

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

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

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Guidance for Industry

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This guidance document represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You may use an alternative approach if the approach satisfies the

requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, please contact the appropriate FDA staff.

I. Introduction

This guidance is intended to describe the Food and Drug Administration's (FDA or Agency) current thinking regarding "Good Reprint Practices" with regard to the distribution by a drug or medical device manufacturer (or representative)¹ of medical journal articles and scientific or medical reference publications (referred to generally as medical and scientific information) that discuss unapproved new uses² for approved drugs³ or approved or cleared medical devices marketed in the United States to healthcare professionals and healthcare entities.⁴

FDA's guidance documents do not establish legally enforceable rights or responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Section 401 of the Food and Drug Administration Modernization Act (FDAMA) (21 U.S.C. § 360aaa, § 551, Federal Food, Drug, and Cosmetic Act (FD&C Act)), described certain conditions under which a drug or medical device manufacturer could choose to disseminate medical and scientific information discussing unapproved uses of approved drugs and cleared or approved medical devices to healthcare professionals and certain entities (including pharmacy benefits managers, health insurance issuers, group health plans, and Federal or State governmental agencies). FDAMA section 401 provided that, if these conditions were met, dissemination of such journal articles or reference publications would not be considered as evidence of the manufacturer's intent that the product be used for an unapproved new use. FDA implementing regulations were codified at 21 CFR Part 99.

In 2000, subsequent to a decision by the United States Court of Appeals for the District of Columbia Circuit, FDA published a Notice (65 Fed. Reg. 14286, March 16, 2000) clarifying the applicability of the FDAMA section 401 provision and the FDA implementing regulations. In that Notice, FDA stated that the statute and implementing regulations constituted a "safe harbor" for a manufacturer that complies with them before and while disseminating journal articles and reference publications about "unapproved new uses" of approved or cleared products. If a manufacturer complied with the FDAMA provision, the distribution of such journal articles or reference publications would not be used as evidence of an intent that the product distributed by the manufacturer be used for an unapproved use.

The Notice also stated that if a manufacturer chose to disseminate materials but not proceed under FDAMA section 401, that failure would not constitute an independent violation of law but could be used as evidence of a manufacturer's intent that the product be used for an unapproved use.

FDAMA section 401 ceased to be effective on September 30, 2006, and the implementing regulations are no longer applicable. In light of the statute's sunset, FDA is providing its current views on the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities.

III. Purpose

As explained in FDA's March 16, 2000 Notice, the FD&C Act and FDA's implementing regulations generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective or cleared through a substantial equivalence determination (e.g., FD&C Act §§ 505(a), 502(o), 501(f)(1)(B), 301(a) and (d); 21 U.S.C. §§ 355, 352(o), 351(f)(1)(B), 331(a) and (d)). The Agency recognizes the value of having new indications and intended uses for products approved or cleared by FDA and encourages sponsors of medical products to seek such approvals or clearances. An approved new drug that is marketed for an unapproved use is an unapproved new drug with respect to that use. (FD&C Act §§ 505(a), 301(d), 21 U.S.C. 355(a), 331(d)). An approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include "adequate directions for use" (FD&C Act § 502(f); 21 U.S.C. § 352(f); 21 CFR 201.100(c)(1)). Similarly, a medical device that is promoted for a use that has not been approved or cleared by FDA is adulterated and misbranded.

FDA does recognize, however, the important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities. Once a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses). These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading.

FDA's legal authority to determine whether distribution of medical or scientific information constitutes promotion of an unapproved "new use," or whether such activities cause a product to violate the FD&C Act has not changed. In recognition of the public health value to

healthcare professionals of receiving truthful and non-misleading scientific and medical information, FDA is providing recommendations concerning "Good Reprint Practices" for the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of drugs and medical devices.⁵

IV. Agency Recommendations for Good Reprint Practices

Scientific and medical information that concerns the safety or effectiveness of an approved drug or approved or cleared medical device for an unapproved new use that is not included in the product's approved labeling or statement of intended uses (including unapproved new uses of approved drugs and approved or cleared devices) is often published in journal articles or reference publications. These publications are often distributed by manufacturers to healthcare professionals or healthcare entities. When a manufacturer disseminates such medical and scientific information, FDA recommends that the following principles of "Good Reprint Practices" be followed.

A. Types of Reprints/Articles/Reference Publications

A scientific or medical journal article that is distributed should:

- be published by an organization that has an editorial board that uses experts who have demonstrated expertise in the subject of the article under review by the organization and who are independent of the organization to review and objectively select, reject, or provide comments about proposed articles; and that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization;
- be peer-reviewed and published in accordance with the peer-review procedures of the organization; and
- not be in the form of a special supplement or publication that has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article.

A scientific or medical reference publication that is distributed should not be:

- primarily distributed by a drug or device manufacturer, but should be generally available in bookstores or other independent distribution channels (e.g. subscription, Internet) where medical textbooks or periodicals are sold;
- written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer; or
- edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.

The information contained in the scientific or medical journal article or reference publication should address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device. These can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a specific clinical hypothesis.⁶

The information must not:

- be false or misleading. For example, a distributed journal article or reference text 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 a significant number of other studies contradict the article or reference text's conclusions; should not have been withdrawn by the journal or disclaimed by the author; and should not discuss a clinical investigation where FDA has previously informed the company that the clinical investigation is not adequate and well-controlled; or
- pose a significant risk to the public health, if relied upon.

The following publications are examples of publications that would not be considered consistent with the "Good Reprint Practices" outlined in this guidance:

- letters to the editor;
- abstracts of a publication;
- reports of Phase 1 trials in healthy subjects; or
- reference publications that contain little or no substantive discussion of the relevant investigation or data.

B. Manner in which to Disseminate Scientific and Medical Information

Scientific or medical information that is distributed should:

- be in the form of an unabridged reprint, copy of an article, or reference publication;
- not be marked, highlighted, summarized, or characterized by the manufacturer in any way (except to provide the accompanying disclosures discussed in this section);
- be accompanied by the approved labeling for the drug or medical device;
- be accompanied, when such information exists, by a comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in medical journals 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);
- be disseminated with a representative publication, when such information exists, that reaches contrary or different conclusions regarding the unapproved use; especially those in cases where the conclusions of articles or texts to be disseminated have been specifically called into question by another published article(s) or text(s); and
- be distributed separately from information that is promotional in nature. For example, if a sales representative delivers a reprint to a physician in his office, the reprint

should not be physically attached to any promotional material the sales representative uses or delivers during the office visit and should not be the subject of discussion between the sales representative and the physician during the sales visit.⁷ Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers' programs.

The journal reprint or reference publication should be accompanied by a prominently displayed and permanently affixed statement disclosing:

- that the uses described in the information have not been approved or cleared by FDA, as applicable to the described drug or medical device;
- the manufacturer's interest in the drug or medical device that is the subject of the journal reprint or reference text;
- any author known to the manufacturer as having a financial interest in the product or manufacturer or who is receiving compensation from the manufacturer, along with the affiliation of the author, to the extent known by the manufacturer, and the nature and amount of any such financial interest of the author or compensation received by the author from the manufacturer;⁸
- any person known to the manufacturer who has provided funding for the study; and
- all significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the journal article or reference text.

V. Summary

FDA recognizes that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products. Accordingly, if a manufacturer follows the recommendations described in Section IV of this guidance, FDA does not intend to consider the distribution of such medical and scientific information in accordance with the recommendations in this guidance as establishing intent that the product be used for an unapproved new use.⁹ However, if a manufacturer engages in other conduct that unlawfully promotes an unapproved use of a medical product -- whether or not the manufacturer also engages in conduct in conformance with the recommendations in this guidance -- such other conduct may result in enforcement action.

Footnotes

¹ As used in this guidance, the term "manufacturer" means a person who manufactures a drug or device or who is licensed by such person to distribute or market the drug or device. The term may also include the sponsor of the approved, licensed, or cleared drug or device.

² The terms "unapproved new use", "unapproved use", and "off-label use" are used interchangeably in this guidance to refer to a use of an approved or cleared medical product that is not included in the product's approved labeling or statement of intended uses.

³ As used in this guidance, the terms "drug" and "device" includes biological products licensed under Section 351(a) of the Public Health Service Act. *See* 42 U.S.C. § 262(j).

⁴ "Healthcare entity" includes hospitals, professional medical organizations, drug formulary committees, and health plans.

⁵ FDA has elsewhere stated its views on the dissemination of information regarding unapproved uses in response to requests for scientific or medical information initiated solely by health care professionals. Such prior FDA statements include: 62 Fed. Reg. 64073, 64086, 64091(December 3, 1997), Guidance for Industry, *Industry-Supported Scientific and Educational Activities*, (November 1997) at 64099, available at <http://www.fda.gov/cder/guidance/isse.htm> and 59 Fed. Reg. 59820, 59823 (November 18, 1994).

⁶ In the case of medical devices, journal articles or reference publications discussing significant non-clinical research may be consistent with this guidance.

⁷ To the extent that the recipients of such information have questions, the sales representative should refer such questions to a medical/scientific officer or department (see footnote 5), and the officer or department to which the referral is made should be separate from the sales and/or marketing departments.

⁸ For purposes of this recommendation, an "author" includes any individual, whether credited in the publication or not, who meets the standards for authorship set forth in the guidelines of the International Committee on Medical Journal Editors' *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication*, section II.A.

⁹ Given the sunset of FDAMA § 401, the other elements that comprised § 401 which are not specifically described in this guidance are no longer applicable.