

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

DRAFT GUIDANCE

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For single copies of this draft guidance, please contact: Office of Policy, Food and Drug Administration, 5600 Fishers Lane, rm. 14-101, HF-11, Rockville, MD 20857, (301) 827-3360.

For questions regarding this draft document, contact Scott D. Danzis, Office of the General Counsel, Food and Drug Division, (301) 827-8570.

~~U.S. Department of Health and Human Services~~
~~Food and Drug Administration~~

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I. Introduction

This draft guidance is intended to describe the Food and Drug Administration's (FDA or Agency) current thinking regarding "Good Reprint Practices" with regard to the distribution of medical journal articles and scientific or medical reference publications (referred to generally as medical and scientific information) that discuss unapproved new uses for approved drugs¹ or approved or cleared medical devices marketed in the United States to healthcare professionals and healthcare entities.

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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 manufacturer² could choose to disseminate

¹ As used in this draft guidance, the term "drug" includes biological products licensed under Section 351(a) of the Public Health Service Act. See 42 U.S.C. § 262(j).

² As used in this draft guidance, the term "manufacturer" means a person who manufactures a drug or device or who is licensed by such person to distribute or market the drug or device.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.

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1 medical and scientific information discussing unapproved uses of approved drugs and cleared or
2 approved medical devices to healthcare professionals and certain entities (including pharmacy
3 benefits managers, health insurance issuers, group health plans, and Federal or State
4 governmental agencies). FDAMA section 401 provided that, if these conditions were met,
5 dissemination of such journal articles or reference publications would not be considered as
6 evidence of the manufacturer's intent that the product be used for an unapproved new use. FDA
7 implementing regulations were codified at 21 C.F.R. Part 99.

8
9 In 2000, subsequent to a decision by the United States Court of Appeals for the District of
10 Columbia Circuit, FDA published a Notice (65 Fed. Reg. 14286, March 16, 2000) clarifying the
11 applicability of the FDAMA section 401 provision and the FDA implementing regulations. In
12 that Notice, FDA stated that the statute and implementing regulations constituted a “safe
13 harbor” for a manufacturer that complies with them before and while disseminating journal
14 articles and reference publications about “new uses” of approved or cleared products. If a
15 manufacturer complied with the FDAMA provision, the distribution of such journal articles or
16 reference publications would not be used as evidence of an intent that the product distributed by
17 the manufacturer be used for an unapproved use. The Notice stated that if a manufacturer chose
18 to disseminate materials but not proceed under FDAMA section 401, that failure would not
19 constitute an independent violation of law.

20
21 FDAMA section 401 ceased to be effective on September 30, 2006, and the implementing
22 regulations are no longer applicable. In light of the statute’s sunset, FDA is providing its current
23 views on the dissemination of medical journal articles and medical or scientific reference
24 publications on unapproved uses of approved drugs and approved or cleared medical devices to
25 healthcare professionals and healthcare entities.

26 27 **III. Purpose**

28
29 As explained in FDA’s March 16, 2000 Notice, the FD&C Act and FDA’s implementing
30 regulations generally prohibit manufacturers of new drugs or medical devices from distributing
31 products in interstate commerce for any intended use that FDA has not approved as safe and
32 effective or cleared through a substantial equivalence determination. (E.g., FD&C Act
33 §§ 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)
34 and (d)). An approved new drug that is marketed for an unapproved use becomes misbranded
35 and an unapproved new drug with respect to that use. Similarly, a medical device that is
36 promoted for a use that has not been approved or cleared by FDA is adulterated and misbranded.

37
38 However, FDA does, however, recognize the important public policy reasons for allowing
39 manufacturers to disseminate truthful and non-misleading medical journal articles and medical or
40 scientific reference publications on unapproved uses of approved drugs and approved or cleared
41 medical devices to healthcare professionals and healthcare entities. Once a drug or medical
42 device has been approved or cleared by FDA, generally healthcare professionals may lawfully
43 use or prescribe that product for uses or treatment regimens that are not included in the product's

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1 approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the
2 product's statement of intended uses). These off-label uses or treatment regimens may be
3 important and may even constitute a medically recognized standard of care. Accordingly, the
4 public health may be advanced by healthcare professionals' receipt of medical journal articles
5 and medical or scientific reference publications on unapproved or new uses of approved or
6 cleared medical products that are truthful and not misleading.

7
8 FDA's legal authority to determine whether distribution of medical or scientific information
9 constitutes promotion of an unapproved "~~new use,~~" or whether such activities cause a product
10 to be misbranded or adulterated has not changed. ~~However, in~~ recognition of the public health
11 value to healthcare professionals of receiving truthful and non-misleading scientific and medical
12 information, FDA is providing recommendations concerning "Good Reprint Practices" for the
13 dissemination of medical journal articles and medical or scientific reference publications on
14 unapproved uses of drugs and medical devices.³

15
16 **IV. Agency Recommendations for Good Reprint Practices**

17
18 Scientific and medical information that concerns the safety or effectiveness of an approved drug
19 or approved or cleared medical device for a new use that is not included in the product's
20 approved labeling or statement of intended uses (including unapproved or new uses of approved
21 drugs and approved or cleared devices) is often published in journal articles or reference
22 publications. These publications are often distributed by manufacturers to healthcare
23 professionals or healthcare entities. When a manufacturer disseminates such medical and
24 scientific information, FDA recommends that the following principles of "Good Reprint
25 Practices" be followed.

26
27 **A. *Types of Reprints/Articles/Reference Publications***

28
29 A scientific or medical journal article that is distributed should:

- 30 ▪ be published by an organization that has an editorial board, that uses experts who have
31 demonstrated expertise in the subject of the article under review by the organization and
32 who are independent of the organization to review and objectively select, reject, or
33 provide comments about proposed articles, and that has a publicly stated policy, to which
34 the organization adheres, of full disclosure of any conflict of interest or biases for all
35 authors, contributors, or editors associated with the journal or organization;
- 36 ▪ be peer-reviewed and published in accordance with the peer-review procedures of the
37 organization; and

³ This draft guidance does not apply to scientific or medical information distributed in response to unsolicited requests for scientific or medical information from health care professionals. See 59 Fed. Reg. 59820, 59823 (November 18, 1994).

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- 1 ▪ not be in the form of a special supplement or publication that has been funded in whole or
2 in part by one or more of the manufacturers of the product that is the subject of the
3 article.

4
5 A scientific or medical reference publication that is distributed should not be:

- 6 ▪ primarily distributed by a drug or device manufacturer, but should be generally available
7 in bookstores or other independent distribution channels where medical textbooks are
8 sold;
9 ▪ written, edited, excerpted, or published specifically for, or at the request of, a drug or
10 device manufacturer; or
11 ▪ edited or significantly influenced by a drug or device manufacturer or any individuals
12 having a financial relationship with the manufacturer.

13
14 The information contained in the above scientific or medical journal article or reference
15 publications should:

16 address adequate and well-controlled clinical investigations that are considered scientifically
17 sound by experts with scientific training and experience to evaluate the safety or effectiveness of
18 the drug or device⁴. ~~The information must not:~~

- 19 ▪ ~~not be false or misleading, such as a journal article or reference text that is inconsistent~~
20 with the weight of credible evidence derived from adequate and well-controlled clinical
21 investigations (e.g., where a significant number of other studies contradict the article or
22 reference text's conclusions), that has been withdrawn by the journal or disclaimed by the
23 author, or that discusses a clinical investigation where FDA has previously informed the
24 company that the clinical investigation is not adequate and well-controlled; and
25 ▪ ~~not pose a significant risk to the public health.~~

26
27 The following publications are examples of publications that would not be considered consistent
28 with the Good Reprint Practices outlined in this draft guidance:

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

34
35 ***B. Manner in which to Disseminate Scientific and Medical Information***

36
37 Scientific or medical information that is distributed should:

- 38 ▪ be in the form of an unabridged reprint, copy of an article, or reference publication;
39 ▪ not be marked, highlighted, summarized, or characterized by the manufacturer in any
40 way;

⁴ In the case of medical devices, journal articles or reference publications discussing significant non-clinical research may be consistent with this draft guidance.

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- 1 ▪ be accompanied by the approved labeling for the drug or medical device;
- 2 ▪ be accompanied by a comprehensive bibliography of publications discussing adequate
- 3 and well-controlled clinical studies published in a medical journal or medical or scientific
- 4 text that have been previously published about the use of the drug or medical device
- 5 covered by the information disseminated (unless the information already includes such a
- 6 bibliography);
- 7 ▪ in cases where the conclusions of article or text to be disseminated have been specifically
- 8 called into question by another article(s) or text(s), be disseminated with a representative
- 9 publication that reaches contrary or different conclusions regarding the unapproved use;
- 10 and
- 11 ▪ be distributed separately from information that is promotional in nature. For example, if
- 12 a sales representative delivers a reprint to a physician in his office, the reprint should not
- 13 be physically attached to any promotional material the sales representative uses or
- 14 delivers during the office visit and should not be the subject of discussion between the
- 15 sales representative and the physician during the sales visit.⁵ Similarly, while reprints
- 16 may be distributed at medical or scientific conferences in settings appropriate for
- 17 scientific exchange, reprints should not be distributed in promotional exhibit halls or
- 18 during promotional speakers' programs.

19
20 The journal reprint or reference publication should be accompanied by a prominently displayed
21 and permanently affixed statement disclosing:

- 22 ▪ that the uses described in the information have not been approved or cleared by FDA, as
- 23 applicable to the described drug or medical device;
- 24 ▪ the manufacturer's interest in the drug or medical device that is the subject of the journal
- 25 reprint or reference text;
- 26 ▪ any author known to the manufacturer as having a financial interest in the product or
- 27 manufacturer or receiving compensation from the manufacturer, if applicable;
- 28 ▪ any person known to the manufacturer who has provided funding for the study, if
- 29 applicable; and
- 30 ▪ any significant risks or safety concerns known to the manufacturer concerning the
- 31 unapproved use that are not discussed in the journal article or reference text.

32 33 **V. Summary**

34
35 FDA recognizes that the public health can be served when health care professionals receive
36 truthful and non-misleading scientific and medical information on unapproved uses of approved
37 or cleared medical products. Accordingly, if a manufacturer follows the recommendations
38 described in Section IV of this draft guidance and there is no unlawful promotion of the product,

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

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- 1 FDA does not intend to use the distribution of medical and scientific information as evidence of
2 an intent by the manufacturer that the product be used for an unapproved use.⁶

⁶ Given the sunset of FDAMA § 401, the other elements that comprised § 401 which are not specifically described in this draft guidance are no longer applicable.