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

REVISED DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)**

**February 2014
Procedural**

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

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1 **Distributing Scientific and Medical Publications on Unapproved**
2 **New Uses — Recommended Practices¹**
3
4

5
6 This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s)
7 current thinking on this topic. It does not create or confer any rights for or on any person and
8 does not operate to bind FDA or the public. You can use an alternative approach if the approach
9 satisfies the requirements of the applicable statutes and regulations. If you want to discuss an
10 alternative approach, contact the FDA staff responsible for implementing this guidance. If you
11 cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of
12 this guidance.
13

14
15
16 **I. INTRODUCTION**
17

18 This guidance describes the Food and Drug Administration’s (FDA’s or Agency’s) current
19 thinking on recommended practices for drug and medical device manufacturers and their
20 representatives² to follow when distributing to health care professionals or health care entities³
21 scientific or medical journal articles, scientific or medical reference texts, or clinical practice
22 guidelines (CPGs) that discuss unapproved new uses⁴ for approved drugs or approved or cleared
23 medical devices⁵ marketed in the United States. For the purposes of this guidance, these
24 materials are generally referred to as *scientific and medical publications*.
25

¹ This guidance was developed by the Center for Drug Evaluation and Research (CDER) in collaboration with the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH) in the Food and Drug Administration.

² As used in this guidance, *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, or a representative of such a person. The term might also include the sponsor of the approved, licensed, cleared, or 510(k) exempt drug or device.

³ As used in this guidance, *health care entity* includes hospitals, professional medical organizations, drug formulary committees, pharmacy benefits managers, health insurance issuers, group health plans, and Federal or State governmental agencies involved in the provision of health care or health insurance.

⁴ 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 cleared indications for use statement. Although this guidance focuses on unapproved uses of approved and cleared medical products, the recommendations in this guidance also apply to manufacturer distribution of publications that discuss unapproved new uses that are not included in the exemption from premarket notification for those class I or class II devices that are otherwise exempt from the requirement to submit a 510(k).

⁵ As used in this guidance, the terms *drug* and *device* refer to drugs and devices intended for use in humans, and include biological products licensed under section 351(a) of the Public Health Service (PHS) Act (42 U.S.C. 262(a)). See 42 U.S.C. 262(j). Different provisions govern the use of drugs in animals, which are not generally addressed in this guidance. See sections 512(a)(4) and (a)(5) of the Food, Drug & Cosmetic Act and this Agency’s regulations at 21 CFR part 530 for specific provisions related to the off-label (or extra-label) use of approved animal and human drugs in animals.

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26 In 2009, FDA issued a guidance titled *Good Reprint Practices for the Distribution of Medical*
27 *Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of*
28 *Approved Drugs and Approved or Cleared Medical Devices* (2009 guidance) to provide
29 guidance on manufacturer distribution of “journal articles” and “scientific or medical reference
30 publications.” FDA is revising its 2009 guidance on good reprint practices to clarify the
31 Agency’s position on manufacturer dissemination of scientific or medical reference texts and
32 CPGs that include information on unapproved new uses of the manufacturer’s products. New
33 explanatory sections have been included on these topics. This revised draft guidance is being
34 issued to enable the public to provide comments.

35
36 FDA’s guidance documents, including this draft guidance, do not establish legally enforceable
37 rights or responsibilities. Instead, guidances describe the Agency’s current thinking on a topic
38 and should be viewed only as recommendations, unless specific regulatory or statutory
39 requirements are cited. The use of the word *should* in Agency guidances means that something
40 is suggested or recommended, but not required.

41
42 Similarly, the use of *should not* in this guidance does not suggest or create an independent legal
43 prohibition, but indicates recommended practice.

II. BACKGROUND

44
45
46
47 The evolution of drug and medical device regulation in the United States has been shaped by
48 experience with the real and substantial risks to the public from uses of drugs and medical
49 devices not shown to be both safe and effective through adequate and well-controlled clinical
50 studies. While physicians may exercise their professional judgment to make individual patient
51 care decisions, the public health often is not well served when those judgments rest on anecdotal
52 experience or even preliminary scientific study—too often, the promise of safety and
53 effectiveness made by such sources has not been demonstrated when adequate and well-
54 controlled clinical studies are completed.⁶

55
56 These public health concerns are not limited to drugs and medical devices that lack FDA
57 approval or clearance for any use. These concerns are also relevant to new intended uses for
58 previously approved or cleared medical products, given that approval of a drug or medical device

⁶ See, e.g., Echt DS, Liebson PR, Mitchell LB et al., “Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial,” *New Eng. J. Med.*, 324(12): 781-88 (1991). The Cardiac Arrhythmia Suppression Trial (CAST) examined the widely held belief (in the absence of well-controlled studies showing this to be true) that treating minor rhythm abnormalities (frequent ventricular premature beats) with anti-arrhythmics after an acute myocardial infarction would improve survival. The well-controlled study (CAST) to test this belief, conducted by the National Institutes of Health, demonstrated that, although the drugs did indeed treat minor rhythm abnormalities, the patients who took those drugs had a 2 ½ fold increase in mortality. See also National Academy of Sciences, “Drug Efficacy Study: Final Report to the Commissioner of Food and Drugs, Food and Drug Administration” (1969), which found that approximately one-third of all pre-1962 marketed drugs did not have a single effective use.

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59 for one intended use does not assure its safety and effectiveness for other uses.⁷ A separate
60 balancing of risks and benefits is necessary for each intended use.⁸

61
62 For these reasons, the modern Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA
63 regulations prohibit manufacturers from introducing new drugs and most class III medical
64 devices into interstate commerce for any intended use that FDA has not determined to be safe
65 and effective.⁹ These authorities also prohibit manufacturers from introducing into interstate
66 commerce devices subject to premarket notification requirements under section 510(k), which
67 includes most class II and some class I devices, for any intended use that is outside FDA's
68 substantial equivalence determination (clearance) for such devices.¹⁰ Devices that are exempt
69 from premarket notification requirements, generally because they are low risk, may be
70 introduced into interstate commerce for the specifically exempt intended use(s) without
71 obtaining FDA clearance.¹¹ To establish a manufacturer's or distributor's intended use for the
72 product, FDA is not bound by the manufacturer's or distributor's subjective claims of intent, but

⁷ Indeed, Congress added the concept of effectiveness to the Food, Drug, and Cosmetic Act's (FD&C Act's) definition of "new drug" (and not merely to other provisions of the FD&C Act) to prevent manufacturers from obtaining approval of a drug for one use, and then marketing the drug for unapproved, or "off-label," uses. *See* S. Rep. No. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (statement of Senators Kefauver, Carroll, Dodd, Hart & Long, explaining reasons for changing the definition of "new drug"). As Senator Kefauver explained, if a manufacturer were not required to demonstrate safety and effectiveness for each new intended use, "[t]he expectation would be that the initial claims would tend to be quite limited." *Id.* Then, once the drug was approved for one use, "the sky would be the limit" and extreme claims of any kind could be made" *Id.* Similar requirements were subsequently extended to medical devices.

⁸ *See, e.g.,* *United States v. Rutherford*, 442 U.S. 544, 555 (1979) ("Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use"); *Rhone-Poulenc, Inc. v. FDA*, 636 F. 2d 750, 752 (D.C. Cir. 1980).

⁹ *See, e.g.,* sections, 505(a), 515 (a), 501(f)(1), and 301(a) and (d), of the FD&C Act (21 U.S.C. 355(a), 360e(a), 351(f)(1) and 331(a) and (d)). The requirement that safety and effectiveness for each intended use be established before introduction of the product into interstate commerce for that use came from experience showing that exclusive reliance on post-hoc remedies, such as enforcement actions for false or misleading labeling, was inadequate to protect the public health, as these remedies were not sufficient to deter manufacturers and distributors—who profit from sales of their products for any use—from making unsubstantiated and misleading claims to encourage use of their products. As the Secretary of Health, Education, and Welfare told Congress, "[i]t is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse-game where a manufacturer can fool the public until the [FDA] finally catches up with him." *The Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the Comm. on the Judiciary*, 87th Cong., 2d Sess. 173 (1962).

¹⁰ *See* sections 502(o), 501(f)(1), 513(f)(1), 515, and 301(a) and (d) of the FD&C Act (21 U.S.C. 352(o), 351(f)(1), 360c(f)(1), 360e and 331(a) and (d)).

¹¹ *See* sections 510(l) and (m) of the FD&C Act (21 U.S.C. 360(l) and (m)).

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73 rather can present objective evidence, which may include a variety of direct and circumstantial
74 evidence.¹²

75
76 Under the FD&C Act, an approved new drug that is accompanied by written, printed, or graphic
77 matter that suggests an unapproved use may be an unapproved new drug with respect to that
78 use.¹³ Furthermore, an approved prescription drug that is intended for an unapproved use
79 (whether referenced in labeling or not) would be considered misbranded, because the drug does
80 not meet the regulatory exemptions from the requirement that its labeling bear “adequate
81 directions for use.”¹⁴ Similarly, a medical device that is intended for an unapproved use is
82 considered adulterated and misbranded.¹⁵

83

¹² See, e.g., *Action on Smoking and Health v. Harris*, 655 F. 2d 236, 239 (D.C. Cir. 1980) (observing that “it is well established that the ‘intended use’ of a product, within the meaning of the [Food, Drug, and Cosmetic] Act is determined from its label, accompanying labeling, promotional claims, advertising and any other relevant source”); *Hanson v. United States*, 417 F. Supp. 30, 35 (D. Minn.), *aff’d*, 540 F. 2d 947 (8th Cir. 1976) (same); *United States v. Travia*, 180 F. Supp. 2d 115, 119 (D.D.C. 2001) (holding that “labeling is not exclusive evidence of the seller’s intent,” and finding nitrous oxide to be a drug from the circumstances of its sale, even where no labeling or oral statements accompanied product); *United States v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692, 698-99 (D. Md. 2001) (stating that “[o]f primary significance in determining whether a product may be deemed a ‘drug’ is its intended use or effect as gathered from the objective evidence disseminated by the vendor” and finding product to be drug where, among other things, marketing suggested that product was substitute for illegal drugs); *United States v. 250 Jars, Etc. of U.S. Fancy Pure Honey*, 218 F. Supp. 208, 211 (E.D. Mich. 1963) (finding distribution of pamphlets and newspaper articles containing claims for the curative power of honey by seller of honey to be evidence of intended use that rendered the seller’s honey a drug); 21 C.F.R. §§ 201.128 (defining indicia of “intended use” for drugs); 801.4 (defining indicia of “intended use” for devices).

¹³ See sections 201(m) and (p) of the FD&C Act, 21 U.S.C. 321 (m) and (p). Introducing an unapproved new drug into interstate commerce is prohibited. Sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d)).

¹⁴ See section 502(f) of the FD&C Act (21 U.S.C. 352(f)) and 21 CFR 201.5, 201.100(c)(1), and 201.115. Under section 502(f) and 21 C.F.R. 201.5, all drugs must bear directions under which a layperson can use the drug safely for each of its intended uses. Prescription drugs may be exempt from this requirement, and thus avoid being misbranded under section 502(f), if they satisfy the exemption from “adequate directions for use” in 21 CFR 201.100. That regulation, among other things, requires that the labeling of a prescription drug “bear adequate information for its use . . . under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented.” Further, if the prescription drug is subject to the new drug approval requirements of section 505 of the FD&C Act, the labeling containing this information must be the labeling authorized by an approved new drug application. The regulations further state that new drugs shall be exempt from section 502(f)(1) of the Act (21 U.S.C. 352(f)(1)) to the extent the exemption is claimed in an application approved under sections 505 or 512 of the Act. This exemption cannot be claimed, however, by a drug that would be a “new drug” if its labeling bore representations for its intended uses. See 21 CFR 201.115.

¹⁵ See sections 501(f)(1), 502(o), 513(f)(1), and 515 of the FD&C Act (21 U.S.C. 351(f)(1), 352(o)), 360c(f)(1), and 360e).

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84 As Congress recognized, starting with the Kefauver-Harris Amendments in 1962,¹⁶ requiring
85 each new indication and intended use of a product to be approved or cleared by FDA is critical to
86 the protection of the public health. FDA regulatory processes not only ensure that each use of a
87 drug or medical device is supported by appropriate scientific evidence, but also that this
88 scientific information is used to develop labeling to support the safe and effective use of each
89 product.¹⁷ Such labeling is in turn required to be provided with the product. Distribution of
90 scientific and medical publications regarding a medical product is not a substitute for the
91 information contained in FDA-approved product labeling.

92
93 In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA).¹⁸
94 Section 401 of FDAMA¹⁹ described certain conditions under which a drug or medical device
95 manufacturer could choose to disseminate medical and scientific information that discusses
96 unapproved uses of approved drugs and cleared or approved medical devices to “health care
97 professionals and certain entities, including pharmacy benefits managers, health insurance
98 issuers, group health plans, and Federal or State governmental agencies,” without such
99 dissemination being considered as evidence of the manufacturer’s intent that the product be used
100 for an unapproved new use. Among those conditions was the expectation that the manufacturer
101 of the product would seek FDA approval for the unapproved new use referenced in the
102 disseminated literature. With this condition, Congress again recognized the important public
103 health value of FDA premarket review and approval.

104
105 FDA’s implementing regulations for section 401 of FDAMA were codified at 21 CFR part 99.
106 Section 401 of FDAMA included a sunset date of September 30, 2006. This statutory provision,
107 as well as FDA’s pre-FDAMA guidance documents regarding reprint distribution and
108 manufacturer sponsorship of continuing medical education, was challenged on First Amendment
109 grounds. Although the district court found section 401 of FDAMA to be unconstitutional, the
110 U.S. Court of Appeals ultimately vacated the lower court’s decision.²⁰

111
112 In 2000, following the U.S. Court of Appeals ruling, FDA published a notice²¹ confirming that
113 the provisions of section 401 of FDAMA and FDA’s implementing regulations would continue
114 to apply. In that notice, FDA also stated that the statute and implementing regulations had

¹⁶ See Pub.L. No. 87-781, 76 Stat. 780 (1962) (“Kefauver-Harris Amendments”); see footnote 7, above. Among other things, the Kefauver-Harris Amendments added the requirement that manufacturers demonstrate that their new drugs are effective, as well as safe, for their intended uses *before* they could be distributed. See 21 U.S.C. § 355(a), (d); see also, 21 U.S.C. 360e(a), (d) (requiring proof of safety and effectiveness for premarket approval of class III devices). As mentioned in footnote 7, the Kefauver-Harris Amendments also revised the FD&C Act’s “new drug” definition to provide that a drug is a new drug if it is not generally recognized as “safe and effective” for its intended uses. *Id.* § 321(p). Because a drug is a “new drug” if it is not generally recognized as safe and effective for each intended use, a new intended use renders an approved drug a “new drug” with respect to the new use, and the manufacturer cannot distribute the drug in interstate commerce for that use without first obtaining FDA’s approval of an application that demonstrates the drug’s safety and effectiveness for the new use. See *Washington Legal Foundation v. Henney*, 202 F. 3d 331, 332-33 (D.C. Cir. 2000) (“it is unlawful for a manufacturer to introduce a drug into interstate commerce with an intent that it be used for an off-label purpose”).

¹⁷ See section 502(f)(1) of the Act; see also, e.g., 21 CFR 201.100; 21 CFR 801.109.

¹⁸ Pub. L. No. 105-115, 111 Stat. 2296.

¹⁹ See section 551 of the FD&C Act (21 U.S.C. 360aaa).

²⁰ See *Henney*, 202 F. 3d 331.

²¹ See 65 FR 14286, March 16, 2000.

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115 constituted a “safe harbor” for a manufacturer that complied with them before and while
116 disseminating “journal articles and reference texts” about unapproved new uses of approved or
117 cleared products. The notice explained that if a manufacturer complied with the FDAMA
118 provisions, distributing such journal articles or reference texts would not have been used as
119 evidence of intent that the product distributed by the manufacturer be used for an unapproved
120 use. The notice clarified further that even if a manufacturer chose to disseminate materials in a
121 way that was inconsistent with section 401 of FDAMA, that dissemination would not be treated
122 as an independent violation of the law, but could have been used as evidence of a manufacturer’s
123 intent that the product be used for an unapproved use.

124
125 On September 30, 2006, section 401 of FDAMA sunset and the implementing regulations in 21
126 CFR part 99 ceased to be applicable. In the wake of the sunset of the legislation, FDA issued
127 guidance, finalized in 2009, on good reprint practices. The 2009 guidance was intended to
128 provide drug and medical device manufacturers and their representatives with recommendations
129 on distributing scientific or medical information on unapproved uses to health care professionals
130 and health care entities, without such dissemination being considered as evidence of the
131 manufacturer’s intent that the product be used for an unapproved new use.

132
133 The 2009 guidance, consistent with the objectives of section 401 of FDAMA (which was no
134 longer law), recognized that the public health may benefit when health care professionals receive
135 truthful and non-misleading scientific or medical publications on unapproved new uses.²² This
136 information can be particularly important given that a health care professional can generally
137 choose to use or prescribe an approved or cleared medical product for an unapproved use, if the
138 off-label use is appropriate based on his or her judgment. The narrow “safe harbor”
139 recommended in the guidance was also consistent with FDA’s continued belief that FDA
140 premarket review and approval are critical to public health.

141
142 FDA is revising its 2009 guidance on good reprint practices in response to stakeholder questions
143 about its application to scientific and medical reference texts and CPGs that include or may
144 include²³ information on unapproved uses. This draft guidance provides recommendations for
145 scientific journal articles, scientific or medical reference texts, and CPGs in separate sections,
146 tailored to each type of publication. Consistent with longstanding FDA policy and practice, if
147 manufacturers distribute scientific or medical publications as recommended in this guidance,
148 FDA does not intend to use such distribution as evidence of the manufacturer’s intent that the
149 product be used for an unapproved new use.

150
151 Although this draft guidance, like the 2009 guidance, recognizes the value to health care
152 professionals of truthful and non-misleading scientific or medical publications on unapproved
153 new uses, it also continues to recognize that this information is in no way a substitute for the

²² For example, such information might be included as part of a manufacturer’s response to an unsolicited request for off-label information. FDA has developed separate draft guidance that addresses how manufacturers can respond to unsolicited requests for off-label information related to their FDA-approved or -cleared products without such responses being used as evidence of intended use. See the draft guidance *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*, December 2011 (available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>). Once finalized, that draft guidance will represent the Agency’s current thinking on this topic.

²³ For further explanation, see footnotes 31 and 39.

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154 FDA premarket review process, which allows FDA to be proactive, rather than reactive, in
155 protecting the public from unsafe or ineffective medical products.

156
157 FDA is issuing this revised draft guidance to enable the public to provide comments on the
158 proposed approach.

159

160 III. RECOMMENDED PRACTICES

161

162 Often scientific and medical information concerning the safety or effectiveness of a medical
163 product's unapproved new use may be published in scientific or medical journal articles,
164 scientific or medical reference texts, and/or in CPGs. These publications are available from their
165 publishers or other distribution channels, but have also been commonly distributed by
166 manufacturers to health care professionals and health care entities.

167

168 Sections A, B, and C, below, provide specific guidance for scientific and medical journal
169 articles, scientific and medical reference texts, and CPGs, respectively. FDA recommends that
170 manufacturers employ the following practices if they choose to disseminate scientific and
171 medical publications that include or may include information on unapproved new uses of
172 approved, cleared, or 510(k) exempt products.

173

174 A. Scientific or Medical Journal Articles

175

176 If a manufacturer who chooses to distribute scientific or medical journal articles that include
177 information on unapproved/uncleared uses of its product(s) does so in accordance with the
178 recommendations of this guidance, FDA does not intend to use that distribution as evidence of
179 the manufacturer's intent that the product(s) be used for an unapproved new use.

180

181 A scientific or medical journal article that includes information on unapproved uses and is
182 distributed by manufacturers should first have been published by an organization that has an
183 editorial board that uses experts who have demonstrated expertise in the subject of the article
184 under review by the organization. Experts should be independent of the organization and should
185 review and objectively select, reject, or provide comments about proposed articles. Also, the
186 organization should adhere to a publicly stated policy of full disclosure of any conflict of interest
187 or biases for all authors, contributors, or editors associated with the journal or organization.

188

189 Additionally, the scientific or medical journal article distributed by a manufacturer *should*:

190

191 1. Be peer-reviewed and published in accordance with the peer-review procedures of the
192 organization.

193

194 2. Be in the form of an unabridged reprint or copy of an article.

195

196 3. Contain information that describes and addresses adequate and well-controlled clinical
197 investigations that are considered scientifically sound by experts with scientific training
198 and experience to evaluate the safety or effectiveness of the drug or device. In the case of
199 devices, significant investigations other than adequate and well-controlled studies, such

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200 as meta-analyses, if they are testing a specific clinical hypothesis, and journal articles
201 discussing significant non-clinical research (such as well-designed bench or animal
202 studies) may be consistent with this guidance.

- 203
- 204 4. Be disseminated with the approved labeling or, in the case of a medical device reviewed
205 under section 510(k) of the FD&C Act (21 U.S.C. 360(k)), labeling for the indications in
206 the product's cleared indications for use statement, for each of the manufacturer's
207 products that is included in the distributed article.
- 208
- 209 5. Be disseminated with a comprehensive bibliography, when such information exists, of
210 publications discussing adequate and well-controlled clinical studies published in
211 scientific journals, medical journals, or scientific texts about the use of the drug or
212 medical device covered by the information disseminated (unless the information already
213 includes such a bibliography).
- 214
- 215 6. Be disseminated with a representative publication, when such information exists, that
216 reaches contrary or different conclusions regarding the unapproved use—especially when
217 the conclusions of articles to be disseminated have been specifically called into question
218 by another publication.
- 219
- 220 7. Be distributed separately from the delivery of information that is promotional in nature.
221 For example, if a sales representative delivers a reprint to a physician in his or her office,
222 the reprint should not be attached to any promotional material the sales representative
223 uses or delivers during the office visit. To the extent that the recipients of the scientific
224 or medical journal article have questions, the sales representative should refer the
225 questions to a medical/scientific officer or department, and the officer or department to
226 which the referral is made should be independent of the sales and/or marketing
227 departments. Similarly, while reprints may be distributed at medical or scientific
228 conferences in settings appropriate for scientific exchange, reprints should not be
229 distributed in promotional exhibit halls or during promotional speakers' programs.

230

231 A scientific or medical journal article that explains a use of a manufacturer's product and is
232 distributed by, or on behalf of, that manufacturer *must not*:

- 233
- 234 1. Be false or misleading.²⁴ For example, a distributed journal article should not be
235 characterized as definitive or representative of the weight of credible evidence derived
236 from adequate and well-controlled clinical investigations if it is inconsistent with the
237 weight of credible evidence or if a significant number of other studies contradict the
238 conclusions set forth in the article; should not have been withdrawn by the journal or
239 disclaimed by the author; and should not discuss a clinical investigation that FDA has
240 previously informed the company is not adequate and well-controlled.
- 241
- 242 2. Contain information recommending or suggesting use of the product that makes the
243 product dangerous to health when used in the manner suggested.²⁵

²⁴ See sections 502(a), 201(m) of the FD&C Act. (21 U.S.C. 352(a), 321(m)).

²⁵ See sections 502(j), 201(m) of the FD&C Act. (21 U.S.C. 352(j), 321(m)).

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244
245 To be consistent with the recommended practices described in this guidance, a scientific or
246 medical journal article regarding an unapproved use that is distributed by a manufacturer *should*
247 *not*:

- 248
- 249 1. Be in the form of a special supplement or publication that has been funded, in whole or in
250 part, by one or more of the manufacturers of the product that is the subject of the article.
251
 - 252 2. Be marked, highlighted, summarized, or characterized by the manufacturer, in writing or
253 orally, to emphasize or promote an unapproved use. (This recommendation does not
254 preclude providing the disclosures discussed elsewhere in this guidance.) For example, if
255 during a sales call to a physician, a sales representative summarizes or characterizes the
256 article to emphasize portions of the article that suggest the manufacturer's drug may be
257 safe or effective for an unapproved use, this might be used as evidence of intended use.²⁶
258
 - 259 3. Be primarily distributed by a drug or device manufacturer; rather, it should be generally
260 available in bookstores or other independent distribution channels (e.g., subscription,
261 Internet) where periodicals are sold.
262
 - 263 4. Be written, edited, excerpted, or published specifically for, or at the request of, a drug or
264 device manufacturer.
265
 - 266 5. Be edited or significantly influenced²⁷ by a drug or device manufacturer or any
267 individuals having a financial relationship with the manufacturer.
268
 - 269 6. Be attached to specific product information (other than the approved product labeling or
270 the product's cleared indications for use statement).

271
272 The scientific or medical journal reprint *should be accompanied by* a prominently displayed and
273 permanently affixed statement disclosing:

- 274
- 275 1. The drug(s) or device(s) included in the journal reprint in which the manufacturer has an
276 interest.
277
 - 278 2. That some or all uses of the manufacturer's drugs or devices described in the information
279 have not been approved or cleared by FDA, as applicable to the described drug(s) or
280 device(s).

²⁶ In addition, a distributed article must not be marked, highlighted, summarized, or characterized by the manufacturer in a manner that renders it false or misleading. See sections 502(a), 201(m) of the FD&C Act. (21 U.S.C. 352(a), 321(m)).

²⁷ FDA considers many factors when assessing whether a manufacturer is exercising significant influence over something or someone. For example, FDA examines the extent of control exercised by a manufacturer in a given scenario. See the FDA guidance for industry, *Industry-Supported Scientific and Educational Activities* (62 FR 64094, December 3, 1997), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070072.pdf>, for more examples of when something or someone may be considered to be independent from the significant influence of a firm.

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- 281
282 3. Any author known to the manufacturer as having a financial interest in the manufacturer
283 or in a product of the manufacturer that is included in the journal article, or who is
284 receiving compensation from the manufacturer, along with the affiliation of the author, to
285 the extent known by the manufacturer, and the nature and amount of any such financial
286 interest of the author or compensation received by the author from the manufacturer.²⁸
287
288 4. Any person known to the manufacturer who has provided funding for the study.
289
290 5. All significant risks or safety concerns associated with the unapproved use(s) of the
291 manufacturer's product(s) discussed in the journal article that are known to the
292 manufacturer but not discussed in the article.
293

294 The following types of journal reprints are examples that *would not* be considered consistent
295 with the recommended practices outlined in this guidance:
296

- 297 • Letters to the editor
298 • Abstracts of a publication
299 • Reports of healthy volunteer studies
300 • Publications consisting of statements or conclusions but which contain little or no
301 substantive discussion of the relevant investigation or data on which they are based
302

303 **B. Scientific or Medical Reference Texts**

304
305 Scientific or medical reference texts²⁹ typically discuss a wide range of topics (e.g., medical
306 diagnosis, pathophysiology and treatments, pharmacology, surgical techniques, and other
307 scientific or medical information).³⁰ Like journal articles, scientific or medical reference texts
308 often contain information about unapproved use(s) of drugs and devices. However, because
309 these reference texts are considerably longer than journal articles, and generally address a wide
310 range of topics, FDA believes that it is appropriate to make specific recommendations for
311 distribution of reference texts that differ somewhat from the recommendations for journal
312 articles. If a manufacturer who chooses to distribute reference texts that include information on
313 unapproved/uncleared uses of its product(s) does so in accordance with the recommendations of
314 this guidance, FDA does not intend to use that distribution as evidence of the manufacturer's
315 intent that the product(s) be used for an unapproved new use.
316

317 A scientific or medical reference text that is distributed in its entirety by a manufacturer *should*:
318

²⁸ For purposes of this guidance, 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 of Medical Journal Editors (available at <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/>).

²⁹ For purposes of this guidance, there is no distinction between scientific and medical reference texts. Therefore, the recommendations presented here apply equally to both.

³⁰ FDA recognizes that certain scientific or medical reference texts address more specialized topics. The recommendations of this guidance also apply to distribution of these more specialized scientific or medical reference texts.

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- 319 1. Be based on a systematic review of the existing evidence.
320
321 2. Be published (in print or electronic format) by an independent publisher, not substantially
322 dependent on financial support from drug or medical device manufacturers, who
323 publishes scientific or medical educational content for health care professionals and
324 students.
325
326 3. Be the most current version.
327
328 4. Be authored, edited, and/or contributed to by experts who have demonstrated expertise in
329 the subject area.
330
331 5. Be peer-reviewed by experts with relevant medical or scientific expertise and published
332 in accordance with the scientific or medical reference text peer-review procedures of the
333 publisher, which should be easily accessible or available upon request.
334
335 6. Be sold through usual and customary independent distribution channels (e.g., booksellers,
336 subscription, Internet) for medical and scientific educational content directed at health
337 care professionals and students.
338
339 7. Be distributed separately from the delivery of information that is promotional in nature.
340 For example, if a sales representative delivers a reference text (including individual
341 chapters) to a physician in his or her office, the reference text or chapter(s) should not be
342 attached to any promotional material the sales representative uses or delivers during the
343 office visit. To the extent that the recipients of scientific or medical reference texts have
344 questions, the sales representative should refer the questions to a medical/scientific
345 officer or department, and the officer or department to which the referral is made should
346 be independent of the sales and/or marketing departments. Similarly, while scientific or
347 medical reference texts may be distributed at medical or scientific conferences in settings
348 appropriate for scientific exchange, they should not be distributed in promotional exhibit
349 halls or during promotional speakers' programs.
350
351 8. Contain a prominently displayed and permanently affixed statement identifying the
352 distributing manufacturer and disclosing that some of the uses for drugs and/or devices
353 described in the reference text might not be approved or cleared by FDA. The statement
354 should also disclose that the author(s) of some chapters also might have a financial
355 interest in the manufacturer or its products, unless the manufacturer has verified that none
356 of the authors for the reference text has a financial interest in the manufacturer or a
357 product being written about.³¹ This statement should be placed by sticker, stamp, or
358 other similar means on the front cover of the textbook.
359

³¹ If a reference text is distributed in its entirety with this statement affixed, manufacturers are not expected to have reviewed every element of the reference text to identify discussions of off-label uses of their products. However, even where an entire reference text is being distributed, manufacturers should determine whether one or more individual chapters of that reference text devote primary substantive discussion to an individual product or products of the manufacturer distributing it, in order to determine whether dissemination of product labeling is recommended.

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360 9. In situations where a reference text is distributed in its entirety but one or more individual
361 chapters of that reference text devote primary substantive discussion to an individual
362 product or products of the manufacturer distributing it, be disseminated with the
363 approved product labeling for each such product or, in the case of a medical device
364 reviewed under section 510(k) of the FD&C Act (21 U.S.C. 360(k)), labeling for the
365 indications in the product's cleared indications for use statement.

366
367 If, in lieu of an entire scientific or medical reference text, a manufacturer distributes an
368 individual chapter(s) that includes information on unapproved/uncleared uses of the
369 manufacturer's product(s), the chapter(s) *should*:

370
371 1. Come from a scientific or medical reference text that follows the recommendations for
372 complete scientific or medical reference texts in this guidance, except that the individual
373 chapter(s) should bear the prominently displayed and permanently affixed statement
374 described below for use on individual chapters, rather than the recommended statement
375 for texts distributed in their entirety.

376
377 2. Be unaltered/unabridged and extracted directly from the scientific or medical reference
378 text in which it appears.

379
380 3. When necessary to provide context, be disseminated with other unaltered/unabridged
381 chapters extracted directly from the same scientific or medical reference text, such as
382 chapters which provide related or supportive information.

383
384 4. Contain a prominently displayed and permanently affixed statement identifying the
385 distributing manufacturer and disclosing:

386
387 (a) The drug(s) or device(s) addressed in the individual chapter(s) in which the
388 manufacturer has an interest;

389
390 (b) That some or all uses of the manufacturer's drugs and/or devices described in the
391 attached information have not been approved or cleared by FDA, as applicable to the
392 described drug(s) or medical device(s);

393
394 (c) Any author known to the manufacturer as having a financial interest in the
395 manufacturer or in a product of the manufacturer that is included in the individual
396 chapter(s), or who is receiving compensation from the manufacturer, along with the
397 affiliation of the author, to the extent known by the manufacturer, and the nature and
398 amount of any such financial interest of the author or compensation received by the
399 author from the manufacturer;

400
401 (d) All significant risks or safety concerns associated with the unapproved use(s) of the
402 manufacturer's products discussed in the individual chapter(s) that are known to the
403 manufacturer but not discussed in the chapter(s).

404

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405 This statement should be placed by sticker, stamp, or other similar means on the front
406 page of each chapter.

407
408 5. Be disseminated with the approved labeling, or, in the case of a medical device reviewed
409 under section 510(k) of the FD&C Act (21 U.S.C. 360(k)), labeling for the indications in
410 the cleared indications for use statement, for each of the manufacturer's products that is
411 included in the distributed chapter(s).

412
413 A scientific or medical reference text, or an individual chapter, that explains a use of a
414 manufacturer's product and is distributed by, or on behalf of, that manufacturer *must not*:

- 415
- 416 1. Be false or misleading.³²
 - 417
418 2. Contain information recommending or suggesting use of the product in ways that make
419 the product dangerous to health when used in the manner suggested therein.³³

420
421 To be consistent with the recommended practices described in this guidance, a scientific or
422 medical reference text, or an individual chapter, that is distributed *should not*:

- 423
- 424 1. Be primarily distributed by a drug or device manufacturer; rather, it should be generally
425 available in bookstores or other independent distribution channels (e.g., subscription,
426 Internet) where textbooks are sold.
 - 427
428 2. Be edited or significantly influenced by a drug or device manufacturer or any individuals
429 having a financial relationship with the manufacturer.
 - 430
431 3. Be marked, highlighted, summarized, or characterized by the manufacturer, in writing or
432 orally, to emphasize or promote an unapproved use. (This recommendation does not
433 preclude providing the disclosures discussed elsewhere in this guidance.) For example, if
434 during a sales call to a physician, a sales representative summarizes or characterizes the
435 text to emphasize passages that suggest that a drug of the manufacturer may be safe or
436 effective for an unapproved use, this might be used as evidence of intended use.³⁴
 - 437
438 4. Be written or published specifically at the request of a drug or device manufacturer.
 - 439
440 5. Be abridged or excerpted³⁵ in any particular manner.
- 441

³² See sections 502(a), 201(m) of the FD&C Act. (21 U.S.C. 352(a), 321(m)).

³³ See sections 502(j), 201(m) of the FD&C Act. (21 U.S.C. 352(j), 321(m)).

³⁴ In addition, a distributed reference text must not be marked, highlighted, summarized, or characterized by the manufacturer in a manner that renders it false or misleading. See sections 502(a), 201(m) of the FD&C Act. (21 U.S.C. 352(a), 321(m)).

³⁵ In situations where the entire reference text is being disseminated, the reference text should be complete and no chapters excerpted in any manner. In situations where individual chapters of a reference text are being disseminated, the individual chapters should be complete. In other words, an excerpt from an individual chapter would not satisfy the recommendations outlined in this guidance pertaining to the dissemination of individual chapters of scientific or medical reference texts.

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- 442 6. Be attached to specific product information (other than the approved product labeling or
443 the product’s cleared indications for use statement).
444

C. Clinical Practice Guidelines

446 CPGs are statements that include recommendations intended to help clinicians make decisions
447 for individual patient care, including in circumstances where there are few or no approved drugs
448 or devices indicated for the patient’s condition or the approved therapies have not proven
449 successful for the individual. A CPG may be much longer and often covers a wider range of
450 topics than a journal article. FDA believes that it is appropriate to make specific
451 recommendations for manufacturer distribution of CPGs that include information on unapproved
452 new uses of that manufacturer’s approved or cleared products that differ somewhat from the
453 recommendations for journal articles. These recommendations are set forth below, along with
454 additional recommendations that incorporate the Institute of Medicine’s (IOM’s) standards for
455 CPG “trustworthiness.”³⁶ These “trustworthiness” standards, among other things, ensure that
456 CPGs are informed by a systematic review of evidence and an assessment of the benefits and
457 harms of alternative care options.
458

459
460 If a manufacturer who chooses to distribute CPGs that include information on
461 unapproved/uncleared uses of its product(s) does so in accordance with the recommendations of
462 this guidance, FDA does not intend to use that distribution as evidence of the manufacturer’s
463 intent that the product(s) be used for an unapproved new use.
464

465 Drug and medical device manufacturers wishing to disseminate CPGs that discuss unapproved or
466 uncleared new uses of products that they market should disseminate only those guidelines that
467 are “trustworthy,” as described below. In keeping with the IOM standards, to be considered
468 “trustworthy,” a CPG *should* at minimum:
469

- 470 1. Be based on a systematic review of the existing evidence.
471
472 2. Be developed by a knowledgeable, multidisciplinary panel of experts and representatives
473 from key affected groups.
474
475 3. Consider important patient subgroups and patient preferences.
476

³⁶ Through the Medicare Improvements for Patients and Providers Act of 2008, Congress required the Secretary of Health and Human Services (HHS) to contract with IOM (through the Agency for Healthcare Research and Quality (AHRQ)) to undertake a study that focused on “the best methods used in developing clinical practice guidelines in order to ensure that organizations developing such guidelines have information on approaches that are objective, scientifically valid, and consistent.” Pub. L. No. 110-275, 122 Stat. 2595. Also, in this legislation, Congress required IOM to submit a report to the Secretary of HHS and the appropriate committees of Congress containing the results of the study, together with recommendations for such legislation and administrative action as IOM determines appropriate. The standards for CPG “trustworthiness,” as incorporated in this guidance, are taken directly from IOM’s study results (as articulated in its 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)).

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- 477 4. Be based on an explicit and transparent (publicly accessible) process by which the CPG is
478 developed and funded that minimizes distortions,³⁷ biases, and conflicts of interest.
479
- 480 5. Provide a clear explanation of the logical relationships between alternative care options
481 and health outcomes, provide clearly articulated recommendations in standardized form,
482 and provide ratings of both quality of evidence and the strength of recommendations.
483
- 484 6. Be reconsidered and revised when important new evidence warrants modifications of
485 recommendations.³⁸
486

487 Manufacturers wishing to distribute a “trustworthy” CPG in its entirety *should*:

- 488
- 489 1. Ensure that the most current version of the CPG is disseminated.
490
- 491 2. Distribute the CPG separately from the delivery of information that is promotional in
492 nature. For example, if a sales representative delivers a CPG to a physician in his or her
493 office, the CPG should not be attached to any promotional material the sales
494 representative uses or delivers during the office visit. To the extent that the recipients of
495 the CPG have questions, the sales representative should refer the questions to a
496 medical/scientific officer or department, and the officer or department to which the
497 referral is made should be independent of the sales and/or marketing departments.
498 Similarly, while a CPG may be distributed at medical or scientific conferences in settings
499 appropriate for scientific exchange, the CPG should not be distributed in promotional
500 exhibit halls or during promotional speakers’ programs.
501
- 502 3. Ensure that the CPG contains a prominently displayed and permanently affixed statement
503 identifying the distributing manufacturer and disclosing that some of the uses of drugs
504 and/or devices described in the CPG might not be approved or cleared by FDA. The
505 statement should also disclose that the author(s) of some sections might have a financial
506 interest in the manufacturer or its products, unless the manufacturer has verified that none
507 of the authors for the CPG has a financial interest in the manufacturer or a product being
508 written about. This statement should be placed by sticker, stamp, or other similar means
509 on the front page of the CPG.³⁹
510
- 511 4. In situations where a CPG is distributed in its entirety but one or more individual sections
512 of that CPG devotes primary substantive discussion to an individual product or products
513 of the manufacturer distributing it, be disseminated with the approved product labeling
514 for each such product or, in the case of a medical device reviewed under section 510(k)

³⁷ Distortion may result from, for example, reliance on incomplete data.

³⁸ For a more in-depth discussion of the standards, including any adherence concerns, please see the IOM report referenced in footnote 36, available at <http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx>.

³⁹ If a CPG is distributed in its entirety with this statement affixed, manufacturers are not expected to have reviewed every element of the CPG to identify discussions of off-label uses of their products. However, even where an entire CPG is being distributed, manufacturers should determine whether one or more individual sections of that CPG devote primary substantive discussion to an individual product or products of the manufacturer distributing it, in order to determine whether dissemination of product labeling is recommended.

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515 of the FD&C Act (21 U.S.C. 360(k)), labeling for the indications in the product’s cleared
516 indications for use statement.

517
518 If, in lieu of an entire CPG, a manufacturer distributes an individual section(s) that includes
519 information on unapproved/uncleared uses of the manufacturer’s product(s),⁴⁰ the section(s)
520 *should:*

- 521
- 522 1. Come from a CPG that satisfies the recommendations set forth in this guidance, including
523 the standards for “trustworthiness,” except that the section should bear the prominently
524 displayed and permanently affixed statement described below for use on individual
525 sections, rather than the recommended statement for CPGs distributed in their entirety.
526
 - 527 2. Be unaltered/unabridged and extracted directly from the CPG in which it appears.
528
 - 529 3. When necessary to provide context, be disseminated with other unaltered/unabridged
530 sections extracted directly from the same CPG, such as sections which provide related or
531 supportive information.
532
 - 533 4. Contain a prominently displayed and permanently affixed statement identifying the
534 distributing manufacturer and disclosing:
535
 - 536 (a) The drug(s) or device(s) addressed in the individual section(s) in which the
537 manufacturer has an interest;
538
 - 539 (b) That some or all uses of the manufacturer’s drugs and/or devices described in the
540 attached information have not been approved or cleared by FDA, as applicable to the
541 described drug(s) or medical device(s);
542
 - 543 (c) Any author known to the manufacturer as having a financial interest in the
544 manufacturer or in a product of the manufacturer that is included in the individual
545 section(s), or who is receiving compensation from the manufacturer, along with the
546 affiliation of the author, to the extent known by the manufacturer, and the nature and
547 amount of any such financial interest of the author or compensation received by the
548 author from the manufacturer;
549
 - 550 (d) All significant risks or safety concerns associated with the unapproved use(s) of the
551 manufacturer’s products discussed in the individual section(s) that are known to the
552 manufacturer but not discussed in the section(s).
553

554 This statement should be placed by sticker, stamp, or other similar means on the front
555 page of each section.
556

⁴⁰ A CPG that addresses only one disease state should be disseminated in its entirety. If a CPG substantively addresses multiple disease states, and manufacturers wish to disseminate only certain sections of the CPG, they should follow the recommendations discussed below.

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557 5. Be disseminated with the approved labeling, or, in the case of a medical device reviewed
558 under section 510(k) of the FD&C Act (21 U.S.C. 360(k)), labeling for the indications in
559 the cleared indications for use statement, for each of the manufacturer's products that is
560 included in the distributed section(s).

561
562 A CPG or individual section(s) of a CPG that explains a use of a manufacturer's product and is
563 distributed by, or on behalf of, that manufacturer *must not*:

- 564
- 565 1. Be false or misleading.⁴¹
 - 566 2. Contain information recommending or suggesting use of the product in ways that make
567 the product dangerous to health when used in the manner suggested therein.⁴²

568
569
570 To be consistent with the recommended practices described in this guidance, a CPG or individual
571 section of a CPG that discusses unapproved new uses of a manufacturer's product *should not*:

- 572
- 573 1. Be primarily distributed by a drug or device manufacturer, but should be generally
574 available through other independent distribution channels (e.g., subscription, Internet).
 - 575 2. Be edited or significantly influenced⁴³ by a drug or device manufacturer or any
576 individuals having a financial relationship with the manufacturer.
 - 577 3. Be marked, highlighted, summarized, or characterized by the manufacturer in writing or
578 orally, to emphasize or promote an unapproved use. (This recommendation does not
579 preclude providing the disclosures discussed elsewhere in this guidance.) For example, if
580 during a sales call to a physician, a sales representative summarizes or characterizes the
581 CPG to emphasize portions that suggest the manufacturer's product may be safe or
582 effective for an unapproved use, this might be used as evidence of intended use.⁴⁴
 - 583 4. Be written or published specifically at the request of a drug or device manufacturer.
 - 584 5. Be abridged or excerpted⁴⁵ in any particular manner.
 - 585 6. Be attached to specific product information (other than the approved product labeling or
586 the product's cleared indications for use statement).
- 587
588
589
590
591

⁴¹ See sections 502(a), 201(m) of the FD&C Act. (21 U.S.C. 352(a), 321(m)).

⁴² See sections 502(j), 201(m) of the FD&C Act. (21 U.S.C. 352(j), 321(m)).

⁴³ Please see footnote 27 for further information regarding FDA's understanding of "significant influence."

⁴⁴ In addition, a distributed CPG must not be marked, highlighted, summarized, or characterized by the manufacturer in a manner that renders it false or misleading. See sections 502(a), 201(m) of the FD&C Act. (21 U.S.C. 352(a), 321(m)).

⁴⁵ In situations where an entire CPG is being disseminated, the CPG should be complete and no sections excerpted in any manner. In situations where individual sections of a CPG are being disseminated, the individual sections should be complete. In other words, an excerpt from an individual section would not satisfy the recommendations outlined in this guidance pertaining to the dissemination of individual sections of a CPG.