Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

DRAFT GUIDANCE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)

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Labeling

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry[1]

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format[2]

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I. INTRODUCTION

This guidance is intended to assist applicants and reviewers in drafting the WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING sections of labeling, as described in the final rule amending the requirements for the content and format of labeling for human prescription drug and biological products (21 CFR 201.56 and 201.57).[3] The recommendations in this guidance are intended to help ensure that the labeling is clear, useful, informative, and to the extent possible, consistent in content and format.

This guidance provides recommendations on the following:

- How to decide which adverse reactions are significant enough to warrant inclusion in the WARNINGS AND PRECAUTIONS section; what information to include when describing those adverse reactions; and how to organize the section

[1] This guidance has been prepared by the Medical Policy Coordinating Committees in the Center for Drug Evaluation and Research (CDER) and 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.

[3] See the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in the *Federal Register* in January 2006.

- What situations warrant a contraindication; what information to provide in those situations when the use of the product is contraindicated; and how to organize the CONTRAINDICATIONS section
- When to include a boxed warning; and what information to include in the BOXED WARNING section

FDA's guidance documents, including this guidance, 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. WARNINGS AND PRECAUTIONS SECTION (§ 201.57(c)(6))

A. Adverse Reactions and Information to Include

1. Observed Adverse Reactions

This section includes clinically significant adverse reactions observed in association with the use of a drug for which there is reasonable evidence of a causal association between the drug and the adverse reaction (a causal relationship need not have been established):

IF

- The adverse reaction is serious (see glossary for definition of serious adverse reaction).

OR

- The adverse reaction does not meet the definition of a serious adverse reaction, but is still considered clinically significant (*otherwise clinically significant*). Adverse reactions that are considered *otherwise clinically significant* could include:

  — Adverse reactions that require discontinuation, dosage or regimen adjustment, or addition of another drug

  — Adverse reactions that could be prevented or managed with appropriate patient selection or avoidance of concomitant therapy

  — Adverse reactions that significantly affect patient compliance

OR

- The product interferes with a laboratory test.

2. Expected Adverse Reactions

There are circumstances in which an adverse reaction can be expected to occur with a drug, despite its not having been observed with that drug, based on observations from

other members of the drug class or animal studies. An expected adverse reaction may not be observed, for example, in clinical trials for newer drugs in a class where the trials are designed to exclude populations that were determined to be vulnerable to the adverse reaction with earlier members of the drug class.

The WARNINGS AND PRECAUTIONS section includes adverse reactions that are expected to occur with a drug, but have yet to be observed if:

- The reaction is *serious* or *otherwise clinically significant* as discussed above

AND EITHER

- Based on what is known about the pharmacology, chemistry, or class of the drug, it appears likely that the adverse reaction will occur with the drug.

OR

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects).

In these cases, the labeling should acknowledge that the adverse reaction has not been observed, but may be expected to occur.

3. Additional Considerations

The following factors should also be considered in determining whether to include an adverse reaction in the WARNINGS AND PRECAUTIONS section of labeling:

- Indication

The relative seriousness of the disease or condition for which a drug is indicated will influence whether an adverse reaction would be considered clinically significant and thus appropriate for inclusion in the WARNINGS AND PRECAUTIONS section. For example, for a drug intended to treat a minor, self-limiting condition (e.g., allergic rhinitis, cosmetic conditions, transient insomnia), a nonserious adverse reaction (e.g., nausea, pruritis, alopecia) may be considered clinically significant and, therefore, appropriate for inclusion in the section. For a drug intended to treat a serious or life-threatening condition (e.g., cancer), the same adverse reaction may be considered much less clinically significant and not appropriate for inclusion in the section.

- Incidence

Typically, the nature of an adverse reaction and a drug's indication are the most influential factors in determining whether an adverse reaction should be included in the WARNINGS AND PRECAUTIONS section. In some cases, however, the absolute risk or rate of an adverse reaction can be an important factor when deciding whether to include the reaction in this section (e.g., when the risk or rate is high).

- Ability to Manage or Prevent an Adverse Reaction

The ability to manage or prevent an adverse reaction through patient monitoring, proper dose selection or titration, or avoidance of concomitant therapy can also be an important factor in deciding whether to discuss an adverse reaction in the WARNINGS AND PRECAUTIONS section.

4. Adverse Reactions Associated with Unapproved Uses

FDA may require a specific warning relating to an unapproved use if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard (§ 201.57(c)(6)(i)). Clinically significant adverse reactions that appear to be linked primarily to an unapproved use of a drug (e.g., use for a disease, condition, or population not included in the INDICATIONS AND USE section, use of an unapproved dose or regimen) should be identified and discussed in the WARNINGS AND PRECAUTIONS section. The discussion should include a statement indicating that safety and effectiveness have not been established in that setting and that the use is not approved by FDA.

5. Drug Interactions

The WARNINGS AND PRECAUTIONS section should include a discussion of any known or predicted drug interactions with serious or otherwise clinically significant outcomes, with a cross-reference to any additional information in the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections.

6. Monitoring

The WARNINGS AND PRECAUTIONS section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions (§ 201.57(c)(6)(iii)), and, if appropriate, information about the frequency of testing and expected ranges of normal and abnormal values.

B. Information to Provide

The WARNINGS AND PRECAUTIONS section should contain the following information for each adverse reaction, if such information is known:

- A description of the adverse reaction and outcome (e.g., time to resolution, significant sequelae)
- An estimate of risk or adverse reaction rate[4]
- A discussion of known risk factors for the adverse reaction (e.g., age, gender, race, comorbid conditions, dose, duration of use, coadministered drugs)
- A discussion of steps to take to reduce the risk of, decrease the likelihood of, shorten the duration of, or minimize the severity of an adverse reaction. These steps could include, for example, necessary evaluation prior to use, titration and other kinds of dose adjustment, monitoring during dose adjustment or prolonged use, avoidance of other drugs or substances, or special care during comorbid events (e.g., dehydration, infection)
- A discussion of how to treat, or otherwise manage, an adverse reaction that has occurred

Although the following issues would typically be discussed elsewhere in labeling, they can also be mentioned in the WARNINGS AND PRECAUTIONS section when such information would help prescribers understand the clinical significance of an adverse reaction:

- A discussion of the mechanism of the adverse reaction
- The source of information about the adverse reaction (e.g., it may be informative to know whether the information is from clinical trials or postmarketing reports, or whether an adverse reaction was seen only in foreign experience with the drug)

The information and advice provided in this section should be reasonably qualified, where appropriate, to convey whatever uncertainties may exist about judgments and conclusions made (e.g., concerning causality assessments, estimated adverse reaction rates, and value of proposed monitoring).

C. Format

1. Subheadings

FDA recommends that each adverse reaction, syndrome, or constellation of reactions (e.g., thrombotic events, hemorrhagic events) included in the WARNINGS AND PRECAUTIONS section have its own subheading. There would ordinarily be no reason

[4] When the risk for an adverse reaction is highest during early exposure, crude risk (# of adverse reactions/# patients exposed) may be the best estimate. For adverse reactions that occur after prolonged exposure, there should be an adjustment for duration of exposure by use of either overall exposed person time if the risk is constant over time, or by calculation of cumulative incidence for a specified exposure time in a survival analysis.

to further subcategorize adverse reactions (e.g., separating observed and expected adverse reactions by placing them under different subheadings).

2. Order of Adverse Reactions

The order in which adverse reactions are presented should reflect the relative public health significance of the adverse reactions. Factors to consider include the relative seriousness of the adverse reaction, the ability to prevent or mitigate the adverse reaction, the likelihood of occurrence, and the size of the population that is potentially affected. In general, the relative seriousness of the adverse reaction and the ability to prevent or mitigate it weigh more heavily than the likelihood of occurrence or the size of the affected population.

3. Emphasis in Text

Bolded text, or other emphasis, can be used to highlight particular adverse reactions or parts of the discussion of particular adverse reactions (e.g., steps to be taken to avoid a problem, subpopulations at particular risk). Emphasis should be used sparingly so that its impact is not diminished. When information is to be emphasized, also consider whether that information should be in a boxed warning (see section IV on BOXED WARNING section).

4. Cross-Referencing

Information discussed in the WARNINGS AND PRECAUTIONS section often is discussed or mentioned in other sections of the labeling (e.g., ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS). Information appearing in other locations should be appropriately cross-referenced.

III. CONTRAINDICATIONS SECTION (§ 201.57(c)(5))

A. When to Contraindicate

A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, must be listed. If there are no known contraindications for a drug, this section must state "None."

1. Observed Adverse Reactions

For observed adverse reactions, the following would ordinarily be reason to contraindicate a drug:

- The risk of the adverse reaction in the clinical situation to which the contraindication will apply, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to the patient.

  AND

- The causal relationship between exposure to the drug and the adverse reaction is well established.

2. Expected Adverse Reactions

Adverse reactions that are expected to occur when a drug is used in a specific clinical situation can be the basis for a contraindication.[5] The following would ordinarily be reason to contraindicate a drug on the basis of an expected adverse reaction.

The risk of the adverse reaction in the clinical situation to which the contraindication will apply, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to the patient

AND EITHER

- Based on what is known about the pharmacology, chemistry, or class of the drug, it appears highly likely that the adverse reaction will occur with the drug.

  OR

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects).

The labeling should acknowledge that the adverse reaction has not yet been observed, but is expected to occur.

3. Likely Clinical Situations

A contraindication usually involves one or more of the following clinical situations:

- Comorbid condition or coexistent physiological state (e.g., existing hepatic disease, renal disease, congenital long QT syndrome, hypokalemia, pregnancy or childbearing potential, CYP 2D6 poor metabolizer[6])

- Demographic risk factor (e.g., age, sex, race, genetic vulnerability)

[5] Expected adverse reactions are distinguishable from "theoretical possibilities" because there are data (e.g., from class, chemistry, animal studies) to support the expected adverse reaction.

[6] Use of a particular drug in a patient with a slow metabolizer status would be contraindicated only if there were no way to lower the dose to adjust for the compromised metabolic state.

- The risks of the drug are such that the drug should never be used in a selected subset of the larger population with a disease[7]

- Coadministered drug where the combination is dangerous (e.g., MAO inhibitor and sympathomimetic drug, a drug known to prolong the QT interval and a drug known to interfere with the metabolism of that drug)[8]

Contraindications based on drug interactions with serious outcomes should be described in the CONTRAINDICATIONS section and cross-referenced to more detailed information in the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections.

B. Information to Provide

For each listed contraindication, provide the following information:

- Brief description of the contraindicated situation or scenario, including any pertinent demographic or identifiable predisposing characteristics

- Description of anticipated consequences of the contraindicated use

C. Format

1. Subheadings

FDA recommends that each contraindication be identified by its own subheading.

2. Order of Contraindications

The order in which contraindications are presented should reflect the relative public health significance of the listed contraindications. Factors to consider include the likelihood of occurrence and the size of the population that is potentially affected.

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[7] The INDICATIONS AND USAGE section must contain information about use of the drug when safety considerations are such that the drug should be reserved for certain patients (e.g., patients with severe disease) or situations (e.g., patients refractory to other drugs) (§ 201.57(c)(2)(i)(B) and (E)). In rare cases, when the risks of the drug clearly outweigh any possible therapeutic benefit and the drug should never be used in a selected patient subset, a contraindication for use of the drug in that subset should also be described in the CONTRAINDICATIONS section.

[8] There should be consistency across labeling for contraindicated products (i.e., if use of drug A with drug B is contraindicated in the labeling for drug A, the use of drug B with drug A should be contraindicated in the labeling for drug B). For drugs that are regulated in different reviewing divisions, there should be cross-divisional coordination and agreement on contraindicated coadministration of drugs.

3. Text Emphasis

Bolded text, or other emphasis, can be used to highlight particular contraindicated situations or parts of the discussions of these situations. Emphasis should be used sparingly so that its impact is not diminished. When information is to be emphasized, also consider whether that information should be in a boxed warning (see BOXED WARNING below).

IV. BOXED WARNING (§ 201.57(c)(1))

A. When to Use a Boxed Warning

A boxed warning is ordinarily used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug

  OR

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

  OR

- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR part 314, subpart H, § 314.520 "Approval with restrictions to assure safe use").

A boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber. Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections should therefore be evaluated to determine whether it should also be placed in a boxed warning.

Boxed warnings are more likely to be based on observed adverse reactions, but there are instances when a boxed warning based on an expected adverse reaction would be appropriate. For example, a contraindication during pregnancy based on evidence in humans that drugs in a pharmacologic class pose a serious risk of developmental toxicity during that time would usually be in a boxed warning for all drugs in that class, even those in which the adverse reaction has not been seen.

A boxed warning can also be considered for a drug that has important risk/benefit information that is unique among drugs in a drug class (e.g., to note that a drug is the

only one in its class to have a particular risk that makes it inappropriate for use as a first line therapy).

B. Information to Provide

A boxed warning provides a brief, concise summary of the information that is critical for a prescriber to be aware of, including any restriction on distribution or use. If there is a more detailed discussion of the concern in either the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, or any other labeling section that contains pertinent information (e.g., DOSAGE AND ADMINISTRATION), a cross-reference to that section must be provided (§ 201.57(c)(1)).

C. Format

FDA recommends the information in the boxed warning be presented in a bulleted format (or some alternative format, such as subheadings) that helps to make the information visually accessible.

GLOSSARY

Adverse Reaction (21 CFR 201.57(c)(7)): For purposes of prescription drug labeling and this guidance, an *adverse reaction* is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and electrocardiogram (ECG).

Adverse Event (or adverse experience): For the purposes of this guidance, an *adverse event* refers to any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related.

Serious Adverse Reaction: For purposes of this guidance, the term *serious adverse reaction* refers to any reaction occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug reactions when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.