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18 September 2000

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

Re: Docket No. 00D-1306 - FDA Draft Guidance for Industry on Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (65 Federal Register 38563; June 21, 2000)

Sir/Madam:

PHARMACIA Corporation submits the following comments on the "Draft Guidance for Industry on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics". Our comments are provided in accordance with the request as stated in the Federal Register (Vol. 65, No. 120 of June 21, 2000) to submit written comments by September 19, 2000.

PHARMACIA is in general agreement with the comments sent to FDA by the Pharmaceutical Research and Manufacturers of America (PhRMA). We are providing comments on the draft Adverse Reaction (AR) Guidance to emphasize those issues of significant importance to the development and implementation of drug safety information. Our specific comments and recommendations on the various sections of the draft Guidance document are provided in the attached table, which is designed to follow the outline of the draft Guidance. General comments are provided below.

- PHARMACIA is in agreement with FDA with regard to the concept of conveying drug safety information in a clear and accessible format and enhancing the development of standardized labeling. However, please recognize that Industry has, historically, done an effective job in the

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development of labeling that accurately communicates necessary safety information. As it is currently written, the draft Guidance is too restrictive, removing much of the flexibility and judgement that is necessary in determining the most appropriate way to summarize and display safety information in product labeling.

- We suggest that before finalizing the draft AR Guidance, FDA conduct a survey or study of end-users to determine whether the new AR labeling requirements will improve the manner in which drug safety information is conveyed.
- Currently approved labeling should be “grandfathered.” Implementation of new AR labeling should be done prospectively for new chemical entities (NCEs) within a new drug class or for a novel compound within an existing class. NCEs in an existing, well established class (e.g., triptans, antidepressants) should not be required to adopt the new requirements. Instead, the labels for these products should be modeled after the previously approved products. Requiring subsequent drugs in a well-established class to adopt the new requirements would present clinicians with different, and potentially conflicting, information for drugs within the same class, possibly leading to confusion in making prescribing decisions. Such confusion would not serve to benefit the patient. In addition, companies manufacturing those drug products would be placed at an unfair competitive disadvantage.
- The new AR labeling requirements should be coordinated with other upcoming labeling initiatives (1) to ensure that the entire labeling document can be clearly and consistently understood by the reader and (2) to maximize the limited resources of both FDA and industry.
- A sample layout of the new AR section should be provided to aid in visualizing and understanding the content and format (Section II) and the organization and presentation of the data (Section III). It is difficult to fully assess the draft Guidance in its present format. An example should be included in the Guidance, possibly replacing Section IV (Presenting Data in the Adverse Reactions Section of Labeling), and the example should contain cross-references to specific sections of the Guidance that provide more detailed instructions.
- The clarity of the draft Guidance should be improved. Specific definitions should be provided for nebulous terms such as “clinically significant,” “important,” etc. Consistent and accurate use of the regulatory terms, “adverse events” and “adverse reactions” should be used. The terms should also be consistent with CIOMs and ICH guidance documents, where applicable, and the appended glossary should provide definitions for all terms used within the Guidance document.

- The tabular presentation of adverse drug event data should be derived from **events** rather than **reactions**. Physicians regularly disagree about whether an individual event in an individual patient is an adverse reaction [1,2,3]. Although ICH E8 offers a regulatory definition of a reaction (as described in the glossary of the draft Guidance), there is no standardized, scientific mechanism for deciding that an individual event occurring in an individual patient is an adverse drug reaction [4,5]. Deciding that the patient is experiencing an adverse reaction is a clinical judgement that requires an assessment of the event in the context of what is known about both the patient and the drug [6].

We appreciate the opportunity to provide comments on this Guidance document, and we would be pleased to discuss these comments with the Agency, at your request.

Sincerely,

A handwritten signature in black ink, appearing to read "Kathleen J. Day". The signature is written in a cursive style with a large initial 'K' and 'D'.

Kathleen J. Day

## References

1. Karch FE, Smith CL, Kerzner B, Mazzullo J, Weintraub M, Lasagna L. Adverse drug reactions—A matter of opinion. *Clin Pharmacol Ther* 1976;19:489-492.
2. Koch-Weser J, Sellers SM, Zacest R. The ambiguity of adverse drug reactions. *Eur J Clin Pharmacol* 1977;11:75-78.
3. Miremont G, Haramburo F, Begaud B, Pere JC, Dangouman J. Adverse drug reactions: physicians' opinions versus a causality assessment method. *Eur J Clin Pharmacol* 1994;46:285-289.
4. Finstein AR. *Clinical Epidemiology: The Architecture of Clinical Research*. Philadelphia: W. B. Saunders; 1985:314-315.
5. Sackett DL, Hayes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. Boston: Little, Brown; 1991:283-302.
6. Johnson JM. Reasonable possibility: causality and postmarketing surveillance. *Drug Info J* 1992.

**PHARMACIA Assessment of the FDA Draft Guidance for Industry,  
Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics**

The following table describes the potential impact and PHARMACIA's recommendation for each specific section as outlined in the draft adverse reactions (ARs) Guidance.

FDA PROPOSAL FOR ADVERSE REACTIONS SECTION	RECOMMENDATION
<b>II. ADVERSE REACTIONS SECTION- CONTENT &amp; FORMAT</b>	
<b>A. OVERVIEW</b> 1. Serious/important adverse reactions (ARs) 2. Most common occurring ARs 3. ARs necessitating clinical intervention	<p>Delete overview in its entirety. An overview is not necessary and should not be included in the labeling. It is redundant, there are too many interpretations of "brief", and information is more appropriately covered in other sections or subsections. There is also the potential for confusion or inconsistency between the overview and the other sections of the label.</p> <p>If the Agency considers an overview section necessary, limit narrative to 'brief' statements and cross-reference to the more detailed sections. Delete item 3. Clinical intervention may not be known or understood, particularly if the product is a new chemical entity. In addition, product labeling should not dictate medical practice, which requires individualized clinical assessment of the patient. Detailed explanations in an overview may add redundancy by overlapping information regarding clinical intervention, if available and supportable, in later adverse reaction sections.</p> <p>It would be helpful to provide an example of an overview for consistency throughout the industry.</p>
<b>B. DISCUSSION OF ADVERSE REACTIONS INFORMATION</b> 1. <b>General Statement</b>	<p>Delete general statement. The statement regarding the significance of adverse reaction data from clinical trials adds unnecessary text and is not informative to physicians, who would have an understanding of the strengths and weaknesses of clinical trial data.</p>
2. <b>Description Of Data Sources</b>	<p>Agree with the inclusion of this information.</p>

**PHARMACIA Assessment of FDA Draft Guidance, Content and Format of Adverse Reactions Section of Labeling for Human Rx Drugs and Biologics**

<p><b>3. Tabular Presentation Of Data</b> Ideally, there should be one primary AR table derived from placebo-controlled and/or dose-response studies.</p> <ul style="list-style-type: none"> <li>- Pooled data from similar studies</li> <li>- By body system in descending order of frequency</li> <li>- Frequency cut-off noted in header/footer</li> <li>- Comparator/placebo AR data included</li> <li>- Quantitative data in tabular form</li> <li>- "N" noted for each column</li> <li>- Note subgroup rates with proper N</li> <li>- %s generally rounded to nearest integer</li> <li>- ARs ≤ placebo not included</li> <li>- Significance test results generally not included</li> </ul>	<p>In general, the tabular presentation of data is acceptable. We believe that the tables should be derived from <i>adverse events</i> (AE) <u>not</u> <i>adverse reactions</i> (AR). How the AEs are determined must also be defined and presented in the labeling (e.g., treatment emergent).</p> <p>The option should exist to include AE rates &lt; placebo because they may be indicative of drug safety/efficacy. Events that are determined to be drug related could be listed in narrative in another section of the AR sections, e.g., in the Commentary on Tabular Data section</p> <p>Comparator information could be very informative and should be included in the section if trials were designed and conducted under appropriate conditions, even if placebo-controlled study data is presented.</p>
<p><b>4. When Additional Tables May Be Needed</b></p> <ul style="list-style-type: none"> <li>- Additional tables should be avoided in most cases</li> <li>- When AR profile differs substantially between settings, populations and are drug related with important implications for use/non-use</li> </ul>	<p>Agree in concept, but the presentation of additional information as a narrative rather than as a table should be an option.</p>
<p><b>5. Commentary On Tabular Data</b> Narrative to supplement/explain the following:</p> <ul style="list-style-type: none"> <li>- Clinically important ARs</li> <li>- Dose-Response Information</li> <li>- Duration of treatment</li> <li>- Subpopulation and risk factors</li> <li>- Vital sign measurements (if relevant)</li> <li>- Unique ARs for multiple indications</li> </ul>	<p>Agree in concept, but the section is written to sound mandatory for each topic. The section should be edited to clarify that only necessary topics need to be discussed. Redundancy may also be introduced in this commentary.</p> <p>It is not the intent of labeling to instruct physicians how to practice medicine. Therefore, medical treatment or intervention, except for issues unique to the specific drug (e.g., discontinuation), should not be discussed in the labeling.</p>

**PHARMACIA Assessment of FDA Draft Guidance, Content and Format of Adverse Reactions Section  
of Labeling for Human Rx Drugs and Biologics**

<p><b>6. Less Common Events</b></p> <ul style="list-style-type: none"> <li>- ARs from clinical trials or postmarketing surveillance (separate sections) that are not covered in table</li> <li>- Drug-related, serious, typical of drug-induced reactions, or plausible from drug's pharmacology</li> <li>- Listed by body system</li> </ul>	<p>Agree with FDA that drug-related, pharmacologically related, and infrequent but serious adverse events should be described in this section. However, the title of the section is somewhat misleading and we suggest changing to "Less Common Events/Reactions" for clarity.</p> <p>This section should be limited to information from clinical trials; spontaneous events should be reported in section 7 only.</p>
<p><b>7. Spontaneous Reports</b> Standard statement and listing (no specified format) of spontaneous ARs based upon seriousness, frequency, and causality.</p>	<p>General statement should be reworded to refer to events rather than reactions, to remove the numbers in front of each factor, to remove the term "strength of", and revise second sentence.</p> <p>Suggested revision: "The following events have been reported during postmarketing use of drug X. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship can not be precisely established. The events, which have been chosen for inclusion, are due to either their seriousness, frequency of reporting, possible causal connection to drug X, or a combination of these factors, include: XXX, YYY, ZZZ"</p>
<p><b>III. PRESENTATION OF DATA IN A TABLE</b></p> <ul style="list-style-type: none"> <li>- Pooling Data</li> <li>- Body System Organization, Frequency Cut-Off</li> <li>- Comparator Adverse Reaction Data</li> <li>- Quantitative Data, Denominator</li> <li>- Subgroup Rates, Percentages</li> <li>- Adverse Reaction Rates <math>\leq</math> Placebo Rates</li> <li>- Significance Testing</li> </ul>	<p>Presentation should allow for the inclusion of events for which the placebo rate equals or exceeds the rate for the drug if this is considered useful information to convey to physicians.</p>

**PHARMACIA Assessment of FDA Draft Guidance, Content and Format of Adverse Reactions Section of Labeling for Human Rx Drugs and Biologics**

<b>IV. PRESENTATION OF DATA IN ADVERSE REACTION SECTION OF LABELING</b>	
<ul style="list-style-type: none"> <li>- Inclusion criteria based upon frequency, AR rate &gt; placebo, extent of dose-response, consistency with the pharmacology of the drug, reaction timing, drug-class effect</li> <li>- Rare, serious events included even 1 or 2</li> <li>- AR rates derived from database, not case by case investigator judgement</li> <li>- Comparative safety claims allowed if based on properly powered studies</li> <li>- Negative finding allowed if adequately supported</li> </ul>	<p>The information in this section seems overly redundant to what has been previously presented in the other sections of the draft guidance. Suggest that an example be included in the Guidance, possibly replacing this section, and that it contain cross-references to specific sections of the guidance for more detailed instruction.</p> <p>The section contains inconsistent use of many regulatory terms (e.g., adverse events, adverse reactions, serious) and requires clarification of the terms used.</p>
<b>V. UPDATING ADVERSE REACTION SECTION</b>	
<ul style="list-style-type: none"> <li>- Sourced from postmarketing epi studies, safety-related labeling supplements, Agency safety issue documents, cases from literature, or spontaneous reporting</li> <li>- Reviewed annually</li> </ul>	<p>Agree in concept with this section. However, the guidance document should not define when or how to do periodic review.</p>

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