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

**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)**

**January 2019
Labeling**

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

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

and/or

*Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002*

*Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**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)**

**January 2019
Labeling**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	2
III.	ACCELERATED APPROVAL LABELING CONSIDERATIONS	3
A.	Indication Approved Under Accelerated Approval	3
1.	<i>Limitations of Usefulness and Clinical Benefit Uncertainty</i>	<i>4</i>
2.	<i>Continued Approval</i>	<i>4</i>
B.	When Clinical Benefit Has Been Verified	5
C.	Withdrawal of an Accelerated Approved Indication	5
1.	<i>Lack of Evidence Concerning the Withdrawn Indication</i>	<i>6</i>
2.	<i>Safety Information Concerning the Withdrawn Indication</i>	<i>6</i>

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in developing the INDICATIONS AND USAGE section of labeling for human prescription drug and biological products that are approved under the accelerated approval regulatory pathway (hereafter accelerated approval) as defined in section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 314, subpart H, or 21 CFR part 601, subpart E. More specifically, this guidance focuses on indications for drugs² approved via accelerated approval on the basis of a surrogate endpoint or a clinical endpoint other than survival or irreversible morbidity.³ This guidance also addresses labeling considerations for indications that were approved under accelerated approval and for which clinical benefit subsequently has been verified and the FDA terminates the conditions of accelerated approval under 21 CFR 314.560 or 21 CFR 601.46. In addition, this guidance addresses labeling considerations when the FDA withdraws approval of an indication that had been approved through the accelerated approval pathway while other indications for the drug remain approved.

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

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

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

³ This guidance focuses on indications that are granted accelerated approval status based on 21 CFR 314.510 and 21 CFR 601.41. This guidance does not address 21 CFR 314.520 and 21 CFR 601.42.

Contains Nonbinding Recommendations

II. BACKGROUND

The accelerated approval process is one of several approaches used by the FDA to expedite the development of drugs for serious or life-threatening diseases and conditions. Section 506(c) of the FD&C Act provides that the FDA may grant accelerated approval to “a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.” For purposes of this guidance, these categories of endpoints are referred to as surrogate endpoints and intermediate clinical endpoints.

This guidance focuses on how accelerated approval based on a surrogate endpoint, or on an intermediate clinical endpoint, is represented in the INDICATIONS AND USAGE section of labeling. In each case, the effect on the endpoint is established by the results of adequate and well-controlled clinical trials.⁴ However, the accelerated approval is subject to the requirement that the applicant conduct additional postmarketing clinical trials to verify and describe the drug’s clinical benefit,⁵ where there is uncertainty as to the relationship of the surrogate endpoint to the clinical benefit, or of the intermediate clinical endpoint to ultimate outcome. Clinical benefit is verified when postmarketing clinical trials show that the drug provides a clinically meaningful positive therapeutic effect, usually an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives.⁶

Labeling for human prescription drugs must contain “a summary of the essential scientific information needed for the safe and effective use of the drug.”⁷ Applications submitted for accelerated approval must include labeling that conforms to the content and format requirements for human prescription drug labeling delineated in 21 CFR 201.56(d) and 201.57. Labeling for drugs approved under the accelerated approval framework is in most ways the same as labeling for drugs with traditional approval.

However, if a drug is granted accelerated approval based on a surrogate endpoint, the INDICATIONS AND USAGE section of the labeling must also include a “succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical

⁴ See 21 CFR 314.126.

⁵ See section 506(c)(2)(A) of the FD&C Act; §§ 314.510 and 601.41.

⁶ See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁷ See 21 CFR 201.56(a)(1).

Contains Nonbinding Recommendations

benefits, with reference to the ‘Clinical Studies’ section for a discussion of the available evidence,” as noted in § 201.57(c)(2)(i)(B).⁸

III. ACCELERATED APPROVAL LABELING CONSIDERATIONS

Certain special labeling considerations arise when the FDA approves a drug (or an indication) under the accelerated approval pathway, including the following: (1) information to be included in the INDICATIONS AND USAGE section of labeling; (2) revisions needed when postmarketing clinical trials have verified and adequately described the drug’s clinical benefit for an indication granted under accelerated approval; and (3) revisions needed when the FDA withdraws approval of one or more indications granted under accelerated approval for a drug whose labeling includes other approved indications.

A. Indication Approved Under Accelerated Approval

Under FDA regulations, the information included in the INDICATIONS AND USAGE section of labeling for drugs approved under accelerated approval must include the indication (i.e., the disease or condition that the drug treats, prevents, mitigates, cures, or diagnoses),⁹ as well as a “succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits. . . .”¹⁰ The information in this section generally should also acknowledge that the drug was approved based upon accelerated approval and that continued approval for the drug (or indication) may be contingent upon verification and description of clinical benefit in a confirmatory trial or trials.

The following is an example of how these elements should be represented in the INDICATIONS AND USAGE section of the full prescribing information:

DRUG X is indicated for {state indication}. This indication is approved under accelerated approval based on {state effect on surrogate endpoint or intermediate clinical endpoint that supported the accelerated approval} [*see Clinical Studies (14.X)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

A similar presentation should be used under the Indications and Usage heading in Highlights, except that the cross-reference to the CLINICAL STUDIES section is not necessary for Highlights.

⁸ The FDA interprets this provision as applying not only to drugs approved under accelerated approval on the basis of a surrogate endpoint, but also drugs approved under accelerated approval based on an effect on a clinical endpoint other than survival or irreversible morbidity. Under § 201.57(c)(2)(i)(B), the requirement to provide a succinct description of limitations of usefulness and any uncertainty about anticipated clinical benefits of a drug also applies to situations where “evidence is available to support the safety and effectiveness of a drug only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group). . . .”

⁹ See § 201.57(c)(2).

¹⁰ See § 201.57(c)(2)(i)(B).

Contains Nonbinding Recommendations

A more detailed description of two elements of the INDICATIONS AND USAGE section is provided below with examples.

1. Limitations of Usefulness and Clinical Benefit Uncertainty

The INDICATIONS AND USAGE section for drugs (or indications) approved based on a surrogate or intermediate clinical endpoint should state the endpoint used in the clinical trials that provided substantial evidence to support accelerated approval, and the limitations of that endpoint. In addition, a cross-reference to the CLINICAL STUDIES section for a discussion of the available evidence should be included. The description of the basis for approval should immediately follow the indication rather than appear under a separate heading or paragraph.

The following is an example of a statement that states the endpoint used in the clinical trials to support the accelerated approval:

This indication is approved under accelerated approval based on tumor response rate [*see Clinical Studies (14.1)*].

Including the term *accelerated approval* is informative because it provides the framework and rationale for the other indication elements that are unique to drugs approved in this manner.

Simply reporting the endpoint used may convey sufficient information about uncertainty with regard to the limitations of usefulness of the drug and of uncertainty about anticipated clinical benefits (the benefit that is anticipated based upon the surrogate or intermediate clinical endpoint used to support accelerated approval). In other circumstances, additional context about the approval should be included in the indication by identifying the clinical outcome(s) that are expected (based on the effect demonstrated on the surrogate or intermediate clinical endpoint) but not yet established.

The following is an example of a statement that provides additional context about the approval by identifying the clinical outcome(s) that have not been established. Such information should be described immediately after the sentence that identifies the endpoint that supported accelerated approval.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase [*see Clinical Studies (14.1)*]. An improvement in survival or disease-related symptoms have not been established.

2. Continued Approval

For indications approved under accelerated approval based on a surrogate or intermediate clinical endpoint, the applicant generally is required to conduct additional postmarketing clinical trials to verify and describe the drug's clinical benefit. Although regulatory postmarketing study requirements typically are not included in labeling, a brief summary of the confirmatory study requirements can further emphasize the limitations of the clinical study results supporting the

Contains Nonbinding Recommendations

accelerated approval. Therefore, the INDICATIONS AND USAGE section should include a statement explaining that continued approval for the indication may be subject to the requirement that confirmatory trials verify the drug's clinical benefit. When summarizing the postmarketing study requirements, the statement should refer to *verification and description of clinical benefit* as described in the following example.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

B. When Clinical Benefit Has Been Verified

Following successful verification and description of clinical benefit in the postmarketing studies, the information in the INDICATIONS AND USAGE section should be revised. The indication generally should reflect the population and condition for which there is substantial evidence of effectiveness, including any new or remaining limitations of use. The statements concerning limitations of usefulness and continued approval should be removed or revised, as appropriate. In addition, other sections of labeling (e.g., ADVERSE REACTIONS and CLINICAL STUDIES) should be revised, as appropriate, to reflect the new data (e.g., the CLINICAL STUDIES section generally should be revised to include a description of the clinical studies that verified clinical benefit).

C. Withdrawal of an Accelerated Approved Indication

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

- The applicant fails to conduct any required postmarketing study with due diligence
- A study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the drug fails to verify and describe such effect or benefit
- Other evidence demonstrates that the drug is not safe or effective under the conditions of use¹¹

If the accelerated approval indication is withdrawn, but the drug remains approved for other indications, the labeling must be revised.¹² For example, it may be necessary to remove information concerning the withdrawn indication from several sections (e.g., INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES) so that the labeling does not imply or suggest that the drug is approved for the withdrawn indication.¹³ In

¹¹ See section 506(c)(3) of the FD&C Act (21 U.S.C. 356(c)(3)); 21 CFR 314.530 and 601.43.

¹² See § 201.56(a)(2).

¹³ See § 201.57(c)(2)(iv) and (v).

Contains Nonbinding Recommendations

addition to removing information, it may sometimes be appropriate to add to the labeling new information concerning the withdrawn indication, as noted below.

1. Lack of Evidence Concerning the Withdrawn Indication

Under § 201.57(c)(2)(ii), if there is a common belief that the drug may be effective for a certain use, or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the drug do not generally outweigh its risks, the FDA may require that the INDICATIONS AND USAGE section state that there is lack of evidence that the drug is effective or safe for that use. When accelerated approval of an indication is withdrawn, the FDA may require that the labeling be revised to include a limitation of use concerning the withdrawn indication.¹⁴

2. Safety Information Concerning the Withdrawn Indication

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

¹⁴ See the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* (July 2018). 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 guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.