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18 September 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: *Draft Guidance: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics*

Chiron Corporation would like to make the following comments and suggestions regarding the proposed draft guidance for the content and format of the adverse reactions section of labeling:

General Comments:

- No discussion is provided within the proposed guidance document regarding the WARNINGS or PRECAUTIONS sections of the labeling. As these sections contain adverse reaction information, it should be made clear what information should be contained in these sections (i.e., what frequency or severity would warrant being placed in the WARNINGS section). Information contained within the WARNINGS or PRECAUTIONS section should not be reiterated in the narrative section following the tabular summary of adverse reaction data.
- If the proposed statements for “Significance of Adverse Reaction Data Obtained from Clinical Trials” and “Adverse Reaction Information from Spontaneous Reports” are to be contained in all labeling, then they add no drug-specific value and they add undue length to product labeling. If this information were to be provided in the labeling, it would be more informative in the Patient Information section.
- No consideration is given within the draft guidance document to the adoption of MedDRA by the Agency and how this will affect adverse reaction labeling.
- As one of the goals of this draft guidance document is to “make the ADVERSE REACTIONS section ... more consistent across different drugs and drug classes,” will the Agency require all labeling to conform to this format—including currently marketed products?
- Adverse “reaction” and adverse “event” are used interchangeably in some sections of the document. For optimal precision and clarity of the guidance document, choice of which phrase to use in a particular sentence should follow the definitions given in the glossary.

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Specific Comments:

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

The suggested statement is vague and does not provide informative information to the physician. Information regarding “significance”, which has regulatory/statistical meaning, would be better placed in Section II.B.2, Description of Data Sources.

Section II.B.2 Description of Data Sources

It is recommend that the database description should also discuss the actual duration of dosing that patients received during the trial and the percentage of patients that were removed from the study(ies) for adverse events. In addition, the “Sample of Database Description” does not contain suggested wording for the selection of data included in the table. Standard wording for the “significance” of the adverse event data could also be provided in this section rather than in a separate section as suggested in Section II.B.1. Suggested revised wording for this section is as follows:

“Drug X was studied primarily in placebo- and active controlled trials (n=_, and n+_, respectively), and in long-term follow up studies. The data described below is from (a) placebo[active] controlled study(ies) that reflects exposure to drug X in [n] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. The population was [age range], [gender distribution], [race distribution] and had [diseases/conditions]. Most patients received dosing at [range] for a median/mean of X [time]. X% of patients were removed from study(ies) for adverse events. Because clinical trials are conducted under a variety of conditions, it is not possible to directly compare the results from this(these) study(ies) with the rates observed in other clinical studies.”

Section II.B.3 Tabular Presentation of Adverse Reaction Data

In requesting presentation of the adverse reaction data in a single table, this section is often contradictory to other sections of the draft guidance document (e.g. Dose-Response Information, Multiple Indications, and Multiple Formulations).

In addition, for more clarity within the guidance document, it is recommended that Section III be contained within Section II and guidance on the commentary and narrative discussion of the table (currently in Section II.B.5) be moved to Section III.

It is recommended that the data source for tabular presentation of the adverse reactions be the “pivotal trial” requested by and agreed upon by the Agency and/or the data provided in the Integrated Summary of Safety in the marketing application, if it is appropriate to integrate the safety data from multiple trials. As a general rule, the safety data should be provided from the largest safety database available for the drug. Pivotal trials with placebo-controlled data should not be necessarily favored over those including active controls. Active control trials demonstrating superiority are often required for initial registration. If the labeling contains the efficacy data from an active-controlled trial, inclusion of the adverse reaction data from the trial is required to provide the physician with the appropriate benefit/risk information. Suggested revised wording for this section is as follows:

“The tabular section is intended to present the best available quantitative display of the relatively common adverse reactions. Ordinarily, there should be only a single table (see section II.B.4 for discussion of when multiple tables may be appropriate). As a general rule, safety data should be provided from the largest available safety database, which ideally should be the pivotal trial required/used for registration purposes. If available, placebo-controlled and/or dose-response studies provide the most informative safety data. 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 data bases 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 not 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. However, if the labeling contains efficacy data from an active-controlled trial, safety data from the trial should be included in the adverse reaction section to provide the physician with the appropriate benefit/risk information. 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).

Section II.B. 4 *When Additional Tables May be Needed*

Discussion of when multiple safety data tables should be used is contradictory within the draft guidance document. Section II.B.4 states that multiple table should be avoided for different disease states, but should be used for different product indications. As suggested above for Section II.B.3, if safety data from active-controlled trials is available, this information can provide important benefit/risk information for the physician. Suggested revised wording for this section is as follows:

4. When Multiple Tables May be Needed

Multiple tables (e.g., separate tables for different studies) should be avoided in most cases. There will almost always be minor differences in the rates of occurrence 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 indication, formulations, demographic subgroups, study durations, dosing routes or regimens and types of studies (e.g., placebo- vs. active-controlled, or intensely monitored small studies vs. a large outcome study). If multiple tables are displayed, there should be an explanation of why the tables are included and what they represent.

Section II.B.5 *Commentary and Elaboration on Tabular Data*

As suggested in the General Comments section, data in the commentary section should only include data that is NOT included within the WARNINGS or PRECAUTIONS section of the labeling. It is recommended that the Agency provide guidance regarding the frequency or severity of adverse reactions that would warrant adverse reaction data being placed in the WARNINGS, PRECAUTIONS or commentary section of the labeling.

- **Discussion of Clinically Important Adverse Reactions**

Discussion of adverse reactions requiring clinical intervention such as discontinuation, dose modification, concomitant medication to treat an adverse reaction symptom, or close monitoring is not currently required by the regulations (201.57) and is merely provided in the Integrated Summary of Safety (ISS). Providing this information would unduly lengthen the labeling text. The overall level of discontinuation from treatment is better provided in the section Description of Data Sources (II.B.2). Providing additional information in the adverse reaction section would be important only if the majority of discontinuations were from particular adverse reaction(s). The most important or common adverse events requiring dose modification are generally presented in the Dosing Modifications section and would be reiterative in the adverse reaction narrative section. The term "concomitant medication" is not used when referring to medications used for treating an adverse reaction. Therefore it is recommended that "concomitant" be removed from any description of treatment medication.

Data on factors that affect the rate or severity of a reaction (disease state, concomitant and/or treatment medications, etc.) are generally not prospectively-defined endpoints and are not supported by a sufficient quantity of data. Therefore, if this information is provided, an appropriate disclaimer regarding the quality of the data should also be provided.

Unless prospectively studied in a clinical trial, suggestion for clinical interventions for adverse reactions should not be provided in the labeling. Although data regarding clinical interventions for adverse reactions are generally captured in clinical trials, it is not appropriate, clinically or legally, to provide treatment recommendations beyond the drug and indication presented in the labeling. If an adverse reaction requires dosing modification, the severity level of the reaction and its appropriate dosing modification can be summarized in a table in the “Dosing Modifications” section of the label.

Suggested revised wording for this section is as follows:

Discussions 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, medication to treat an adverse reaction symptom or close monitoring). If sufficient data is available regarding factors that may affect the rate or severity of a reaction (e.g., disease state, concomitant therapy, demographic subgroup, or dose), this information should be provided along with a description of the quality and quantity of data supporting the conclusions. Elaboration on the nature of a reaction should be provided if needed to explain the clinical significance of the reaction.

- **Dose-Response Information, Duration of Treatment and Subpopulation and Risk Factor Data**

Unless there is sufficient data from well-monitored clinical studies regarding dose-response information and/or adverse reaction rates that increase or decrease with continued use or use by special subpopulations (see previous section), it is recommended that this information not be provided in the labeling. Data from post-marketing reports should be provided in a separate section.

- **Vital Signs**

If relevant, vital signs information that would be considered adverse reaction data should be provided in the tabular summary. Therefore, it is recommended that this bullet point be removed from this section of the guidance document.

- **Multiple Indications and Multiple Formulations**

If there are unique adverse reaction profiles for certain indications, this data should be provided in a tabular format and would be reiterative in the commentary section. Therefore, it

is recommended that this bullet point be removed from this section of the guidance document.

Section II.B.6 *Presentation of Less Common Events*

The definition of adverse reaction, as presented in the draft guidance document, is an undesirable effect, reasonably associated with the use of the drug. In the clinical trial setting, causal relationship is defined at the time of the event by the investigator. In standard labeling, all of these adverse reactions are listed in the labeling. The “significance” of these adverse reactions is not necessarily known and is not commented on in the listing. Adverse events not plausibly related to study drug are not included in the listings regardless of the frequency (“including those that are infrequent”). “Infrequent” should only be used in the guidance document according to its regulatory definition (210.57(g)(2)).

Although, as the draft guidance document states, “it is very difficult to establish that very low frequency adverse events are caused by a drug,” these events can provide information to physicians about previous experience with the drug. The selective inclusion of data from the section (i.e., to those events that are “serious”) will not only provide less informative data to the physician, but could greatly increase the number of post-marketing reports of “unlabeled” events. Data not derived from clinical trials, such as spontaneous reports, should be included in a separate section of the labeling (Section II.B.7).

Under MedDRA, there are 26 body systems, including such categories as diagnostic procedures. Considering this complication, would it be appropriate to eliminate or condense body systems under MedDRA, based on both the class of the product and the types of adverse reactions seen in clinical trials?

Suggested revised wording for this section is as follows:

The ADVERSE REACTIONS section should also discuss 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. Long and exhaustive lists of adverse events not plausibly related to drug therapy, should be avoided. 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.

Adverse reactions not presented in a tabular display, 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.

Section II.B.7 Adverse Reaction Information from Spontaneous Reports

Guidance regarding adverse reaction data from spontaneous reports would be more appropriately placed in Section V (Updating the Adverse Reaction Section of Labeling). In addition, it would be helpful to add the statement from draft Section II.B.6 here, "Unless they are meaningful and informative (not usually the case), rates of numbers of spontaneous reports should not be cited". Suggested revised wording for the statement to precede this section is as follows:

The following adverse reactions were identified during postapproval use of drug X. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling were based on the seriousness of the reaction, the number of reports and/or the reasonable possibility of a causal relationship to use of the marketed product.

Section III ORGANIZING AND PRESENTING ADVERSE REACTION DATA IN A TABLE

- **Pooling Data**

It would only be appropriate to pool data that was categorized using the same adverse event dictionary. For categorizing events under COSTART, the preferred term would generally be considered "the most meaningful and specific terms possible." However, under MedDRA, what would the Agency propose as "the most meaningful and specific terms possible"? Chiron suggests that a MedDRA guideline for labeling of adverse events be produced that redefines such terms as "frequent" and "rare" based on MedDRA and also gives recommendations for use of preferred terms vs. low- or high-level group terms, preferably with specific examples based on current labeling practices.

- **Body System Organization**

Commonly, adverse reactions are presented in tables by body system and then alphabetical order, and not by decreasing frequency. Listing adverse reactions by frequency is further complicated when the data is from a placebo-controlled trial, where a more frequent adverse event by percentage may not be greatly increased over the rate observed with placebo.

Under MedDRA, there are 26 body systems, including such categories as diagnostic procedures. Considering this complication, would it be appropriate to eliminate or condense body systems under MedDRA?

- **Frequency Cut-off**

Ordinarily, a frequency cut-off appropriate to the patient population and number and severity of events is used for presentation of data in a table, rather than a frequency cut-off based on “the size of the database and design of the trial.” For consistency in labeling, the frequency cut-off should be noted in the table header, and not included as a footnote to the table.

Suggested revised wording for this section is as follows:

Ordinarily, a frequency cut-off appropriate to the patient population or frequency and severity of events should be identified. The frequency cut-off chosen should be noted in the table header and only adverse reactions occurring at that frequency and above should be presented in the table.

- **Subgroup Rates**

By “gender-specific events”, is the Agency referring to those events which can only occur in a specific sex (such as erectile dysfunction or menstrual irregularities)? In Section II.B.5, subgroup analysis of adverse reactions by gender (presumably to evaluate reactions that may be more common in one gender than in the other) was proposed to be contained within the commentary section following the tabular summary rather than in the table itself. Please clarify.

- **Adverse Reaction Rates Less than or Equal to Placebo Rates**

In certain circumstances, inclusion of adverse reactions for which the placebo rate equals or exceeds the rate for drug can be informative for the physician from a benefit/risk perspective, e.g. the decreased rate of infections seen with the use of interferon-beta as compared with placebo. This data could also be informative if the lack of an adverse event were contradictory to the understood pharmacology of a drug (i.e., lack of an increase in bleeding during use of an anticoagulant). Therefore, it is recommended that adverse reaction rates that are less than or equal to placebo rates be included in the table.

- **Characterizing Adverse Reactions**

In characterizing overall adverse reaction experience, terms such as “well-tolerated” can provide appropriate clinical significance. Although an adverse reaction to a drug may be “serious,” if the toxicity is not seen as dose-limiting, does not result in discontinuation and is reversible, the adverse reaction may indeed be “well-tolerated”.

V. Updating the Adverse Reactions Section of Labeling

How will the Agency determine if spontaneous reports are “sufficiently compelling to warrant inclusion”?

Sincerely,

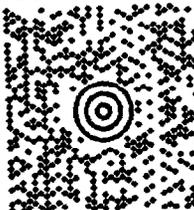
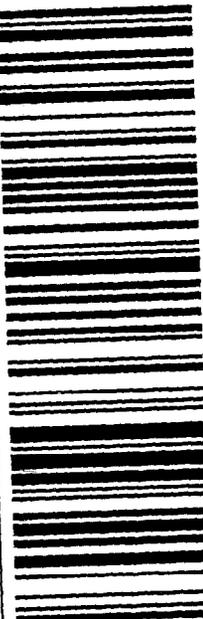
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for Michele D. Jumper, Ph.D.
Manager, Regulatory Affairs

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<p style="text-align: right;">LTR 1 OF 1</p> <p>MARCELLA PAOLOCCI 510-923-6342 CHIRON CORPORATION 4560 HORTON STREET EMERYVILLE CA 94608</p> <p>SHIP TO: FDA ROOM 1061 DOCKETS MANAGEMENT BRACH (HFA-305) 5630 FISHERS LANE ROCKVILLE MD 20852</p>	<p style="font-size: 2em; font-weight: bold;">MD 207 0-04</p>  	<p style="font-size: 3em; font-weight: bold;">1</p> <p>UPS NEXT DAY AIR TRACKING #: 1Z 966 667 01 9732 5139</p>		<p>BILLING: PREPAID</p> <p>Reference No.1: Comments: Adverse Reac Reference No.2: of Labeling for Human</p>  <p style="font-size: 0.8em;">UPS 02.00.21e Mozilla/4.5 [en] (WinNT; U)</p>
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