
Guidance for Industry

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway

DRAFT GUIDANCE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)**

**March 2014
Labeling**

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TABLE OF CONTENTS

I. INTRODUCTION..... 1

II. BACKGROUND 2

III. ACCELERATED APPROVAL LABELING CONSIDERATIONS..... 3

A. Indication Approved Under Accelerated Approval.....3

 1. *Indication(s)*..... 3

 2. *Limitations of Usefulness and Clinical Benefit Uncertainty*..... 4

 3. *Continued Approval*..... 4

B. When Clinical Benefit Has Been Verified..... 5

C. Withdrawal of an Accelerated Approved Indication..... 5

 1. *Lack of Evidence Concerning the Withdrawn Indication* 6

 2. *Safety Information Concerning the Withdrawn Indication*..... 6

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1 **Guidance for Industry¹**
2 **Labeling for Human Prescription Drug and Biological Products**
3 **Approved Under the Accelerated Approval Regulatory Pathway**
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8 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
9 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
10 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
11 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
12 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
13 the appropriate number listed on the title page of this guidance.
14

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17
18 **I. INTRODUCTION**
19

20 This guidance is intended to assist applicants in developing the INDICATIONS AND USAGE
21 section of labeling for human prescription drug and biological products for indications that are
22 approved under the accelerated approval regulatory pathway (hereafter accelerated approval) as
23 defined in section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR
24 part 314, subpart H, or 21 CFR part 601, subpart E. More specifically, this guidance focuses on
25 indications and usage statements for drugs approved on the basis of a surrogate endpoint or an
26 effect on a clinical endpoint other than survival or irreversible morbidity.² This guidance also
27 addresses labeling considerations for indications that were approved under accelerated approval
28 and for which clinical benefit subsequently has been verified and the FDA terminates the
29 conditions of accelerated approval under 21 CFR 314.560 or 21 CFR 601.46, or when the FDA
30 withdraws accelerated approval of an indication while other indications for the drug remain
31 approved.
32

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

¹ This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² The term *drug* as used in this guidance refers to both human drugs and biological products.

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40 **II. BACKGROUND**

41
42 The accelerated approval process is one of several approaches used by the FDA to make
43 prescription drugs more rapidly available for the treatment of serious or life-threatening diseases.
44 Section 506(c) of the FD&C Act provides that the FDA may grant accelerated approval to “a
45 product for a serious or life-threatening condition . . . upon a determination that the product has
46 an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a
47 clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is
48 reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical
49 benefit, taking into account the severity, rarity, or prevalence of the condition and the availability
50 or lack of alternative treatments.”

51
52 This guidance focuses on how accelerated approval based on a surrogate endpoint, or on a
53 clinical endpoint that can be measured earlier than irreversible morbidity or mortality, is
54 represented in the INDICATIONS AND USAGE section of labeling. In each case, the effect on
55 the endpoint is established by the results of adequate and well-controlled clinical trials. The
56 accelerated approval is subject, however, to the requirement that the applicant conduct additional
57 postmarketing clinical trials to verify and describe the drug’s clinical benefit,³ where there is
58 uncertainty as to the relationship of the surrogate endpoint to the clinical benefit, or of the
59 observed clinical endpoint to ultimate outcome. Typically, clinical benefit is verified when
60 postmarketing clinical trials show that the drug provides a clinically meaningful positive
61 therapeutic effect, that is, an effect on how a patient feels, functions, or survives.⁴

62
63 Labeling for human prescription drugs must contain “a summary of the essential scientific
64 information needed for the safe and effective use of the drug.”⁵ Labeling must conform to the
65 content and format requirements delineated in 21 CFR 201.56(d) and 201.57. Special provisions
66 exist for older drug labeling under § 201.56(e) and 21 CFR 201.80. Labeling for drugs approved
67 under the accelerated approval framework is in most ways the same as labeling for drugs with
68 traditional approval. However, if a drug is granted accelerated approval based on a surrogate
69 endpoint, the INDICATIONS AND USAGE section of the labeling will also include a “succinct
70 description of the limitations of usefulness of the drug and any uncertainty about anticipated
71 clinical benefits, with reference to the ‘Clinical Studies’ section for a discussion of the available
72 evidence,” as noted in § 201.57(c)(2)(i)(B).⁶

73
74

³ Section 506(c)(2)(A) of the FD&C Act; 21 CFR 314.510 and 21 CFR 601.41.

⁴ See the draft guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*. When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁵ 21 CFR 201.56(a)(1).

⁶ The FDA interprets this provision as applying not only to drugs approved on the basis of a surrogate endpoint, but also drugs approved based on an effect on a clinical endpoint other than survival or irreversible morbidity.

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75 III. ACCELERATED APPROVAL LABELING CONSIDERATIONS

76
77 Certain labeling issues specific to the accelerated approval process should be considered if any of
78 the following three conditions apply: (1) the FDA grants approval of a drug (or a specific
79 indication) under accelerated approval; (2) postmarketing clinical trials have verified and
80 adequately described the drug’s clinical benefit for an indication granted under accelerated
81 approval; or (3) the FDA withdraws approval of one or more indications granted under
82 accelerated approval for a drug whose labeling includes other approved indications.

83 84 A. Indication Approved Under Accelerated Approval

85
86 The information included in the INDICATIONS AND USAGE section of labeling for drugs
87 approved under accelerated approval generally should describe the following three elements:

- 88
89 1. Indication(s)
90 2. Limitations of Usefulness and Clinical Benefit Uncertainty
91 3. Continued Approval

92
93 The following is an example of how these three elements would be represented in the indications
94 and usage statement in the full prescribing information:

95
96 Drug X is indicated for {state indication}. This indication is approved under accelerated
97 approval based on {state effect on surrogate endpoint or clinical endpoint that supported the
98 accelerated approval} [see *Clinical Studies (14.X)*]. An improvement in {identify the
99 specific clinical benefit that remains to be established} has not been established. Continued
100 approval for this indication may be contingent upon {either (“verification and description of
101 clinical benefit”) or (“demonstration of” followed by identification of the particular expected
102 clinical benefit(s) that will be the objective of the postmarketing study)} in confirmatory
103 trials.

104
105 A similar approach should be used when developing indications and usage statements under the
106 Indications and Usage heading in Highlights, except that the cross-reference to the CLINICAL
107 STUDIES section (as discussed below) is not necessary in the Highlights statement.

108
109 A more detailed description of each of the three elements is provided below with examples.

110 111 I. Indication(s)

112
113 The INDICATIONS AND USAGE section “must state that the drug is indicated for the
114 treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition or of a
115 manifestation of a recognized disease or condition, or for the relief of symptoms associated with
116 a recognized disease or condition.”⁷

117

⁷ See § 201.57(c)(2).

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118 An example of an indication statement is as follows:

119

120 Drug X is indicated for the treatment of locally advanced or metastatic non-small cell lung
121 cancer.

122

123 2. *Limitations of Usefulness and Clinical Benefit Uncertainty*

124

125 Labeling for drugs approved based on a surrogate or clinical endpoint that can be measured
126 earlier than irreversible morbidity or mortality includes a succinct description of the limitations
127 of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference
128 to the CLINICAL STUDIES section for a discussion of the available evidence.

129

130 The description of the limitations of usefulness of the drug and any uncertainty about anticipated
131 clinical benefits can be communicated by first identifying the surrogate endpoint or clinical
132 endpoint that supported accelerated approval, then identifying the specific clinical benefit that
133 remains to be established. This description should immediately follow the approved indication
134 rather than appear under a separate subheading or paragraph, because the information provides
135 details that are specific to the indication.

136

137 For health care providers who frequently prescribe drugs approved under accelerated approval,
138 including the term *accelerated approval* in the indications and usage statement is informative
139 because it provides the framework and rationale for the other indications statement elements that
140 are unique to drugs approved in this manner.

141

142 An example of a description of the limitations of usefulness and clinical benefit uncertainty in
143 the indications statement is as follows:

144

145 This indication is approved under accelerated approval based on tumor response rate [*see*
146 *Clinical Studies (14.1)*]. An improvement in survival or disease-related symptoms has not
147 been established.

148

149 3. *Continued Approval*

150

151 For indications approved under accelerated approval based on a surrogate endpoint, or on a
152 clinical endpoint that can be measured earlier than irreversible morbidity or mortality, the
153 applicant is generally required to conduct additional postmarketing clinical trials to verify and
154 describe the drug's clinical benefit. Although regulatory postmarketing study requirements
155 typically are not included in labeling, a brief summary of the confirmatory study requirements
156 can further emphasize the limitations of usefulness given the available data supporting the
157 accelerated approval. Therefore, the INDICATIONS AND USAGE section should include a
158 statement explaining that continued approval for the indication may be subject to the requirement
159 that confirmatory trials verify the drug's clinical benefit.

160

161 When summarizing the postmarketing study requirements, the statement should refer to
162 *verification and description of clinical benefit*. Where it is possible to identify the particular

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163 expected clinical benefit(s) (that will be the objective of the postmarketing study), it is preferable
164 to do so. Examples are illustrated below.

165
166 Continued approval for this indication may be contingent upon verification and description of
167 clinical benefit in confirmatory trials.

168
169 or

170
171 Continued approval for this indication may be contingent upon demonstration of
172 improvement in survival in confirmatory trials.

B. When Clinical Benefit Has Been Verified

173
174
175
176 Following successful verification and description of clinical benefit in the postmarketing studies,
177 the information in the INDICATIONS AND USAGE section should be revised. The indications
178 statement should generally reflect the population and condition for which there is substantial
179 evidence of safety and effectiveness, including any new or remaining limitations of use. The
180 previous statements concerning limitations of usefulness and continued approval should be
181 removed or revised, as appropriate. In addition, other sections of labeling (e.g., ADVERSE
182 REACTIONS and CLINICAL STUDIES) should be revised, as appropriate, to reflect the new
183 data.

C. Withdrawal of an Accelerated Approved Indication

184
185
186
187 Approval of a drug or indication approved under accelerated approval may be withdrawn either
188 at the request of the applicant or by the FDA for the following reasons (among others):

- 189
- 190 • The applicant fails to conduct any required postmarketing study with due diligence
 - 191
 - 192 • A study required to verify and describe the predicted effect on irreversible morbidity or
 - 193 mortality or other clinical benefit of the drug fails to verify and describe such effect or
 - 194 benefit
 - 195
 - 196 • Other evidence demonstrates that the drug is not safe or effective under the conditions of
 - 197 use⁸
 - 198

199 If the accelerated approval indication is withdrawn, but the drug remains approved for other
200 indications, the labeling must be revised.⁹ For example, it may be necessary to remove
201 information concerning the withdrawn indication from several sections (e.g., INDICATIONS
202 AND USAGE, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES) so that the

⁸ See section 506(c)(3) of the FD&C Act (21 U.S.C. 356(c)(3)); 21 CFR 314.530 and 601.43.

⁹ See § 201.56(a)(2).

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203 labeling does not imply or suggest that the drug is approved for the withdrawn indication.¹⁰ In
204 addition to removing information, it may sometimes be appropriate to add to the labeling new
205 information concerning the withdrawn indication, as noted below.

206

1. Lack of Evidence Concerning the Withdrawn Indication

208

209 Under § 201.57(c)(2)(ii), if there is a common belief that the drug may be effective for a certain
210 use, or if there is a common use of the drug for a condition, but the preponderance of evidence
211 related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of
212 the drug do not generally outweigh its risks, the FDA may require that the INDICATIONS AND
213 USAGE section state that there is lack of evidence that the drug is effective or safe for that use.
214 When accelerated approval of an indication is withdrawn, the FDA may require that the labeling
215 be revised to include a limitation of use concerning the withdrawn indication.

216

2. Safety Information Concerning the Withdrawn Indication

218

219 Under § 201.57(c)(6)(i), a specific warning relating to a use not provided for under the
220 INDICATIONS AND USAGE section may be required by the FDA in the WARNINGS AND
221 PRECAUTIONS section of labeling if a drug is commonly prescribed for a disease or condition
222 and such usage is associated with a clinically significant risk or hazard. Because the drug was
223 previously indicated for the now-withdrawn use and may continue to be considered for that use
224 by some health care providers, important adverse reactions or other risks associated with the
225 withdrawn indication may be appropriate to include in the WARNINGS AND PRECAUTIONS
226 and/or ADVERSE REACTIONS sections of the revised labeling. The description of the risk or
227 hazard also should be accompanied by a statement that the drug is not approved for the
228 withdrawn indication.

229

¹⁰ See § 201.57(c)(2)(iv).