guidance specifies that the required manufacturer disclosures should be placed by “sticker, stamp, or other similar means”²¹ on the front cover or front page of each text or chapter.

In general, if an entire text is disseminated, and the required manufacturer disclosures are affixed to the cover of the text, FDA will not expect manufacturers “to have reviewed every element of the reference text to identify discussions of off-label uses of their products.”²² However, if entire chapters of the reference text devote primary substantive discussion to the products of the manufacturer, then the reference text must also be disseminated with the

¹⁶ See Revised Draft Guidance, *supra* note 2 at 10.

¹⁷ For example, the recommendations contemplate how and where the required information should be affixed to the reference text and the need to attach approved labeling or cleared indications for use for each product referenced in the reference text or individual chapter(s) disseminated.

¹⁸ See Revised Draft Guidance, *supra* note 2 at 10 and 12.

¹⁹ See *id.* at 12.

²⁰ See *id.*

²¹ See Revised Draft Guidance, *supra* note 2 at 11 and 13.

²² See *id.* at FN 31.

approved product labeling or cleared indications for use for each product discussed, as required for journal articles.²³

Expansion to Include Clinical Practice Guidelines

Unlike the 2009 Guidance, the Revised Draft Guidance includes specific recommendations regarding the dissemination of CPGs.²⁴ In general, the recommendations related to the dissemination of CPGs are similar to FDA's recommendations for the dissemination of scientific or medical reference texts. However, there are two significant differences with respect to CPGs:

- The Revised Draft Guidance recommends that manufacturers should disseminate only those CPGs that are considered “trustworthy” and establishes six minimum requirements, which are based on standards developed by the Institute of Medicine (“IOM”),²⁵ that CPGs should satisfy in order to be considered “trustworthy.” Specifically, a CPG *should*:
 - 1) be based on a systematic review of the existing evidence;
 - 2) be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups;
 - 3) consider important patient subgroups and patient preferences;
 - 4) be based on an explicit and transparent (publicly accessible) process by which the CPG is developed and funded that minimizes distortions, biases, and conflicts of interest;
 - 5) provide a clear explanation of the logical relationships between alternative care options and health outcomes, provide clearly articulated recommendations in standardized form, and provide ratings of both quality of evidence and the strength of recommendations; and
 - 6) be reconsidered and revised when important new evidence warrants modifications of recommendations.²⁶
- Although manufacturers may distribute either the entire CPG or an individual section or sections of a CPG, CPGs that address only one disease state should be disseminated in their entirety.²⁷

²³ See *id.* at 11-12.

²⁴ Defined as “statements that include recommendations intended to help clinicians make decisions for individual patient care, including circumstances where there are few or no approved drugs or devices indicated for the patient’s condition or the approved therapies have not proven successful for the individual.” See *id.* at 14.

²⁵ See *id.* (FDA has incorporated IOM’s standards for CPG “trustworthiness” directly from IOM’s report: Robin Graham, et al., Institute of Medicine of the National Academies, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, *Clinical Practice Guidelines We Can Trust* (2011)).

²⁶ See *id.* at 14-15.

²⁷ See *id.* at FN 40.

Compliance Considerations

Although the Revised Draft Guidance is not yet final, it represents a useful reference for manufacturers to assess their current compliance efforts with respect to where FDA may ultimately exercise its discretion regarding reprint or reference material dissemination. Manufacturers should carefully review the Revised Draft 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 FDA.

Concurrent with evaluating the Revised Draft Guidance for purposes of comment submission, each manufacturer may want to consider the following issues when evaluating its current reprint and reference material dissemination policies:

- What changes to the manufacturer's standard operating procedures ("SOPs") governing the review and approval of reprints and accompanying materials that are intended for distribution will need to be made to address the key issues identified in the Draft Revised Guidance?
- Will any changes need to be made to ensure that each of the manufacturer's review committees responsible for approval of product-related communications has the training and expertise to properly evaluate whether a CPG is "trustworthy"?
- Will changes to the manufacturer's SOPs governing the dissemination of reprints by sales representatives be required to address the new recommendations set forth in the Draft Revised Guidance?

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*This Client Alert was authored by **Amy K. Dow**, **Ryan R. Benz**, and **Daniel G. Gottlieb**. For additional information about the issues discussed in this Client Alert, please contact one of the authors or the Epstein Becker Green attorney who regularly handles your legal matters.*

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