Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Iris Masucci at 301-796-2500 or (CBER) the Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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)

July 2018
Labeling

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Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

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Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in drafting the INDICATIONS AND USAGE section of labeling as described in the regulations for the content and format of labeling for human prescription drug and biological products[2] (21 CFR 201.57(c)(2)).[3]

Recommendations include the following:

- General principles to consider when drafting the INDICATIONS AND USAGE section of the labeling
- What information to include in the INDICATIONS AND USAGE section
- When to include additional descriptors or qualifiers as part of the indication in the INDICATIONS AND USAGE section
- When to include limitations of use in the INDICATIONS AND USAGE section

[1] This guidance has been prepared by the Office of Medical Policy 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] This guidance applies to drugs, including biological drug products. For the purposes of this guidance, *drug product* or *drug* will be used to refer to human prescription drug and biological products that are regulated as drugs, except when there is a difference in the regulation. In such cases, *biological products* will be used. This guidance does not apply to those biological products that are also devices.

[3] See the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922, January 24, 2006) and additional labeling guidances at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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- How to write, organize, and format the information within the INDICATIONS AND USAGE section

The purpose of this guidance is to help ensure that the INDICATIONS AND USAGE section is clear, concise, useful, and informative and, to the extent possible, consistent within and across drug and therapeutic classes. Applicants should follow the recommendations in this guidance when developing the INDICATIONS AND USAGE section for a new drug and when revising this section for a currently approved drug, including when seeking approval of a new indication.

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.

II. GENERAL PRINCIPLES

The primary role of the INDICATIONS AND USAGE section of labeling is to enable health care practitioners to readily identify appropriate therapies for patients by clearly communicating the drug's approved indication(s). Among other information, the INDICATIONS AND USAGE section states the disease or condition, or manifestation or symptoms thereof, for which the drug is approved, as well as whether the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of that disease or condition, including relief of symptoms (21 CFR 201.57(c)(2)). Other sections of labeling (e.g., DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS), as applicable, also provide essential details that enable safe and effective use of a drug, and labeling should be considered in its entirety for individual prescribing decisions.

To comply with the general labeling requirements in 21 CFR 201.56 and 201.57, the INDICATIONS AND USAGE section must:

- Reflect the scientific evidence accurately

- Be concisely written to include the information necessary to clearly convey the use(s) for which the drug has been shown to be safe and effective

- Use terminology that is clinically relevant and scientifically valid and understandable to health care practitioners

Additionally, indications that are straightforward, clear, concise, and consistently written will facilitate the indexing of indications in electronic drug databases. This may, in turn, assist health care practitioners in searching indications in electronic medical information systems, thereby providing easier access to the information in FDA-approved labeling needed for clinical decision making.

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A. Scope of the Indication(s)

Governing regulations articulate parameters for the evidentiary standard necessary for an indication to be listed in the INDICATIONS AND USAGE section of labeling. For drug products other than biological products, absent an applicable waiver, "all indications listed in the INDICATIONS AND USAGE section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies" as defined in 21 CFR 314.126(b) (§ 201.57(c)(2)(iv)).[4] For biological products, indications "must be supported by substantial evidence of effectiveness" (§ 201.57(c)(2)(v)). Any statements in this section of the labeling comparing the safety or effectiveness of drug or biological products with other agents for the same indications must be similarly supported – that is, for drugs, they must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies and, for biological products, they must be supported by substantial evidence of effectiveness (§ 201.57(c)(2)(iii)).

Pursuant to the governing regulations, "[i]ndications or uses must not be implied or suggested in other sections of the labeling if not included" in the INDICATIONS AND USAGE section (§ 201.57(c)(2)(iv) and (v)). However, FDA may require a specific warning relating to an unapproved use in the WARNINGS AND PRECAUTIONS section of the labeling if the drug is commonly prescribed for a disease or condition and if such usage is associated with a clinically significant risk or hazard (§ 201.57(c)(6)(i)).[5]

1. Scope of an Indication Relative to the Population Studied

The INDICATIONS AND USAGE section should clearly communicate the scope of the approved indication, including the population to which the determination of safety and effectiveness is applicable. The indicated population may mirror the studied population, for example, in terms of patient demographics or severity of disease or condition, but can sometimes differ. In some cases, FDA's expert reviewers may fairly and responsibly conclude, based on their scientific training and experience, that the available evidence supports approval of an indication that is broader or narrower in scope than the precise population studied.[6] Applicants should discuss the scope of a proposed indication with the applicable review division.[7]

Indications may be written to include certain patient populations that may have been absent or specifically excluded from the clinical studies that supported approval (e.g., geriatric patients,

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[4] The Director of CDER may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in 21 CFR 314.126(b) with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A waiver petition must explain why the study, as conducted, will still yield substantial evidence of effectiveness (see 21 CFR 314.126(c)). Additionally, an applicant may submit a request to the Director of CDER or the Director of CBER asking for a waiver of any requirement under 21 CFR 201.56, 201.57 or 201.80 (see 21 CFR 201.58).

[5] See the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

[6] See generally 21 U.S.C 355(d).

[7] See 21 CFR 312.41.

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pregnant women, patients taking certain concomitant drugs, patients with a different severity or stage of a disease). An indication for a broader population than the patient population studied in controlled trials may be appropriate after careful consideration of the generalizability of the evidence, consistencies in the disease process across different groups, and the drug's overall benefits and risks.

For example, if a study evaluating a drug in adults enrolled patients of a certain age range and excluded patients taking certain concomitant drugs, and available evidence does not suggest the drug would be unsafe or ineffective in adult patients outside that age range or in those taking the other drugs, the indication should be worded to reflect the broader age group (i.e., "in adults") rather than the exact ages studied. In addition, unless available evidence suggests otherwise, the indication should not exclude use in patients taking the concomitant drugs. Recommendations regarding age groups outside of an adult population are discussed in section II.A.2.

Similarly, if a drug were studied only in patients with a moderate form or stage of a disease and there is reason to believe, based on the generalizability of the data, consistencies in the disease process, and the drug's benefits and risks, that the drug would be both safe and effective in a broader group with the condition, an indication covering the broader population may be appropriate. In some cases, an indication covering the overall disease population can be considered. Specifics regarding the patient population studied should be described in the CLINICAL STUDIES section of the labeling.

Conversely, an indication may be approved for a population narrower than that which was studied. For example, a study may enroll and randomize patients, but then stratify participants by the presence or absence of a specific genomic marker. If the study demonstrated benefit only in patients who had tested positive for the marker, FDA's expert reviewers may fairly and responsibly conclude, based on their scientific training and experience, that the available evidence supports approval of an indication in a population that is narrower in scope than the population that was studied.[8]

There may also be circumstances in which the indication should reflect the precise population studied. For example, some study designs such as prognostic enrichment strategies (e.g., enrolling only people with a prior myocardial infarction in a study examining the effects of an antiplatelet drug) and most predictive enrichment strategies (e.g., enrolling only people with a specific genomic marker) may identify the population in which the benefits outweigh the risks or the only population in which effectiveness is reasonably likely.[9] In such cases, the indication should reflect only the population studied, unless and until evidence becomes available to support a determination that broader safety and effectiveness can be expected.

2. Age Groups in Indications

[8] See generally 21 USC 355(d).

[9] See the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, this guidance will represent FDA's current thinking on this topic.

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Approval of a drug in pediatric patients[10] is generally based on sufficient data from studies in the following populations:

- A pediatric population only
- Both adult and pediatric populations
- Adults, with supporting data in a pediatric population (e.g., safety, pharmacokinetic data) that allow extrapolation of effectiveness to a pediatric population[11]
- One pediatric population that allows extrapolation of effectiveness to another pediatric population[12]

In certain circumstances (see section II.A.1), it may be appropriate to consider an indication for an adult population in an age group broader than the population that was studied. However, this approach is generally not appropriate across pediatric populations or between adult and pediatric populations because of the statutory requirements related to pediatric assessments[13] and the unique clinical considerations for pediatric patients. For example, pediatric patients may metabolize drugs differently from adults (in an age-related manner), are susceptible to different safety risks, and often require different dosing regimens even after correction for weight.

For these reasons, age groups should be included in indications. As such, an indication should state that a drug is approved, for example, "in adults," "in pediatric patients X years of age and older," or "in adults and pediatric patients X years of age and older."

Applicants should discuss the scope of and age groups for a proposed indication with the applicable review division.[14]

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[10] The labeling regulations define *pediatric patients* as those ranging in age from birth through 16 years (21 CFR 201.57(c)(9)(iv)).

[11] Although it may be appropriate to extrapolate effectiveness, it is generally not appropriate to extrapolate safety with respect to pediatric populations.

[12] See section 505B(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 201.57(c)(9)(iv). See also the draft guidance for industry and review staff *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling*. When final, this guidance will represent FDA's current thinking on this topic.

[13] The Pediatric Research Equity Act (Public Law 108-155) generally requires certain applications for, among other things, a new indication to contain a pediatric assessment unless the applicant has obtained a waiver or deferral. Pediatric assessments "shall contain data, gathered using appropriate formulations for each age group for which the assessment is required that are adequate (i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective" (section 505(B)(a) of the FD&C Act).

[14] See 21 CFR 312.41.

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B. Distribution of Information Among Labeling Sections

Generally, the section of the full prescribing information to which particular drug information is most relevant will contain the most detailed discussion of such information. Other sections should discuss only those aspects of the information that are pertinent to those other sections' scopes and purposes. There may be instances when it is necessary to include information in the INDICATIONS AND USAGE section that is discussed in greater detail elsewhere in the labeling. For example, the INDICATIONS AND USAGE section may include a limitation of use that has a cross-reference to a more detailed discussion of the information supporting the limitation in the WARNINGS AND PRECAUTIONS section (see section III.B). Because detailed information about topics such as clinical studies and risks related to limitations of use will generally be found elsewhere in the labeling, the information in the INDICATIONS AND USAGE section should be concise.

C. Updating the INDICATIONS AND USAGE Section

The INDICATIONS AND USAGE section "must be updated when new information becomes available that causes the labeling to be inaccurate, false, or misleading" (§ 201.56(a)(2)).[15] In addition, it is appropriate in certain circumstances for application holders to update this section to reflect current practices for writing indications for a particular group of drugs (for example, when more information becomes available about the drug, drug class, or specific disease or when the endpoints become better established). Application holders should review the INDICATIONS AND USAGE section regularly to ensure that it reflects current science and, to the extent possible, maintains consistency within a pharmacologic or therapeutic class.[16]

III. CONTENT AND FORMAT OF THE INDICATIONS AND USAGE SECTION

The INDICATIONS AND USAGE section includes the indication and, as appropriate, any identified limitations of use.[17] The INDICATIONS AND USAGE section "must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition" (§ 201.57(c)(2)). When drafting the INDICATIONS AND USAGE section, applicants should consider what information is needed to clearly convey the approved indication and whether other information in addition to the identification of the disease or condition is warranted.

For many drugs, the indication will be sufficiently conveyed by stating the disease or condition being treated, prevented, mitigated, cured, or diagnosed, and the approved age group(s) (see section II.A.). For example, indications may be straightforward for many conditions (e.g.,

[15] Application holders update their labeling using the procedures in 21 CFR 314.70 or 601.12, as applicable.

[16] See generally 21 CFR 201.56(a).

[17] See 21 CFR 201.57(c)(2).

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symptomatic conditions such as pain, allergic rhinitis). In such circumstances, endpoints and descriptions of benefit should be summarized in the CLINICAL STUDIES section of labeling and should not be included in the indication.

On the other hand, other scenarios may warrant the inclusion of more information in the indication. Such scenarios could include cases in which a drug may target different aspects of a disease (e.g., in multiple sclerosis) or cases where endpoints are not well-standardized (e.g., in heart failure); in these scenarios, the specific benefits of the drug should be stated. For example, for a drug indicated for the treatment of insomnia, the indication should state whether the drug affects sleep onset, sleep maintenance, or both, in order to facilitate appropriate prescribing for an individual patient. Similarly, for many outcome studies, when there is an overall effect on a composite endpoint, the indication should identify the components of the composite (e.g., cardiovascular death, myocardial infarction, and stroke). In such cases, it would be critical to clearly state in the indication what benefit the drug has been shown to convey (see section III.C.1).

Details of studies that describe the basis for approval (e.g., "Effectiveness was demonstrated in two 12-week trials in patients with FEV_1 less than 60% of predicted.") should not be included in the INDICATIONS AND USAGE section. This section is not intended to be a description of the data supporting the determination of effectiveness, and the inclusion of such statements here could have the unintended consequence of inappropriately limiting use of the drug in practice (e.g., inadvertently suggesting short-term use of a drug indicated for a chronic condition). Likewise, discussions of disease definitions (e.g., diagnostic criteria for major depressive disorder) should not be included. These types of details should be discussed in the CLINICAL STUDIES section of labeling (see section III.C.1).

Specific components of and other considerations for the INDICATIONS AND USAGE section are discussed in detail in sections A through D below.

A. Indication

The indication should begin "DRUG-X is indicated" and must include the following elements required under 21 CFR 201.57(c)(2)(i):

- The disease, condition, or manifestation of the disease or condition (e.g., symptom(s)) being treated, prevented, mitigated, cured, or diagnosed

- When applicable, other information necessary to describe the approved indication (e.g., descriptors of the population to be treated, adjunctive or concomitant therapy, or specific tests needed for patient selection)

The following subsections provide details on each element of an indication listed above, along with illustrative examples demonstrating how to draft these elements so they are clear, concise, and easily identifiable and searchable.

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1. The Disease, Condition, or Manifestation Being Treated, Prevented, Mitigated, Cured, or Diagnosed

The INDICATIONS AND USAGE section must state that the drug "is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for relief of symptoms associated with a recognized disease or condition" (§ 201.57(c)(2)). The disease, condition, or manifestation should be included in the indication using high-level terms that are clinically relevant and scientifically valid (e.g., asthma, diabetes mellitus, pain). Although FDA does not endorse any particular resource for terms used to describe diseases, conditions, or symptoms, all terminology should be well understood and easily recognizable by health care practitioners.

2. Other Information Necessary To Describe the Approved Indication

In addition to identifying the disease, condition, or symptom for which the drug is approved, there may be additional critical aspects of an indication that are important to include. Examples of such situations are described in items a through c below.

a. Selected patient subgroups or disease subpopulations for whom the drug is approved

In some cases, additional descriptors or qualifiers are critical to include as part of the indication to clearly identify the patient population for whom the drug is approved. In addition to including the approved age group(s) (see section II.A.2), other circumstances in which such additional information would be important include, but are not limited to, indicating a drug for patients previously treated with other therapies (e.g., hormone-refractory prostate cancer), patients with a certain classification of a disease (e.g., World Health Organization Group I pulmonary arterial hypertension), or patients with other important identifying variables (e.g., immunocompetent patients). For example, if a drug is for use only in patients with a history of coronary disease events (i.e., as secondary prevention), the indication should clearly convey the patient population for which the drug is approved.

If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with the target disease or condition, "this section must include…a succinct description of the limitations of usefulness" (§ 201.57(c)(2)(i)(B)). Thus, the indication should include information on the subgroup(s) for whom the drug is approved. For example:

- DRUG-X is indicated for the treatment of adult and pediatric patients 12 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

If a drug should be reserved for use in specific situations (e.g., cases refractory to other drugs) because of safety concerns, "this section must include…a statement of the information" pertaining to such situations (§ 201.57(c)(2)(i)(E)). For example:

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- DRUG-X is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response to TNF antagonist therapy.

For drugs approved for use only after other drug therapies have failed (e.g., an indication for second-line use), consideration should be given as to whether it is necessary to specify the name of the drug(s) or drug class(es) the patients are to have initially received or instead to word the indication more broadly (e.g., for use in previously treated patients).

b. Adjunctive or concomitant therapy or therapeutic modalities to use before initiating drug therapy, such as diet or exercise or another drug

If the drug is approved for use only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or another drug), "[t]his section must include…a statement that the drug is indicated as an adjunct to that mode of therapy" (§ 201.57(c)(2)(i)(A)). For example:

- DRUG-X is indicated in adults for the treatment of high-grade malignant glioma as an adjunct to surgery and radiation.

For drugs approved for use as adjunctive therapy, consideration should be given as to whether it is necessary to specify the name of the drug(s) or drug class(es) the patients are to receive concomitantly or instead to word the indication more broadly (e.g., as adjunctive therapy or as part of a combination regimen).

c. Specific tests needed to select patients in whom to use the drug

If specific tests are necessary for selection or monitoring of patients who need the drug, "[t]his section must include…the identity of such tests" (§ 201.57(c)(2)(i)(C)).[18] For example:

- DRUG-X is indicated for the treatment of adult patients with metastatic non-small cell lung cancer whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

In general, information on tests used for monitoring appears in other labeling sections (e.g., DOSAGE AND ADMINISTRATION or WARNINGS AND PRECAUTIONS).[19]

[18] When appropriate, the labeling should identify the type of FDA-approved or cleared in vitro companion diagnostic device with which the product is approved, rather than a particular manufacturer's device. See the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*.

[19] See the following two guidances for industry: (1) *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* and (2) *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

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B. Limitations of Use

Limitations of use are presented separately from the indication within the INDICATIONS AND USAGE section (see section III.D.2). A limitation of use is included when there is reasonable concern or uncertainty among FDA's expert reviewers, who are qualified by scientific training and experience, about a drug's risk-benefit profile. Limitations of use should be distinguished from contraindications. A contraindication "must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit" (§ 201.57(c)(5)). However, there are cases in which the evidence falls short of requiring a contraindication, but suggests that use of the drug may be inadvisable. There are also cases in which there is sufficient uncertainty about the drug's benefits in certain clinical situations to suggest that the drug should generally not be used in those settings. In these cases, a limitation of use may be appropriate. To avoid redundancy within the labeling, contraindications should not be restated as limitations of use in the INDICATIONS AND USAGE section.

Limitations of use should be included in the INDICATIONS AND USAGE section only when the awareness of such information is important for practitioners to ensure the safe and effective use of the drug. In most cases, limitations of use will identify a particular patient population in which a drug should generally not be used. If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population, the INDICATIONS AND USAGE section "must include…a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the 'Clinical Studies' section for a discussion of the available evidence" (§ 201.57(c)(2)(i)(B)). Such information would be appropriate to include as a separate limitation of use — rather than narrowing the language of the indication itself — when needed to inform practitioners that there is a reasonable concern or uncertainty about the drug's safety or effectiveness outside the specific population for which the drug is approved.

In contrast, information that essentially narrows or further defines a drug's approved indication and is used to direct appropriate therapy (e.g., identifying particular subsets of the population for whom the drug is approved, drugs to be used only after other drug therapies have failed, or specific tests needed to identify patients to be treated) should be incorporated directly into the indication whenever possible (see section III.A.2). This information should not be presented as a separate limitation of use. Whereas a limitation of use most often will be included to identify a patient population in which the drug should generally *not* be used (i.e., discouraging its use), information that specifies the patient population in which the drug *should* be used (i.e., encouraging its use) should, wherever possible, be incorporated in the indication itself. For example, if a drug should be used only after failure of or as an adjunct to another drug or treatment modality, the indication should include this information rather than having it presented separately as a limitation of use.

Although there are invariably areas of uncertainty about a drug's effectiveness, not all drugs will include limitations of use in the INDICATIONS AND USAGE section. Information considered for a limitation of use should be evaluated to decide if it may be better suited to another section of the labeling (e.g., WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS,

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CLINICAL STUDIES). For example, although there may be circumstances in which a limitation of use will be further described in (and cross-referenced to) a subsection in the WARNINGS AND PRECAUTIONS section, most warnings and precautions will typically not be repeated as limitations of use. Only information that provides a clearer understanding of the scope of the approved indication to facilitate safe and effective prescribing decisions should be included as a limitation of use. Moreover, an absence of data in a particular population subset should generally not appear as a limitation of use unless there is reasonable concern about the drug's safety or effectiveness in that group.

1. Situations in Which Limitations of Use Would Be Appropriate

The following are examples of situations in which it may be appropriate to include a separate limitation of use within the INDICATIONS AND USAGE section:

a. Drugs for which there is reasonable concern or uncertainty about effectiveness or safety in a certain clinical situation

As recommended in section II.A.2, the approved age group(s) should be included in an indication. If there is a concern or uncertainty about safety or effectiveness in a population outside the approved age group (e.g., younger patients), a limitation of use should be included about that population. The inclusion of a limitation of use will differentiate between (1) a circumstance in which use of the drug in a certain population outside of the approved population raises a reasonable concern or uncertainty about safety or effectiveness and (2) a circumstance in which an indication is simply directed to a certain group (e.g., patients within a particular age range). The concern that warranted the limitation of use should typically be described elsewhere in labeling (e.g., WARNINGS AND PRECAUTIONS and USE IN SPECIFIC POPULATIONS sections), with a cross-reference in the limitation of use to the section of labeling where this detailed information can be found. For example:

- DRUG-X is indicated for the treatment of hypertension in adults and pediatric patients 1 year of age and older.

  <u>Limitations of Use</u>
  In patients younger than one year of age, DRUG-X can adversely affect kidney development *[see Warnings and Precautions (5.X) and Use in Specific Populations (8.4)]*

The governing regulation states that "[i]f there is a common belief that a 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 do not generally outweigh its risks, FDA may require that [the INDICATIONS AND USAGE] section state that there is a lack of evidence that the drug is effective or safe for that use or condition" (§ 201.57(c)(2)(ii)). A limitation of use may be of particular importance in these circumstances if proven alternative therapies exist for the condition in question. For example:

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- DRUG-X is indicated in adults for the acute treatment of migraine headache with or without aura.

  Limitations of Use
  Multiple clinical trials failed to establish the effectiveness of DRUG-X for the prophylaxis of migraine headaches *[see Clinical Studies (14.X)]*.

b. Drugs approved without evidence of benefits known to occur with other drugs in the same class

If a drug is approved without having demonstrated a particular benefit that has been demonstrated with other drugs in the same pharmacologic or therapeutic class, it may be important to convey the differences among products under a "Limitations of Use" heading in the INDICATIONS AND USAGE section. For example, the INDICATIONS AND USAGE section for a new HMG-CoA reductase inhibitor that is approved based on its serum lipid-lowering effects (without evidence of a beneficial effect on cardiovascular morbidity and mortality) would typically be presented as follows:

- DRUG-X is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides and to increase HDL cholesterol in adult patients with primary hyperlipidemia or mixed lipidemia.

  Limitations of Use
  The effect of DRUG-X on cardiovascular morbidity and mortality has not been determined.

c. Drugs with dose, duration, or long-term use considerations

If information on limitations of use or uncertainty about anticipated benefits is relevant to the recommended dosing intervals, to appropriate treatment duration when treatment should be limited, or to any dosage modification, the INDICATIONS AND USAGE section "must include…a concise description of the information, with a reference to the more detailed information in the 'Dosage and Administration' section" (§ 201.57(c)(2)(i)(D)). Under these circumstances, information about important dose or duration considerations, such as how long a drug can safely be used or uncertainty about the risks and benefits of treatment beyond a certain period (e.g., long-term cumulative toxicity), should be included as a limitation of use. For example:

- DRUG-X is indicated for the management of elevated plasma uric acid levels in adult patients with tumor lysis syndrome.

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> <u>Limitations of Use</u>
> The activity of DRUG-X may be neutralized by the development of anti-drug antibodies if more than a single course of treatment is administered *[see Dosage and Administration (2.X) and Warnings and Precautions (5.X)]*.

It is generally not necessary to limit duration of use in the INDICATIONS AND USAGE section unless such a limited duration is essential to ensure the safe and effective use of the drug. If clinical trials evaluated the effectiveness of a drug for a chronic condition only in short-term trials of sufficient duration to support such an approval (e.g., drugs for major depressive disorder or hypertension), but the drug is indicated for long-term use due to the chronic nature of the condition and because there is no known or anticipated safety or efficacy concern from continued use, a description of the duration of use from the clinical trials or information about the lack of longer term data generally should not be included in the INDICATIONS AND USAGE section. Information on the length of the clinical trials should instead be discussed in detail in the CLINICAL STUDIES section of the labeling.

If there are specific conditions that should be met before the drug is used on a long-term basis (e.g., demonstration of responsiveness to the drug after short-term use in an individual patient), the INDICATIONS AND USAGE section "must include…a statement of the conditions; or if the indications for long term use are different from those for short term use, a statement of the specific indications for each use" (§ 201.57(c)(2)(i)(F)). For drugs with these characteristics, a limitation of use may be used to address such issues. For example:

- DRUG-X is indicated for the treatment of severe spasticity in adult patients with spinal cord injury, brain injury, or multiple sclerosis.

  <u>Limitations of Use</u>
  Prior to implantation of a device for chronic intrathecal infusion of DRUG-X, confirm a positive clinical response to DRUG-X in a screening phase *[see Dosage and Administration (2.X)]*.

*2. Situations in Which Limitations of Use Generally Would **Not** Be Appropriate*

Limitations of use generally would ***not*** be appropriate in the following situations:

a. To restate information already included in the indication

For example, if an indication is clearly worded as being approved for use in combination with another drug, there is no need for a limitation of use stating that the subject drug should be used only in combination and not as monotherapy.

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b. To address the absence of data in populations in which the drug was not studied

For example, if an oncology drug was studied in and is indicated for use in patients with a cancer of a specific mutation, there should not be a limitation of use about the absence of data in patients with typical (wild-type) forms, unless there is reasonable concern about the drug's safety or effectiveness in such patients. Likewise, if a drug is approved to reduce the risk of rejection in patients receiving a heart transplant, there should not be a limitation of use about the lack of data on use in lung transplants. Similarly, if a vaccine is approved for use in children 12 months through 12 years of age, there should not be a limitation of use about the absence of data in other age groups.

C. Other Considerations for Writing the INDICATIONS AND USAGE Section

1. Identification of Outcomes, Endpoints, and Benefit(s) the Drug Conveys

The approved indication will generally convey the benefit of the treatment (i.e., the disease, condition, manifestation, or symptoms of the disease or condition being treated, prevented, mitigated, cured, or diagnosed), and it is usually not necessary to fully describe the specific way benefit was measured in clinical trials (i.e., identifying outcomes or endpoints) when the treatment affects a broad range of manifestations of the disease (e.g., an indication for the symptoms of allergic rhinitis). In some cases, however, a broad disease indication may not be appropriate because, for example, the drug may affect only certain signs, symptoms, or manifestations of the disease (see section III). An indication identifying an outcome or endpoint may be considered, for example, when the drug's effect on the overall disease is not well understood, when different drugs have different effects on various manifestations of the diseases, when clinical trials evaluated only one or some of the manifestations of the disease, or when the endpoints are different from typical effectiveness measures. For example:

- DRUG-X is indicated to improve walking in adult patients with multiple sclerosis.

For certain other conditions, the drug's indication may be to reduce the risk of significant morbidity and mortality, which describes the demonstrated benefit more accurately than would a more broadly written indication indicating the product simply as a treatment for the condition itself. In such cases, the specific endpoint(s) for which the drug has demonstrated benefits should be incorporated into the indication. For example:

- DRUG-X is indicated to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, and revascularization procedures in adult patients with clinically evident coronary heart disease.

The CLINICAL STUDIES section of labeling "must discuss those studies that facilitate an understanding of how to use the drug safely and effectively" (§ 201.57(c)(15)). The information presented in that section ordinarily includes, among other things, a description of the study population, endpoints, and results. For example, if an indication were written for an overall effect on a composite endpoint, the details on the endpoints studied and results (e.g., which

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572 component of a composite endpoint drove the overall combined finding) would be discussed in
573 detail in the CLINICAL STUDIES section. Additionally, if only one component of a composite
574 primary endpoint was affected and indicating the drug for the composite would misrepresent the
575 true result, an indication for the single component can be considered, with the explanation of the
576 study results summarized in the CLINICAL STUDIES section.
577
578 *2. Accelerated Approval*
579
580 If a drug is approved for an indication based on an effect on a surrogate endpoint or an
581 intermediate clinical endpoint under section 506(c) of the Federal Food, Drug, and Cosmetic Act
582 (FD&C Act) (21 U.S.C. 356(c)) and 21 CFR 314.510 or 601.41 (i.e., accelerated approval), the
583 INDICATIONS AND USAGE section "must include…a succinct description of the limitations
584 of usefulness of the drug and any uncertainty about anticipated clinical benefits, with a reference
585 to the Clinical Studies section for a discussion of the available evidence"
586 (§ 201.57(c)(2)(i)(B)).[20]
587
588 *3. Required or Recommended Language*
589
590 Under governing statutory and regulatory provisions, certain products have required or
591 recommended language for the INDICATIONS AND USAGE section. For example:
592
593 • Labeling for systemic antibacterial drug products must include a specific
594 statement in the INDICATIONS AND USAGE section about strategies for
595 reducing the development of drug-resistant bacteria and maintaining the
596 effectiveness of the subject drug and other antibacterial drugs (21
597 CFR 201.24(b)).
598
599 • Section 505(u)(2)(B) of the FD&C Act (21 U.S.C. 355(u)(2)(B)) requires that
600 labeling for certain products containing a single enantiomer of a previously
601 approved racemic drug include a statement that the non-racemic product is not
602 approved, and has not been shown to be safe and effective, for any condition of
603 use of the previously approved racemic drug. For such products approved under
604 505(u), this information should be presented as a limitation of use.
605
606 • Other FDA guidances (e.g., clinical/medical guidances) recommend specific
607 wording for the INDICATIONS AND USAGE section for certain indications.[21]
608

[20] See the draft guidance for industry *Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway*. When final, this guidance will represent FDA's current thinking on this topic.

[21] Additional labeling guidances are available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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609 *4. Preferred Wording and Wording Generally To Avoid*[22]
610
611 Consistent with this guidance and the regulatory framework, as a general matter, care should be
612 taken when considering use of the following terms and phrases:
613
614 a. "Reduce the risk" versus "prevent"
615
616 If the indication for a drug is to reduce the risk of the occurrence of a particular clinical outcome,
617 phrases such as "reduce the risk of" or "reduce the incidence of" should be considered rather
618 than using "prevent" in the indication. The use of a term such as *prevent* may imply a guarantee
619 of success that is not supported by the data. However, for certain indications, the use of terms
620 such as *prevent* (e.g., for preventive vaccines) or *prophylaxis* (e.g., drugs for post-exposure
621 prophylaxis) in the indication may be appropriate because, in a given context, these terms are
622 well established and understood by the clinical community.
623
624 b. "Only"
625
626 The INDICATIONS AND USAGE section should be worded clearly to convey the approved use
627 of the drug, making inclusion of the word "only" unnecessary (i.e., the indication generally
628 should ***not*** state "DRUG-X is indicated only for…").
629
630 c. "Also indicated"
631
632 When a new indication is added to the INDICATIONS AND USAGE section, the phrase "is also
633 indicated" generally should ***not*** be used because it may imply that the new indication is less
634 important than the existing indication(s).
635
636 d. Product identification in the indication
637
638 The indication should include the proprietary name (or trade name). If the product does not have
639 a proprietary or trade name, the indication should include the nonproprietary name (i.e.,
640 established name for a drug product or proper name for a biological product).
641
642 To avoid unnecessary clutter and to enhance clarity, other information (such as the non-
643 proprietary name, dosage form, route of administration) generally should not be included in the
644 indication. The established pharmacologic class appears with the indication only in Highlights
645 (§ 201.57(a)(6)).
646
647 **D. Formatting the INDICATIONS AND USAGE Section**
648
649 *1. Format for Multiple Indications*
650
651 When a drug is approved for more than one indication, the format of the INDICATIONS AND
652 USAGE section should be carefully considered. For some drugs, it may be preferable to assign a
653 subsection to each indication (e.g., 1.1 Disease-A, 1.2 Disease-B), but for others, it may be

[22] See generally 21 CFR 201.56.

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preferable to present distinct indications using only bullets (e.g., "DRUG-X is indicated for:" followed by a bulleted list) immediately under the main section heading or within a subsection.

2. Format for Limitations of Use

Limitations of use are presented separately from the indication within the INDICATIONS AND USAGE section, under the heading *Limitations of Use* and not usually under a separate numbered subsection. If, however, a drug has multiple indications and the limitations of use apply to all of them, it may be preferable to use a separate numbered subsection for *Limitations of Use* within the section. The INDICATIONS AND USAGE section should be formatted to clearly show if the limitations apply to all or to only some of the indications.