Guidance for Industry

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

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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Guidance for Industry[1] Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format[2]

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I. INTRODUCTION

This guidance is intended to help applicants and reviewers in drafting the ADVERSE REACTIONS section of prescription drug labeling as required by 21 CFR 201.57(c)(7). Its primary purpose is to aid in (1) selecting information for inclusion in the section, (2) characterizing adverse reactions selected for inclusion, (3) organizing and presenting the information within the section, and (4) updating adverse reaction information. The goal of this guidance is to assist applicants in designing ADVERSE REACTIONS sections that contain the drug safety information important to patient management decisions and that convey the information in a clear and accessible format.

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. BACKGROUND

As this guidance seeks to bring greater consistency to the content and format of the ADVERSE REACTIONS section, the Agency emphasizes that reviewer and applicant judgment remain critical in assessing how or whether to present information on an adverse reaction. FDA reviewers and applicants should assess such factors as seriousness, severity, frequency, and

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

[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.

strength of causal association in determining which adverse reactions to include in the ADVERSE REACTIONS section and in characterizing those reactions. In general, the ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided (see § 201.57(c)(7) and the Glossary at the end of this guidance for a definition of Adverse Reaction). Such lists are not informative and tend to obscure the more clinically meaningful information.

III. ADVERSE REACTIONS SECTION — CONTENT AND FORMAT

The ADVERSE REACTIONS section is required to list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable (§ 201.57(c)(7)(i)). Separate lists are required for adverse reactions identified from clinical trials (§ 201.57(c)(7)(ii)(A)) and those identified from spontaneous reports after a drug has been marketed (§ 201.57(c)(7)(ii)(B)). This section of the guidance provides recommendations for ensuring that information about the most clinically important adverse reactions is readily accessible (see III.A), and for organizing the information on adverse reactions from clinical trials (see III.B) and from postmarketing safety reports (see III.C).

A. Making the Most Clinically Important Information Accessible

Typically, adverse reactions for a given drug will have varying clinical significance (ranging from serious to minor) and certain adverse reactions that have relatively serious clinical implications will be discussed, often in greater detail, in other sections of labeling (e.g., WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING). The ADVERSE REACTIONS section should make it easier for health care practitioners to recognize and retain the adverse reactions information that is most important to prescribing decisions. The beginning of the ADVERSE REACTIONS section should identify the most clinically significant adverse reactions and direct practitioners to more detailed information about those reactions, if any. For example, the section should first:

- Identify and cross-reference all serious and otherwise important adverse reactions described in greater detail in other labeling sections, especially BOXED WARNING or WARNINGS AND PRECAUTIONS (e.g., see WARNINGS AND PRECAUTIONS (5.1)).

- Identify the most commonly occurring adverse reactions (e.g., all adverse reactions occurring at a rate of 10 percent or greater in the treatment group and at a rate at least twice the placebo rate).

- Identify adverse reactions, if any, that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials.

B. Adverse Reactions From Clinical Trials

The presentation of adverse reactions identified from clinical trials is the major component of the ADVERSE REACTIONS section. The ADVERSE REACTIONS section must include a listing of all such reactions that occurred at or above a specified rate that is appropriate to the drug's safety database (see III.B.3), a separate listing of those adverse reactions that occurred below the specified rate, but for which there is some basis to believe there is a causal relationship between the drug and the event (see III.B.4), and, to the extent information is available and relevant, additional detail about the nature, frequency, severity, duration, dose-response, and demographic characteristics of those adverse reactions with significant clinical implications (§ 201.57(c)(7)(ii)(A)). The following is the recommended organization of adverse reactions identified from clinical trials.

1. Description of Data Sources

The presentation of adverse reactions information identified from clinical trials must be preceded by information necessary to interpret the adverse reactions (§ 201.57(c)(7)(i)). This information would ordinarily include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose, schedule, duration), demographics of the exposed population, designs of the trials in which exposure occurred (e.g., placebo-controlled, active-controlled), and any critical exclusions from the safety database.

Sample Database Description

The data described below reflect exposure to drug X in [n][3] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo- and active-controlled trials (n = __, and n = ___, respectively), and in long-term follow up studies. The population was [age range], [gender distribution], [race distribution] and had [diseases/conditions]. Most patients received doses [describe range, route of administration, frequency, duration, as appropriate].

2. Statement on the Significance of Adverse Reaction Data Obtained From Clinical Trials

To help place in perspective the significance of adverse reaction data obtained from clinical trials, the following statement, or an appropriate modification, should precede the presentation of adverse reactions from clinical trials:

[3] All n's refer to those exposed to drug and not control.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

3. Presentation of Common Adverse Reactions (the Adverse Reactions Table)

The ADVERSE REACTIONS section next should list the adverse reactions identified from clinical trials that occurred at or above a specified rate appropriate to the database (for purposes of this guidance, "common" adverse reactions). The listing must include the rate of occurrence of an adverse reaction for the drug and any comparators (active- or placebo-controls), unless such data cannot be determined or presenting the rates for a comparator would be misleading (§ 201.57(c)(7)(ii)(A)). To permit side-by-side comparison of adverse reaction rates, common adverse reactions are typically presented in a table.[4]

a. Use Best Available Data

The data in the listing of common adverse reactions should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative. If these data are unavailable or not sufficiently informative, the primary table should be based on active-controlled data. If concurrently controlled data are unavailable, overall rates from well-monitored, single-arm databases can be used to provide some indication of what was observed in treated patients. In general, only the most informative data should be presented in the table. For example, if placebo-controlled data were available and sufficiently informative, there would usually be no need to present in a table active-controlled data, single-arm trial data, or the overall safety data, even if they are from larger databases. If a data source is not used in the development of a table, but provides important information about adverse reactions listed in the table that is not found in the trials used in the development of the table (e.g., information about prolonged duration of therapy), that information can be discussed in the commentary following the table (see III.B.5).

b. Description of Data Sources for the Table

The table should be accompanied by a description of the data sources reflected in the table, the basis for including adverse reactions in the table

[4] A table can include less common, even rare, important events when the database is large enough to provide a meaningful comparison to a control group.

(e.g., all reactions occurring at > n% in the treated group and for which the rate for drug exceeds the rate for placebo), and the way in which adverse reaction rates were derived (e.g., for a given adverse reaction, was the rate derived from all reported adverse events of that type not present at baseline or from a subset of reported events deemed by investigators to be drug-related). The description of data sources should indicate the types of studies from which the information in the table was derived and whether the study data were pooled. This information can be provided in text preceding the table, in a footnote to the table, in the title to the table, or some combination of these.

c. How Many Tables?

A single adverse reaction table will usually be adequate. However, it may be more informative to present data in more than one table when a drug's adverse reaction profile differs substantially from one setting or population to another, the adverse reactions that differ are clearly drug related, and the data have important implications for use (or nonuse) and monitoring. Situations in which there may be important differences between rates include different indications, formulations, demographic subgroups, study durations, dosing regimens, and types of studies (e.g., intensely monitored small studies vs. a large outcome study). In these situations, the content of the additional table or tables should be limited to only those adverse reactions for which there were meaningful differences in rates.

4. Presentation of Less Common Adverse Reactions

The ADVERSE REACTIONS section next should present those adverse reactions that occurred below the specified rate for inclusion in the common adverse reactions table or listing, but for which there is some basis to believe there is a causal relationship between the drug and the event (for purposes of this guidance, "less common" adverse reactions). It is difficult to establish that very low frequency adverse events are caused by a drug, and there will often be large numbers of these events reported, most of them not caused by the drug. Lengthy lists of adverse events unlikely to have been caused by the drug are of little or no value to prescribers, and are therefore inappropriate for inclusion in labeling.

Serious, low-frequency adverse events generally will be listed when there is reason to suspect that the drug may have caused the event. Typical reasons to suspect causality for an event include (1) timing of onset or termination with respect to drug use, (2) plausibility in light of the drug's known pharmacology, (3) occurrence at a frequency above that expected in the treated population, and (4) occurrence of an event typical of drug-induced adverse reactions (e.g., liver necrosis, agranulocytosis, Stevens-Johnson syndrome). For serious events that are typical of drug-induced adverse reactions, the occurrence of even a single

event could be a basis for inclusion in the list. When none of these reasons exist, however, an event should be excluded from the list. For example, in a large study of a non-cardiovascular drug in elderly patients, a certain number of acute myocardial infarctions might be expected unrelated to the study drug. If the rate in the study does not exceed the expected rate, those adverse events should be excluded from the ADVERSE REACTIONS section.

Non-serious, low-frequency adverse events should be listed only when there is strong evidence that the drug caused the event. Such evidence may include, for example, positive challenge/dechallenge tests or rate of occurrence in a large controlled trial that, although low, is markedly imbalanced between drug and control arms.

5. Commentary on Listings of Common and Less Common Adverse Reactions

For adverse reactions with significant clinical implications (e.g., those that are most commonly occurring, that result in discontinuation or dose modification, or that require monitoring), the listings of common and less common adverse reactions must be supplemented with additional details about the nature, frequency, severity, dose-response, and demographic characteristics of the adverse reaction, to the extent data are available and important (§ 201.57(c)(7)(ii)(A)). It is more likely that supplemental information will be needed for the more commonly occurring adverse reactions.

a. Information on Nature, Frequency, and Severity

To the extent information is available and important and bears on the nature, frequency, and severity of clinically important adverse reactions, the commentary must discuss applicable factors (§ 201.57(c)(7)(ii)(A)). Examples include:

- Concomitant therapy
- Time course of the reaction
- Steps that can diminish the likelihood or severity of, or prevent, adverse reactions
- Changes in adverse reaction rates as a function of duration of therapy (e.g., increasing or decreasing (tolerance) rates with increasing duration of therapy, adverse reactions that emerge only with long-term use)

b. Dose-Response Information

The commentary must identify clinically significant adverse reactions that exhibit a dose response (§ 201.57(c)(7)(ii)(A)). It may be helpful to

include a small table showing the dose response for adverse reactions for which dose response would be expected to influence dose selection.

c. Demographic and Other Subgroups

The commentary must include clinically important information about observed differences, or lack of observed differences, in adverse reactions in various demographic groups (e.g., age, racial, gender) (§ 201.57(c)(7)(ii)(A)). If information is available and important, the commentary should also discuss observed differences, or lack of observed differences, for other subgroups (e.g., renal failure, liver failure, different severity levels of same disease). Where there is no reliable information on differences or similarities in adverse reaction profiles among demographic subgroups, that fact should be disclosed, along with an explanation of why such information is unavailable (e.g., clinical trials were not designed or powered to detect differences in these populations).

d. Multiple Indications

The commentary should summarize any important differences or similarities in the adverse reactions profiles for different indications. If there are substantial and clinically important differences in adverse reaction profiles between indications, and the differences cannot be adequately summarized in the commentary, there should be separate listings of adverse reactions for each indication. When warranted, clinically important differences or similarities in adverse reaction profiles for multiple indications can also be identified in a more prominent location in the ADVERSE REACTIONS section (e.g., at the beginning of the section).

e. Multiple Formulations

If a drug has multiple formulations and a certain formulation or formulations present unique adverse reaction concerns, the commentary should identify clinically important concerns.

C. Presentation of Adverse Reaction Information From Spontaneous Reports

The ADVERSE REACTIONS section must list adverse reactions identified from domestic and foreign spontaneous reports (§ 201.57(c)(7)(ii)(B)). This listing must be separate from the listing of adverse reactions identified in clinical trials (§ 201.57(c)(7)(ii)(B)) and must also be preceded by information necessary to interpret the adverse reactions (§201.57(c)(7)(i)). To help practitioners interpret the significance of data obtained from postmarketing spontaneous reports, the following statement, or an appropriate modification, should precede these data:

> *The following adverse reactions have been identified during postapproval use of drug X. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.*

Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. When an adverse reaction identified from spontaneous reporting is included in the labeling, the number of spontaneous reports ordinarily is not cited, because the number can quickly become outdated. If the number of reports is cited, the period of observation should be stated.

IV. GENERAL PRINCIPLES FOR SELECTING AND CHARACTERIZING DATA IN THE ADVERSE REACTIONS SECTION

A. Selecting Adverse Events for Inclusion

The definition of adverse reactions does not include all adverse events observed during use of a drug. It is limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug (§ 201.57(c)(7)). Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs.

B. Rare, Serious Reactions

For serious adverse events that are unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception), there is a basis to believe there is a causal relationship between the event and the drug at a very low rate of occurrence. Therefore, these events are generally listed in the adverse reactions section even if there are only one or two reported events, unless it is clear that a causal relationship can be excluded.

C. Determining Adverse Reaction Rates

The rate of an identified adverse reaction is ordinarily derived from all reported adverse events of that type in the database used. Determining a rate based on a subset of reported events that individual investigators believe to be causally related to drug exposure is discouraged. Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations.

D. Avoiding Nonspecific Terms

In characterizing overall adverse reaction experience, nonspecific terms that lack a commonly understood or precise meaning are discouraged, as use of such terms can be misleading. For example, the phrase *well-tolerated* is a vague and subjective judgment about a drug's adverse reaction profile for which there are no commonly understood parameters. In addition, the terms *rare*, *infrequent*, and *frequent* do not provide meaningful information about the frequency of occurrence of adverse reactions. Specific frequency ranges (e.g., adverse reactions occurring in < 1/500) provide more precise information about incidence.

E. Comparative Safety Claims

Comparative safety claims for drugs in terms of frequency, severity, or character of adverse reaction must be based on data from adequate and well-controlled studies (as defined in 21 CFR 314.126), unless this requirement is waived (§ 201.57(c)(7)(iii)).[5] Details of studies that are the basis for comparative safety claims would ordinarily be discussed in the CLINICAL STUDIES section of the labeling. Care should be taken to avoid inclusion of comparator rates that would imply a comparative safety claim that is unsubstantiated or otherwise misleading (e.g., if an excessive dose of an active comparator was used). If the requirement that claims be based on adequate and well-controlled studies is waived to permit inclusion of comparative rates (e.g., because the identity and rates of adverse reactions for the active comparator are important to understanding the significance of the information), the comparator rates should be qualified by a disclaimer indicating that the data are not an adequate basis for comparison of rates between the study drug and the active control.[6]

F. Negative Findings

A negative finding can be reported if the absence of the reaction is convincingly demonstrated in a trial of adequate design and power.

V. GENERAL PRINCIPLES FOR PRESENTING ADVERSE REACTIONS DATA IN A TABLE OR LIST

A. Pooling Data

If there are no major study-to-study differences in study design, study population, and adverse reaction rates, an overall pooling of safety data from multiple studies may increase the precision of adverse reaction rates and provide a more clinically useful representation of a drug's adverse reaction profile.

[5] The requirement can be waived under 21 CFR 201.58, or 21 CFR 314.126(c), if applicable.

[6] Also see the discussion of comparative data in the guidance for industry on *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*.

B. Classifying Adverse Reactions

Adverse reactions should be classified using meaningful and specific terms that best communicate the nature and significance of the reaction. There should ordinarily be a common classification scheme across all studies in the safety database. Events that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, adverse events reported in more than one body system that appear to represent a common pathophysiologic event should be grouped together to better characterize the reaction. For example, an allergic-type adverse event that has respiratory (wheezing) and dermatologic (rash, urticaria) manifestations should be classified as a single adverse reaction (e.g., hypersensitivity).

C. Categorizing Adverse Reactions

Within a listing, adverse reactions must be categorized by body system, by severity of reaction, in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency cannot be reliably determined, adverse reactions must be listed in decreasing order of severity (§ 201.57(c)(7)(ii)).

D. Frequency Cutoff

The frequency cutoff for the listing of common adverse reactions identified from clinical trials (usually the adverse reactions table) must be appropriate to the safety database (§ 201.57(c)(7)(ii)(A)). Factors that could influence selection of a frequency cut-off include the size of the safety database, the designs of the trials in the database, and the nature of the indication. The frequency cutoff should be noted in the listing or table header, in the text accompanying the listing or table, or in a footnote.

E. Quantitative Data

For quantitative data (e.g., abnormal laboratory values, vital signs, ECGs), it is usually preferable to present rates of abnormal values and to specify the cutoff value for inclusion (e.g., five times the upper limit of normal) than to refer to a grading system.

F. Denominator

The denominator (N = number of patients) should be provided for each column in a table or listing, except for the listing of adverse reactions identified from postmarketing spontaneous reports (see III.C).

G. Subgroup Rates

The rates for reactions that are specific to a subgroup (e.g., gender-specific reactions such as menstrual irregularity) should be determined using the appropriate denominator, and that denominator should be identified in a footnote. If rates of specific adverse reactions were gathered for only a subgroup of patients or studies (e.g., an adverse effect on a laboratory test), that fact should be disclosed in a footnote.

H. Percentages

Adverse reaction rates expressed in percentages should ordinarily be rounded to the nearest integer. An exception would be for particularly serious adverse reactions (e.g., stroke, intracranial hemorrhage, agranulocytosis) occurring at low rates in a large study where fractions of a percent may be meaningful.

I. Adverse Reaction Rates for Drug Less Than for Placebo

Adverse reactions for which the placebo rate equals or exceeds the rate for the drug (after rounding) should not be included in the ADVERSE REACTIONS section unless there is some compelling factor (e.g., timing) that suggests that the event is caused by the drug. In that case, the adverse reaction should be discussed in the commentary following the table.

J. Significance Testing

Results of significance testing should be omitted unless they provide useful information and are based on a prespecified hypothesis in an adequately designed and powered study.

VI. UPDATING THE ADVERSE REACTIONS SECTION

A. Sources of Information

Sources of information to be considered when updating the ADVERSE REACTIONS section of labeling include controlled trials or epidemiologic studies conducted after marketing approval, manufacturer's safety-related labeling supplements, and other analyses of postmarketing adverse events, including single cases or case series from the literature or from spontaneous reporting.

B. New or Outdated Information

Applicants are urged to review at least annually the content of the ADVERSE REACTIONS section to ensure that the information remains current. We expect the labeling to be consistent with newly acquired information from controlled trials or spontaneous reports and with the evolution of labeling in the pertinent drug class. Conversely, when there is reliable new adverse reaction information (either overall information or information relevant to a particular adverse reaction) that is inconsistent with the information in the ADVERSE REACTIONS section, we expect the outdated information to be deleted from all affected sections of the labeling or appropriately

modified, and the new information incorporated in all relevant parts of the labeling. The applicant must update the labeling when new information becomes available that causes the labeling to become inaccurate, false, or misleading (21 CFR 201.56(a)(2)).

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 ECG.

Adverse Event (or adverse experience): For the purposes of this guidance, the term *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 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.