Guidance for Industry

Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics

DRAFT GUIDANCE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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U.S. Department of Health and Human Services
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Draft - Not for Implementation

Guidance for Industry[1]

Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics

I. INTRODUCTION

This guidance is intended to assist sponsors in developing the adverse reactions section of labeling for human prescription drugs and biologics. The ADVERSE REACTIONS section of the labeling should contain drug safety information that is important to prescribing decisions and should convey that information in a clear and accessible format. To make the ADVERSE REACTIONS section more useful and accessible to prescribers and more consistent across different drugs and drug classes, this guidance describes what information should be included in the section. The guidance also provides a common format that includes an overview subsection that highlights the most important adverse reactions and a subsection that contains a more detailed discussion of adverse reactions data.

Although this guidance seeks to bring greater consistency to the content and format of the ADVERSE REACTIONS section, the Agency recognizes that individual judgment remains critical in assessing how or whether to present information on an adverse reaction. FDA reviewers and sponsors should assess such factors as seriousness, severity, frequency, and strength of causal association in determining which adverse reactions should be included in the ADVERSE REACTIONS section and which merit additional emphasis in the overview part of that section. In general, the ADVERSE REACTIONS section should include only information that would be useful to clinicians when making treatment decisions and in monitoring and advising patients. Long and 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.

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[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). This guidance represents the Agency=s current thinking on the content and format of the ADVERSE REACTIONS section of labeling for human prescription drugs and biologics. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

II. ADVERSE REACTIONS SECTION - CONTENT AND FORMAT

The ADVERSE REACTIONS Section should contain an *Overview* and a more detailed *Discussion of Adverse Reaction Information*.

A. Overview — Content and Format

The overview is intended to briefly highlight the information in a drug=s adverse reaction profile that is most important to prescribing decisions and to observing, monitoring, and advising patients. The overview is not intended to summarize all information contained in the adverse reactions section. The overview should not ordinarily present precise numerical rates of adverse reactions. These should be presented in the tables and accompanying text as described below. The overview should contain listings of the following:

1. Serious and Important Adverse Reactions Described in Other Labeling Sections

2. The Most Commonly Occurring Adverse Reactions

3. The Adverse Reactions Most Frequently Resulting in Clinical Intervention (e.g., discontinuation of the drug, dosage adjustment, or need for concomitant medication to treat an adverse reaction symptom)

These listings should cross-reference more detailed discussions of the listed reactions in other sections of the labeling (e.g., see WARNINGS section regarding liver failure) or elsewhere in the ADVERSE REACTIONS section.

B. Discussion of Adverse Reactions Information — Content and Format

The discussion of adverse reactions information should be organized as follows:

1. Statement Concerning the Significance of Adverse Reaction Data Obtained from Clinical Trials

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

> *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. The adverse reaction information from clinical trials does,*

however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

2. Description of Data Sources

The presentation of adverse reaction data should be preceded by a description of the database from which adverse reaction data have been drawn (see sample below). The description should discuss overall exposure (number of patients, duration); composition of control groups (e.g., placebo or active control, pooled placebo-controlled studies or pooled dosage groups[2]); the basis for including adverse reactions in the table (e.g., all reactions occurring in at least 1 percent in the treatment group and at a rate greater than placebo); any critical exclusions from the safety database, and any unusual components of the safety database. In the event that adverse reaction rates are based on selected events (e.g., rates derived only from events considered by investigators to be drug-related), as opposed to all reported events, the description should discuss the rationale for not basing rates on all reported events.

Sample of 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 [range].

3. Tabular Presentation of Adverse Reaction Data

This tabular section is intended to present the best available quantitative display of the relatively common adverse reactions.[4] Ordinarily, there should be only a single table (see section II.B.4 for discussion of when multiple tables may be appropriate). Selecting which data to include in a table will often involve a trade-off between optimal quality and precision of the data (e.g., data from placebo-controlled or dose-response studies) and size of the population studied (often large in uncontrolled or active-controlled trials). Data in the primary table should be derived from placebo-controlled

[2]See discussion of pooling issues in section III of this guidance.

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

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

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. The table should be preceded by a description of the data sources reflected in the table.

In general, there is no need to present less informative data in a table. For example, if placebo-controlled data are adequate, there is no need to present active-controlled data, single-arm trial data or the overall database in a table, even if they are larger databases. If lower quality data sources contribute a critical element not found in the more rigorous trials (e.g., prolonged duration of therapy or important comparative data on a specific adverse reaction), these data can be discussed in the commentary subsection following the table (see section II.B.5; see section III for specific guidance on presenting adverse reaction data in a table).

4. When Additional Tables May be Needed

Multiple tables (e.g., separate tables for different studies or disease states) should be avoided in most cases. There will almost always be differences in the rates of adverse reactions from different sources and population subsets, but these differences are typically not important. An additional table or tables may be needed, however, 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 product indications, formulations, demographic subgroups, study durations, dosing regimens, and types of studies (e.g., intensely monitored small studies vs. a large outcome study). Additional tables should focus on reactions for which there are substantial differences in rates and be accompanied by an explanation of why the tables are included and what they represent.

5. Commentary and Elaboration on Tabular Data

The data table should be followed by narrative discussion to supplement or explain the information provided in the table or to define terms used. To the extent applicable, the commentary should address the following:

- **Discussion of Clinically Important Adverse Reactions:** To the extent they are not adequately discussed in other labeling sections (e.g., WARNINGS, PRECAUTIONS), the commentary should provide additional information about the more clinically important adverse reactions listed in the table (e.g., the

most commonly occurring reactions and those requiring clinical intervention such as discontinuation, dose modification, concomitant medication to treat an adverse reaction symptom, or close monitoring). The commentary should discuss factors that may affect the rate or severity of a reaction (e.g., disease state, concomitant therapy, demographic subgroup, or dose) and elaborate on the nature of a reaction if such elaboration is needed to explain the clinical significance of the reaction. For adverse reactions requiring clinical intervention, the commentary should discuss the intervention that is indicated.

- **Dose-Response Information:** The commentary should identify adverse reactions that exhibit a dose-response and describe the manner in which dose-response was investigated. It may be helpful to include a small table showing rates of dose-related adverse reactions.

- **Duration of Treatment:** The commentary should discuss adverse reaction rates that increase or decrease with continued use, and adverse reactions that emerge with long-term use.

- **Subpopulation and Risk Factor Data:** The commentary should include reliable information about observed differences in adverse reaction rates in various demographic groups and disease subsets. Additionally, reliable negative information (i.e., lack of observed differences) should be reported for certain demographic groups (e.g., pediatric, racial, geriatric, gender) and those disease subsets where concerns about differences in adverse reactions are greatest (e.g., renal or hepatic failure, patients receiving concomitant medications). Where there is no reliable information concerning rates in subpopulations, that fact should be disclosed along with an explanation of why such information is unavailable (e.g., clinical trials were not powered to detect differences in these populations).

- **Vital Signs**: If relevant and not provided elsewhere, the commentary should include results of vital sign measurements such as blood pressure, heart rate, and electrocardiogram.

- **Multiple Indications:** If a drug has multiple indications and certain indications have unique adverse reaction profiles or problems, the commentary should identify significant differences. If there are substantial and clinically important differences in adverse reaction profiles for different indications, it may be useful to separate adverse reaction data presentations (including tables, see section II.B.4) for relevant indications.

- **Multiple Formulations:** If a drug has multiple formulations and a certain formulation or formulations present unique adverse reaction concerns, the

commentary should identify significant differences. If there are substantial and clinically important differences in adverse reaction profiles for different formulations, it may be useful to separate adverse reaction data presentations (including tables, see section II.B.4) for relevant formulations.

6. Presentation of Less Common Events

The ADVERSE REACTIONS section should also discuss significant adverse reactions that occur less commonly than those presented in the table or tables (i.e., at rates below the frequency cut-off for inclusion in the table). These reactions may be identified from any source in the overall safety database or from spontaneous reports received after the drug has been marketed. Long and exhaustive lists of adverse events, including those that are infrequent, commonly observed in the absence of drug therapy, or not plausibly related to drug therapy, should be avoided.

Because it is very difficult to establish that very low frequency adverse events are caused by a drug, events included should be limited to those that are serious, that are typical of drug-induced reactions (e.g., liver necrosis, agranulocytosis, Stevens-Johnson syndrome), that have a relatively strong causal relationship, such as a positive re-challenge, or that are particularly plausible in light of the drug=s pharmacology. In general, events that would be expected to occur in the observed or studied population at a similar frequency absent drug therapy (e.g., acute infarctions in the elderly, palpitations, upper respiratory infections, minor symptomatic complaints such as headaches, diarrhea, nausea, and dry mouth) should be omitted. In contrast, events that are serious but very unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, significant hemolytic anemia, thrombocytopenia, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception, acute renal failure) should be included, even if there are only one or two reports.

Less common adverse reactions should be presented as a listing and categorized by body system. Adverse reactions identified from the overall clinical trials database and those identified from spontaneous reports should usually be presented in separate listings. If listed together, there should be a mechanism to distinguish adverse reactions identified from spontaneous reports (e.g., italics). Unless they are meaningful and informative (usually not the case), rates or numbers of spontaneous reports should not be cited. This is particularly true of adverse reactions from spontaneous reports as that information quickly becomes outdated. If numbers of reports are cited, the period of observation should be stated.

7. Adverse Reaction Information from Spontaneous Reports

To help place in perspective the significance of data obtained from postmarketing spontaneous reports, these data should be preceded by the following statement, or an appropriate modification:

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 to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Drug X.

III. ORGANIZING AND PRESENTING ADVERSE REACTIONS DATA IN A TABLE

! **Pooling Data:** To obtain more precise adverse reaction rates, it is often important to pool data from studies that are not identical in design. If there are not major study-to-study differences in rates, an overall pooling is probably the most clinically useful representation of a drug=s adverse reaction profile. Adverse reactions from different studies should be categorized using the most meaningful and specific terms possible. Whenever possible, similar events (e.g., sedation, somnolence, and dulled sensations) should be grouped in a single category to avoid diluting or obscuring the true effect.

! **Body System Organization:** Data presented should be organized by body system and, within body system category, by order of decreasing frequency. However, adverse reactions reported in more than one body system that represent a common pathophysiologic event (e.g., allergic reaction) may be grouped together to better characterize the event.

! **Frequency Cut-off:** Ordinarily, a frequency cut-off appropriate to the size of the database and design of the trial should be identified and only adverse reactions occurring at that frequency and above should be presented in the table. The frequency cut-off chosen should be noted in the table header or in a footnote. Any adverse reactions occurring at lower than the specified frequency, but deemed important because of their nature or seriousness, can be described in the subsection discussing less common events (see section II.B.6).

! **Comparator Adverse Reaction Data:** Adverse reaction rates from placebo or other comparator arms (e.g., active control, different dosage groups) should be included in the table unless inclusion of such rates would be misleading (for example, if a suboptimal or excessive dose of an active comparator was used) or would constitute or imply an unfair or unsubstantiated comparative safety claim.

! **Quantitative Data:** For quantitative data (e.g., abnormal laboratory values, vital signs, or EKGs), it is preferable to present rates of abnormal values in tabular form, and to specify the

cut-off value for inclusion (e.g., five times the upper limit of normal) rather than refer to a grading system.

! **Denominator:** The denominator (N = number of patients) should be provided for each column in a table or list.

! **Subgroup Rates:** The rates for subgroup specific events (e.g., gender specific events) 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., adverse effect on a laboratory test), this should be indicated in a footnote.

! **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 or intracranial hemorrhage, agranulocytosis) occurring at low rates in a large study where fractions of a percent may be meaningful.

! **Adverse Reaction Rates # to Placebo Rates:** Adverse reactions for which the placebo rate equals or exceeds the rate for drug (after rounding) should not be included in a table. Such reactions should ordinarily be omitted or listed in a footnote following the table. There may be cases in which the timing, severity, or some other feature of an adverse event suggest the event is caused by the drug, notwithstanding a rate similar to or less than placebo. In such cases, the adverse reaction should be discussed in the commentary following the table.

! **Significance Testing:** Results of significance testing should be omitted unless they provide critically useful information and are based on a prespecified hypothesis in a study adequately powered to test that hypothesis.

IV. PRESENTING DATA IN THE ADVERSE REACTIONS SECTION OF LABELING

! **Selecting Events for Inclusion:** Selection or exclusion of adverse events for presentation in the ADVERSE REACTIONS section should be based on factors such as frequency of reporting, whether the adverse reaction rate for drug exceeds the placebo rate, extent of dose-response, extent to which the adverse reaction is consistent with the pharmacology of the drug, timing of the reaction relative to time of drug exposure, and whether the adverse reaction is known to be caused by related drugs.

! **Rare, Serious Events:** Serious adverse events that are unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, significant hemolytic anemia, thrombocytopenia, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception, acute renal failure) should be included in labeling even if there are only one or two reported events.

! **Determining Adverse Reaction Rates:** The rate of an identified adverse reaction should ordinarily be derived from all adverse events reported in the database being used to derive the rate; that is the rate should generally not be derived only from those events believed by investigators, on a case-by-case basis, to be causally related to drug exposure.

! **Characterizing Adverse Reactions:** In characterizing overall adverse reactions experience, subjective and nonspecific terms (e.g., *well tolerated*) should be avoided, as they have no precise meaning and can be misleading. Use of the terms *rare*, *infrequent*, and *frequent* should generally be avoided. If the terms are used, their use should be consistent with their regulatory definitions (see 21 CFR 201.57(g)(2)).

! **Comparative Safety Claims:** Explicit comparative safety claims may be included only if based on data from active control trials of adequate design and power to permit valid comparison.[5] Mention of significance testing should be avoided, unless the study was designed to test a comparative safety hypothesis.

! **Negative Findings:** A negative finding can be reported if the absence of the event is convincingly demonstrated in a trial adequate to support such a conclusion.

V. UPDATING THE ADVERSE REACTIONS SECTION OF LABELING

! **Sources:** Sources of information to update the ADVERSE REACTIONS section of labeling include controlled trials or epidemiologic studies conducted after marketing approval, manufacturer's safety-related labeling supplements, safety issue documents from consulting CDER or CBER Divisions (in CBER, Office of Biostatistics and Epidemiology: in CDER, Office of Postmarketing Drug Risk Assessment) and single cases or case series from the literature or from spontaneous reporting that are sufficiently compelling to warrant inclusion in labeling.

! **Inconsistent or Outdated Information:** Sponsors are urged to periodically review (at least annually) the content of the ADVERSE REACTIONS section to ensure that it remains accurate. The labeling should be reviewed to ensure consistency with newly acquired information from controlled trials or spontaneous reports and with the evolution of labeling in the pertinent drug class, and to seek out any defects in labeling that may have accumulated with time. When there is reliable new adverse reactions information (either overall information or information relevant to a particular adverse reaction) that is inconsistent with the information in the ADVERSE REACTIONS section, any outdated information should be deleted from affected parts of the section and other affected sections of the labeling (e.g., WARNINGS, PRECAUTIONS), or appropriately modified, and the new information incorporated in all

[7] 21 CFR 201.57(g)(4). Such trials should also be described in the CLINICAL STUDIES section of labeling.

relevant parts of the labeling. It is the responsibility of the sponsor to, at any time, correct any information that is false or misleading.

GLOSSARY

Adverse Reaction: An adverse drug 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 (21 CFR 201.57(g)).[6] Adverse events and 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 experience): 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.[7]

Serious Adverse Reaction: The term *serious adverse reaction*, as used in this guidance, refers to a serious adverse event (or experience) as defined below for which there is at least a reasonable possibility that the event is associated with, or caused by the drug, and which may have occurred in either the premarketing or postmarketing setting.

Regulations on postmarketing reporting of adverse experiences (21 CFR 314.80 for drugs and 21 CFR 600.80 for biologics) define a serious adverse experience as:

> *Any adverse experience 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/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 a serious adverse drug experience 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood*

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[6] The guidance for industry on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (International Conference on Harmonisation (ICH E8) defines adverse reactions as Aall noxious and unintended responses to a medicinal product related to any dose where ›responses to a medicinal product: means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.@ This definition is considered to be consistent with the definition in 201.57(g).

[7] The guidance for industry on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E8)* defines an adverse drug event as Aany untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.@ The regulations on postmarketing reporting of adverse drug experience (21 CFR 314.80(a) for drugs and 21 CFR 600.80 for biologics) define an adverse drug experience in the postmarketing setting as Aany adverse event associated with the use of a drug or biological product in humans, whether or not considered drug related . . . .@

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or abuse.