
Guidance for Industry

Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

**June 2014
Procedural**

Guidance for Industry

Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices

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1 **Guidance for Industry¹**
2 **Distributing Scientific and Medical Publications on Risk**
3 **Information for Approved Prescription Drugs and Biological**
4 **Products—Recommended Practices**
5

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7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current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

14 **I. INTRODUCTION**
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16
17 This draft guidance describes the Food and Drug Administration's (FDA's or Agency's) current
18 thinking on recommended practices for drug manufacturers (firms) and their representatives to
19 follow if they choose to distribute to health care professionals² or health care entities³ scientific
20 or medical journal articles that discuss new risk information for approved prescription drugs^{4,5,6}
21 marketed in the United States. The recommendations in this draft guidance are intended to
22 address issues specific to the distribution of new information about risks associated with a drug
23 that further characterizes risks identified in the approved labeling.
24

25 The recommendations in this draft guidance are intended to apply to distribution of new risk
26 information (as that term is further explained in section II of this document) for drugs intended
27 for human and animal use. Throughout this draft guidance, the Agency provides references to
28 regulations and guidances specific to drugs intended for human use. Unless otherwise indicated,
29 the Agency generally takes a similar approach when addressing the issues raised in this draft
30 guidance as they pertain to animal drugs.
31

32 FDA's guidance documents, including this draft guidance, do not establish legally enforceable
33 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

¹ This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Center for Veterinary Medicine (CVM) at the Food and Drug Administration.

² For purposes of this draft guidance, *health care professionals* include those providing care to either human or animal patients.

³ As used in this draft guidance, *health care entities* include hospitals, professional medical organizations, drug formulary committees, pharmacy benefit managers, health insurance issuers, group health plans, and Federal or State governmental agencies involved in the provision of health care or health insurance. For purposes of the draft guidance, *health care entities* also include any such similar organizations involved in animal health care.

⁴ As used in this draft guidance, the term *drug* includes drugs approved for use in humans or animals and drugs regulated as biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262(a)).

⁵ For animal drugs, this draft guidance also applies to over-the-counter and Veterinary Feed Directive drugs.

⁶ This guidance does not apply to products regulated as medical devices.

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34 be viewed only as recommendations, unless specific regulatory or statutory requirements are
35 cited. The use of the word *should* in Agency guidances means that something is suggested or
36 recommended, but not required.

37

38 **II. BACKGROUND**

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40 In February 2014, FDA issued a draft guidance titled *Distributing Scientific and Medical*
41 *Publications on Unapproved New Uses—Recommended Practices* (Draft Revised Reprints
42 Guidance).⁷ That draft guidance revised an earlier guidance from 2009 to clarify the Agency’s
43 position on manufacturer dissemination of scientific or medical publications that include
44 information on unapproved new uses of the manufacturer’s products. The Draft Revised Reprints
45 Guidance was issued to enable the public to provide comments. Stakeholders have raised
46 questions regarding the Agency’s position on manufacturer dissemination of new scientific or
47 medical information about safety information contained in the labeling for approved drugs.
48 Because this concerns dissemination of new risk information related to approved uses of a drug,
49 this issue is distinct from the dissemination of information on unapproved new uses of approved
50 drugs.

51

52 In response to those questions, the Agency is issuing this draft guidance to clarify and solicit
53 public comments on the Agency’s position on manufacturer dissemination of new risk
54 information regarding lawfully marketed drugs for approved uses to health care professionals or
55 health care entities. FDA recognizes that the safety profile of a drug evolves throughout its
56 lifecycle as the extent of exposure to the product increases and that it can be helpful for health
57 care practitioners to receive significant new risk information about an approved product in a
58 timely manner. FDA anticipates that the earliest distribution of new risk information will
59 generally involve distribution of recently published studies, as opposed to textbooks or clinical
60 practice guidelines. Accordingly, FDA is providing guidance for firms that choose to distribute
61 new risk information in the form of a reprint or digital copy of a published study.

62

63 FDA believes that recommendations specific to the distribution of new risk information about
64 approved prescription drugs and biological products are needed for two reasons. First, in general
65 there are differences in the purpose, nature, and reliability of the evidence used to determine the
66 effectiveness of a drug (e.g., to support a new intended use) and the evidence that is the basis for
67 the product’s risk assessment (see section III.A). Therefore, FDA believes guidance is needed to
68 address the spectrum of data sources that could be appropriate for distribution to provide new
69 risk information. Second, new risk information may contradict or otherwise deviate from the risk
70 information in the approved labeling, which may cause confusion or otherwise contribute to
71 patient harm. If the new information is unreliable or presented without the appropriate context, it
72 could influence prescribing decisions or patient monitoring in a way that could harm patients.
73 For example, postmarket data concerning an adverse reaction identified in the approved labeling
74 may suggest that the adverse reaction is less severe or occurs at lower frequency than indicated
75 in the approved labeling, or may call into question the basis for concluding that there is a causal
76 relationship between the reaction and the drug. That information could, for example, lead to use

⁷ See the 2014 draft guidance for industry entitled *Distributing Scientific and Medical Publications on Unapproved Uses—Recommended Practices*. Although this draft guidance addresses only human products, the general principles are the same for animal drugs.

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77 of the drug in a patient for whom the approved labeling indicates an increased risk for the
78 adverse reaction. Therefore, FDA is proposing recommendations for study or analysis and
79 distribution criteria to help ensure that new risk information that rebuts, mitigates, or refines risk
80 information in approved labeling meets appropriate standards for reliability and is presented with
81 appropriate disclosure of its limitations.

82
83 For purposes of this draft guidance, the term *new risk information* refers to information that
84 becomes available after a drug is marketed that rebuts or mitigates information about a risk
85 already identified in the approved labeling⁸ or otherwise refines risk information in the approved
86 labeling in a way that does not indicate greater seriousness of the risk. New risk information
87 could, for example, include data indicating that the severity or rate of occurrence of an event is
88 lower than described in the approved labeling or call into question a causal relationship between
89 a drug and an event in the approved labeling. New risk information could also supplement risk
90 information in approved labeling derived from a general population with information about risks
91 in subpopulations of interest (e.g., data that show that the risk of an event in patients with hepatic
92 disease is similar to the risk in a general population).⁹

93
94 New risk information does not include, and this guidance is not intended to apply to, information
95 about a newly identified risk (not previously included in the approved labeling) or new
96 information that indicates that a risk already identified in approved labeling is more serious than
97 is reflected in that labeling.

98
99 Nothing in this draft guidance is intended to change a firm's existing obligations under the
100 Federal Food, Drug, and Cosmetic Act (FD&C Act), the Public Health Service Act (PHS Act)
101 and implementing regulations to update its approved labeling, to accurately reflect what is
102 known about the safety profile of the drug, to ensure that the labeling is not false or misleading,
103 or for other reasons.¹⁰

III. OVERVIEW OF FDA RISK ASSESSMENT—PRE- AND POSTMARKET

A. Premarket Risk Assessment

⁸ As used in this draft guidance, *approved labeling* refers to the labeling reviewed and approved under section 351 of the Public Health Service Act, or section 505 or 512 of the Federal Food, Drug, and Cosmetic Act or a conditional approval under section 571 of such act. See 21 CFR 201.56, 201.57, 201.100, and 201.105.

⁹ The term “new risk information” for purposes of this draft guidance should not be confused with the term “new safety information,” as defined in section 505-1(b)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for purposes of FDA determinations about (among other things) the exercise of its authority under section 505(o)(4) of the FD&C Act to require and, if necessary, order labeling changes if it becomes aware of new safety information it believes should be included in the labeling of a drug. Although in some cases, the same information may constitute new risk information as used in this draft guidance and new safety information as defined in section 505-1(b)(3) of the FD&C Act, this draft guidance is not intended to address new safety information nor the implementation of section 505(o)(4). For information regarding section 505(o)(4), see the 2013 guidance for industry entitled *Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act*.

¹⁰ See, e.g., 21 CFR 201.56(a)(2) (“[approved] labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading”), 21 CFR 314.70 and 601.12 (concerning supplements and other changes to an approved application, including labeling), and 21 CFR 514.8(c) (concerning supplements and other changes to an approved application for a new animal drug, including labeling).

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109 As reflected in the statutory new drug and new animal drug approval standards in sections 505
110 and 512 of the FD&C Act and the standard for licensure under section 351 of the PHS Act, the
111 evidence that is the basis for the risk assessment of a drug differs from the evidence that is the
112 basis for an effectiveness determination. The effectiveness determination is generally intended
113 to evaluate a drug's positive effect based on adequate and well-controlled trials designed to
114 evaluate a specific efficacy variable (or a discrete number of efficacy variables) for the purpose
115 of distinguishing the effect of the drug from other influences.¹¹ In contrast, FDA's premarket
116 risk assessment is intended to identify and characterize the nature, frequency, and severity of the
117 usually broad spectrum of adverse events and other risks associated with the use of a product
118 based on a range of data sources. For human drugs, the supporting data are generally not derived
119 from studies designed to test a specific safety hypothesis. The assessment is based largely on
120 observations of adverse events from studies intended to assess effectiveness and includes all
121 patients exposed to the investigational drug during its development. For animal drugs, there are
122 generally data from safety studies in the target animal, in addition to observations of adverse
123 events from studies intended to assess effectiveness.¹² For both human and animal drugs,
124 relevant data are weighted and integrated, based on the nature and reliability of the data sources,
125 into a coherent assessment of what adverse reactions are reasonably associated with the use of a
126 product and, to the extent possible, their frequency and severity.¹³

127
128 Risk information is presented in various sections of the approved labeling. The ADVERSE
129 REACTIONS section is the repository for all adverse reactions associated with a drug.
130 Depending on the seriousness or other important clinical implications of an adverse reaction, it
131 may also be discussed in greater detail in other labeling sections, in particular the WARNINGS
132 AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING sections.¹⁴ For
133 example, the ADVERSE REACTIONS section of approved human drug labeling is explicitly
134 required to "describe the overall adverse reaction profile of the drug based on the entire safety
135 database."¹⁵ The threshold for inclusion of an adverse event¹⁶ in approved human drug labeling
136 is a determination that "there is some basis to believe there is a causal relationship between the
137 drug and the occurrence of the adverse event."¹⁷ Whether there is some basis to believe there is
138 a causal relationship is a matter of judgment based on factors such as: (1) the frequency of
139 reporting of the event, (2) whether the adverse event rate for a drug exceeds the placebo rate, (3)
140 the extent of dose-response, (4) the extent to which the adverse event is consistent with the
141 pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6)

¹¹ 21 CFR 314.126; 21 CFR 514.117

¹² Target animals are the specific animals (e.g., species, class, etc.) for which the drug is intended for use. This draft guidance pertains only to risk information relevant to target animal safety. The Agency conducts a separate review with respect to the human food safety of drugs given to food animals which takes different factors into account.

¹³ See the 2005 guidance for industry entitled *Premarketing Risk Assessment* for a more detailed discussion of premarket assessment of safety to support drug approval.

¹⁴ See, e.g., the 2011 guidance for industry entitled *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Drug and Biological Products—Content and Format*.

¹⁵ 21 CFR 201.57(c)(7)

¹⁶ The term *adverse event* refers to the universe of untoward medical occurrences observed in conjunction with exposure to a drug, whether or not considered drug-related (see 21 CFR 312.32(a)). Adverse reactions are a subset of adverse events for which there is evidence to conclude there is some basis to believe there is a causal relationship between the drug and the adverse event (see 21 CFR 201.57(c)(7)).

¹⁷ 21 CFR 201.57(c)(7)

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142 the existence of dechallenge and rechallenge experience, and (7) whether the adverse event is
143 known to be caused by related drugs.¹⁸

144
145 As these factors suggest, the strength of the evidence of a causal relationship between a drug and
146 an adverse event (and, where applicable, the assessment of rate of occurrence) may vary across
147 different drugs and diseases, and across different adverse reactions for the same drug, based on
148 the types of data sources available in the premarket safety database, the size of the premarket
149 population exposed to the drug, the pharmacology of the drug, and the nature of the event.
150 Placebo-controlled and dose-response studies, if available, will generally be more informative
151 than active-control and single-arm studies, and a larger premarket population will generally be
152 more informative than a smaller one. Also, certain types of events are more strongly suggestive
153 of a causal relationship than others. For example, a single occurrence, or a small number of
154 occurrences, of a hypersensitivity reaction to a drug in which the patient was rechallenged with
155 the drug and reacted, or an event that very rarely occurs spontaneously in a population not
156 exposed to a drug (e.g., agranulocytosis, Stevens-Johnson Syndrome), can provide strong
157 evidence of a causal relationship. However, a limited number of occurrences of a serious event
158 that would be expected to occur in the study population independent of exposure to a drug (e.g.,
159 cardiovascular events in an elderly study population) provide more ambiguous evidence of a
160 causal relationship. Therefore, a premarket risk assessment, although a thorough and rigorous
161 assessment of the available safety data from the entire population exposed to a drug prior to
162 marketing, may be limited in its ability to fully characterize a drug's safety profile by the nature
163 of the supporting data and the size of the population exposed.

B. Postmarket Risk Assessment

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166 Because of the inherent limitations of the premarket risk assessment, postmarketing
167 pharmacovigilance activities—both active (new controlled and epidemiologic studies) and
168 passive (spontaneous reports)—may be critically important to developing and refining the safety
169 profile of a drug. For example, new adverse reactions may be identified through postmarket
170 reports of adverse events, particularly rare serious events that occur at a frequency too low to
171 have been identified and characterized premarketing. Also, new data and information may be
172 developed to further characterize previously identified adverse events. The types of data that can
173 contribute to further developing the safety profile of a drug after marketing include data from
174 controlled trials intended to evaluate a specific safety endpoint, controlled and uncontrolled trials
175 evaluating efficacy (e.g., new uses), pooled analyses of new and existing risk information from
176 controlled trials, epidemiologic studies evaluating a particular safety endpoint or safety
177 generally, registries, and analyses of postmarketing reports of adverse events obtained through
178 active (e.g., Sentinel) or passive surveillance processes. In some cases, additional new studies—
179 controlled trials or epidemiologic studies—may be postmarketing requirements or commitments
180 made at the time of approval or thereafter (e.g., a cardiovascular outcome study is often required
181 for a new drug to treat type 2 diabetes).¹⁹

¹⁸ See the 2006 guidance for industry entitled *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* for a more detailed discussion of how to identify adverse reactions for inclusion in approved labeling.

¹⁹ See the 2005 guidance for industry entitled *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* for a more detailed discussion of postmarketing safety assessment.

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IV. CRITERIA FOR DETERMINING WHETHER NEW RISK INFORMATION IS APPROPRIATE FOR DISTRIBUTION TO HEALTH CARE PROFESSIONALS AND HEALTH CARE ENTITIES

FDA recognizes that the safety profile of a drug evolves throughout its lifecycle as the extent of exposure to the product increases and that it can be helpful for health care practitioners to receive significant new risk information about an approved product in a timely manner. Firms may distribute to healthcare entities and healthcare professionals new risk information under appropriate circumstances, even if such data are not consistent with the risk information currently in approved labeling. Before distributing new risk information that suggests that an adverse reaction or other risk currently in approved labeling is not causally related to a drug or is less consequential than is reflected in the labeling, or that otherwise refines the characterization of an adverse reaction identified in approved labeling, firms should carefully consider the reliability and persuasiveness of the data. As discussed in section III.A, there are cases in which even one occurrence of an adverse event can provide strong evidence that the drug caused the event. In contrast, where existing evidence provides some basis to believe that there is a causal relationship between an event and a drug,²⁰ the evidence offered to overcome that prior showing should generally be from a study or analysis in a population large enough to detect a meaningful difference in the rate of occurrence of an event in patients who are exposed to the drug versus those who are not.

FDA does not intend to object to the distribution of new risk information that rebuts, mitigates, or refines risk information in the approved labeling, and is distributed by a firm in the form of a reprint or digital copy of a published study, if the study or analysis and the manner of distribution meet the principles set out below. Distribution of information that is not consistent with this guidance may render the labeling of a drug false or misleading under section 502(a) of the FD&C Act.

DATA SOURCE

- The study or analysis should meet accepted design and other methodologic standards for the type of study or analysis (e.g., provides a clear description of the hypothesis tested, acknowledges and accounts for potential bias and multiplicity) and should be sufficiently well-designed and informative to merit consideration in assessing the implications of a risk.
- To rebut a prior determination (reflected in the approved labeling) that there is some basis to believe there is causal relationship between the drug and the occurrence of an adverse event, or to otherwise mitigate a described risk, the study or analysis should also be at least as persuasive as the data sources that underlie the existing risk assessment of causality, severity, and/or incidence of the adverse reaction as reflected in approved labeling (e.g., data from a new controlled trial designed to estimate the relative risk of the event, a pharmacoepidemiologic study that is capable of reliably estimating the relative

²⁰ See 21 CFR 201.57(c)(7).

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- 227 risk, or a rigorous meta-analysis of all relevant data from new and existing controlled
228 trials).
- 229
- 230 • The conclusions of the study or analysis should give appropriate weight and
231 consideration to, and should be a fair characterization of, all relevant information in the
232 safety database, including contrary or otherwise inconsistent findings. As discussed
233 above, there is a broad spectrum of potential data sources that can contribute in some way
234 to characterization of a product's safety; new risk information should be considered in
235 light of all relevant existing information and integrated with that data to the extent
236 possible.
 - 237
 - 238 • The study or analysis should be published in an independent, peer-reviewed journal.

DISTRIBUTION

- 240
- 241 • The reprint or digital copy should be accompanied by a cover sheet that clearly and
242 prominently discloses:
 - 243 ○ The study design, critical findings, and significant methodologic or other
244 limitations of the study or analysis that may limit the persuasiveness or scope of
245 findings that rebut, mitigate, or refine risk information in the approved labeling.
246 Limitations should be discussed in relation to the specific circumstances of the
247 study and its conclusions about a risk.²¹
 - 248
 - 249 ○ That the information is not consistent with certain risk information in the
250 approved labeling (should specifically identify the inconsistent information).
 - 251
 - 252 ○ That FDA has not reviewed the data.
 - 253
 - 254 ○ Any financial interests or affiliations between the study author(s) and the firm.
 - 255
 - 256 • The reprint or digital copy should be accompanied by the approved labeling for the
257 product.
 - 258
 - 259 • The reprint or digital copy, when distributed, should be separate from any promotional
260 material.
 - 261
 - 262 • Any statements made by a representative of the firm to a recipient concerning the reprint
263 should be consistent with its content and the information in the disclosure cover sheet.
 - 264
 - 265

²¹ Randomized, controlled trials designed to assess relative risk of occurrence of an adverse reaction would generally provide the most persuasive information, although they can have quality and interpretation problems. Other types of data sources that could be relied on to rebut, mitigate, or refine risk information, such as pharmacoepidemiologic studies or meta-analyses, will generally warrant more extensive discussions of their limitations.