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Re: Docket No. 00D-1306 - FDA Draft Guidance for Industry on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (65 Federal Register 38563; June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

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is submitting this set of comments on the "Draft Guidance for Industry on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics". PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invest over \$26 billion annually in the discovery and development of new medicines. For this reason, PhRMA and its member companies are keenly interested in all aspects of the drug development process, including the format and content of prescription drug labeling. On behalf of our Committees focusing on clinical drug safety and regulatory affairs, we appreciate the opportunity to provide comments on the draft guidance.

PhRMA companies support the Agency's stated goal of making the ADVERSE REACTIONS section of labeling more useful and accessible to prescribers, and more consistent across different drugs and drug classes. We agree that clear and user friendly labeling is a primary tool in ensuring that drug products are used safely and appropriately, and we wish to work with the Agency to achieve this objective. However, we are concerned that implementation of the proposed draft guidance will not result in clearer and more useful labeling. Our major concerns focus on the following areas:

- Comprehensiveness of safety information and the need to consider all safety information in labeling as a whole, not as separate and unrelated sections (e.g., WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, etc.)
- The need for consistency between the information required in the labeling and information that is required by other published FDA guidances (e.g., for the Integrated Summary of Safety, reviewer guidance for safety reviews, etc.).

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- The fact that the format and content of prescription drug labeling is governed by regulation, and the proposed draft guidance document appears to implement changes to these regulations without following the appropriate procedures for doing so.
- Issues concerning implementation, and the inherent difficulties in applying the proposed draft guidance to all currently marketed products, especially those that have been on the market for many years with well-established safety profiles.

The following comments expand on these issues, and are divided into General Comments on the concept of the draft guidance document, and Specific Comments on the various sections of the draft guidance document. Numbering of the section on Specific Comments corresponds to the numbering used in the draft guidance document.

General Comments

1. PhRMA suggests that any effort to modify the regulatory requirements for the format and content of the ADVERSE REACTIONS section of the labeling would be better served by expanding the scope to consider the totality of safety information contained in prescription drug product labeling, rather than focusing on only one part of that information. FDA, industry, prescribers, and other stakeholders must consider the totality of safety information presented in the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE sections. We believe that a meaningful revision of one section cannot be done in isolation, but requires careful and coordinated consideration of the impact on other sections. Any effort to meet FDA's objective of clearer, more informative, and more consistent labeling depends on careful consideration of the totality of drug safety information for a given product.
2. PhRMA understands FDA's overall intent for recent labeling initiatives, i.e., *"to make prescription drug labeling a better information source for health care practitioners"* by making it *"clearer, more informative, more accessible, and more consistent from drug to drug."* However, FDA should not lose sight of the fundamental statutory objective of prescription drug labeling, that is, to provide adequate directions for use of the product. PhRMA believes that prescription drug labeling, in its current format and with the current content presented in accordance with 21 CFR 201.57, succeeds in providing adequate directions for use of drug products.

The US Package Insert is both a medical and a legal document, and existing product labeling for prescription drug products is the subject of substantial litigation regarding adequacy of warnings. The Agency should clarify and articulate explicitly that the initiative to provide new guidance on the ADVERSE REACTIONS section of labeling is based upon the premise that existing labeling can be improved, rather than that existing labeling is deficient.

3. In view of FDA's intent to limit the inclusion of information to suspected adverse drug reactions (ADRs), and not adverse events (AEs), it is important to consider including a special post-marketing section of the labeling that would contain adverse events

that had been observed, but for which a causal relationship with the drug has not been established. Inclusion of such a section would fulfill the "duty to warn" the patient and treating practitioner.

4. Terminology and definitions - The draft document introduces a number of terms without accompanying definitions (e.g., "important," "clinically significant," "common," etc.). Absent clear definitions of these terms, labeling will be based on negotiations about what is "important" and "clinically significant", and will ultimately result in less consistency, rather than more consistency, across different drugs and drug classes. We recommend that FDA establish regulatory definitions of all such terms. Where internationally agreed definitions have already been established (e.g., CIOMS III definitions for frequency; ICH definitions of adverse event, adverse reaction, and serious, etc.), they should be used.

Although the term "**adverse reaction**" is used throughout the document, there are some sections that refer to "**adverse events**." The definitions clearly state that for an adverse event to be considered an adverse reaction, it needs to be reasonably associated with use of the drug; however, section II B 2, Description of Data Sources, requires a rationale for not basing rates on all reported events. If the tables are meant to include only adverse reactions, one should not have to justify including only suspected reactions.

5. Implementation - To enhance understanding of the proposed labeling principles and to facilitate implementation, FDA should include a comprehensive example of the proposed new design of the ADVERSE REACTIONS section, using a real or fictitious product, and compare it with the current labeling content and format for that product. An illustration of the expected size of each subsection would be particularly helpful.

This draft document clearly represents an important step to provide guidance on the format and content of product labeling that will be informative for the end-user. However, we believe that the proposal represents a major change from current practice and requires considerable discussion. There are many subtle issues not addressed in the draft guidance; implementation of a new labeling "system" must be approached cautiously, with considerable thought and flexibility. There may be significant practical difficulties that will inhibit the ability to achieve the objective of this guidance. The end-result may, in fact, be counter-productive. Rather than abandon the current labeling format completely, PhRMA suggests that FDA consider adopting "performance" standards, rather than "engineering" standards, to improve the clarity and accessibility of the ADVERSE REACTIONS section where possible.

Before implementing any of the proposed changes in the ADVERSE REACTIONS section of product labeling, we suggest that (a) a broad base of stakeholders, including health care professionals, be surveyed to assess comparative comprehension of labeling reformatted in accordance with this draft guidance and (b) pilot studies be conducted to evaluate the proposed approaches for conveying drug safety information. It is the comprehensibility and utility to end-users (healthcare professionals and eventually consumers) that should drive the process.

Goals would be to develop a minimum requirement for end-users and to assess whether one or more approaches are superior to others.

PhRMA believes that it is not appropriate to apply the final guidance to all marketed products, and we recommend grandfathering older products. The rationale for this position includes: (a) For marketed prescription drug products, it is not clear that revisions of labeling to comply with the draft guidance will add value in terms of improving the directions for use and improving communication of safety information to health care professionals. (b) For products currently on the market, complying with the draft guidance would require new analyses of clinical trial data. This will be difficult, if not impossible, for older established products for which the specific data of interest in this draft guidance may not have been collected at the time clinical trials were conducted. In addition, for many marketed products, clinical trial data may no longer be available in databases. The industry and FDA have gone through this process of retroactive application of new rules and guidances governing pediatric labeling and geriatric labeling, and we recognize the difficulties of trying to apply contemporary standards to data that were collected under vastly different circumstances for different clinical research objectives. (c) FDA already has a very high workload of labeling supplements. It is not clear that another massive influx of labeling supplements for marketed products with well-established safety profiles will add value in terms of improving the directions for use and improving communication of safety information to health care professionals. Recognizing the need for some starting point, PhRMA recommends that the revised labeling regulations and final guidance apply to all new molecular entities first approved on or after the effective date of the final rule for the format and content of labeling. This would focus the proposed guidance on new products where the databases are available to do the required new analyses and prepare labeling in compliance with the new requirements.

Assuming implementation for new molecular entities approved on or after the effective date of the final rule, PhRMA recognizes that exceptional circumstances may arise where revision of existing labeling to comply with the final rule and guidance is appropriate. In such exceptional circumstances, there should be a generous implementation period to allow for the necessary analyses, exhaustion of existing supplies of packaged inventory and printed materials, and lead time to make the change once the revised labeling is approved by FDA. Not allowing a sufficient lead time to make this change would impose a significant burden on companies, including, in some situations, the extra costs of changes to a company's packaging procedures and equipment to accommodate the additional space required in the package inserts.

Realizing that there are several guidance documents on various sections of the US package insert in preparation, as well as a proposed rule on US package insert format changes expected in the near future, it would be appropriate for FDA to wait for all of these documents to be finalized and apply them simultaneously, rather than implementing them in a piecemeal fashion.

The change in labeling from the current emphasis on adverse **events** to adverse **reactions** and its impact on labeling (e.g., some **events** included in previous labeling may be deleted in revised labeling) will need to be communicated to health care practitioners and other users of prescription drug product labeling. What steps will FDA take to minimize confusion of physicians and others with regard to this change?

FDA should also address how updating of class labeling will be impacted by the proposals set forth in the guidance document.

6. Other General Considerations - It would be logical and helpful for FDA to develop a companion guidance document on Good Review and Labeling Practices for FDA reviewers as an additional means to enhance uniformity in product labeling.

Certain information that appears to be required for preparation of the proposed section, such as medical interventions for an adverse reaction, is not currently routinely captured in clinical trials and not uniformly provided with spontaneous reports. Thus, obtaining this information would require considerable re-engineering of the processes and procedures used by companies in clinical development programs and in post-marketing reporting of suspected ADRs.

The guidance does not specify any particular coding system, such as MedDRA. PhRMA concurs with this approach and specifically recommends that the guidance not limit sponsors to one particular dictionary.

The guidance document does not address adverse reactions associated with off-label use of a product. We recommend that the guidance document incorporate or refer to the principles outlined in the CIOMS III document¹ regarding this issue.

Finally, PhRMA assumes that the brief examples of labeling text presented in the guidance are neither exclusive nor preferential. It would be very helpful if FDA would confirm this assumption.

7. PhRMA maintains that it is inappropriate for FDA to use a guidance document to implement changes in the content and format of the Adverse Reactions section, or other sections, of prescription drug product labeling. Current FDA regulations (21 CFR 201) contain specific and detailed requirements for the labeling of prescription drug products, which have a clear statutory basis in Section 502 of the Federal Food, Drug, and Cosmetic Act. Therefore, PhRMA maintains that proper regulatory procedure and numerous precedents require that FDA follow the notice and comment procedure for proposed rulemaking (21 CFR 10.40) as a means to initiate the process of proposing changes in the format and content of prescription drug product labeling. PhRMA is submitting separate and detailed comments to the Docket regarding this issue.

¹ Guidelines for Preparing Core Clinical Safety Information on Drugs. Report of CIOMS Working Group III (Second edition, 1999). Council for International Organizations of Medical Sciences, Geneva.

Specific Comments

I. Introduction

The second paragraph in this section addresses the need for greater consistency in content and format of the ADVERSE REACTIONS section of the label, and goes on to state that individual judgment remains critical in assessing how or whether to present information on an adverse reaction. While it would be desirable to have an FDA-accepted evidence standard for safety data, similar to FDA's assessment of efficacy data as described in the May 1998 "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," we recognize that assessment of safety information is currently more of an art, than a science, and that judgment is a critical component of this assessment. However, the introduction of individual sponsor and reviewer judgment will inevitably lead to less, rather than more, consistency among labels for different products, and we think that the guidance document should acknowledge this possibility. We interpret this section of the proposed guidance document as recognizing that it is acceptable for individual companies to apply different algorithms and conventions in determining when an event is a reaction for purposes of labeling, and would appreciate FDA's confirmation of this interpretation.

We would urge FDA to describe/define what is meant by "the most important adverse reactions," "commonly observed in the absence of drug therapy," and "not plausibly related to drug therapy" in light of adverse reactions reporting requirements and underlying guidance.

II. Adverse Reactions Section - Content and Format

Section A - Overview - Content and Format

General - PhRMA companies currently provide product labeling that contains complete information on the contraindications, warnings, precautions and adverse reactions associated with the product. We urge health care providers to read this complete information concerning the safety of the product. Given this current status, PhRMA questions whether an Overview section would provide useful information, or whether it would just be confusing to the reader. It seems to add yet one more place for providing information on serious/important risks, unnecessarily increasing the complexity of the document, and reducing its readability. Because the adverse reactions that are included in the Overview are defined as "important," readers may erroneously assume that all other adverse reactions listed in the package insert are not important. This section also adds one more level to the "warning hierarchy" already present in package inserts (i.e., CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, SERIOUS and IMPORTANT REACTIONS, ADVERSE REACTIONS). There is also the risk that physicians will read only the Overview section, and not the entire ADVERSE REACTIONS section and other safety information in the package insert. If the Overview section is retained, we suggest the addition of a statement reminding the reader that it is necessary to read the entire package insert for full prescribing information. The following comments on this section are based on the assumption that the Overview section will be retained:

1. Please clarify what, if any, impact the Overview section will have on the content of "black box" Warnings.
2. The Overview section should include a brief statement regarding the data sources, in addition to the more detailed description of data sources in the "Discussion" section.
3. The document states that the Overview section will provide information on serious and "important" adverse reactions. As mentioned above, there is no definition of "important" in current regulations. FDA should establish a regulatory definition of "important adverse reactions" as part of a proposed rule before incorporating this new term in a guidance document. Rather than developing new definitions for terms related to adverse reactions, standard terms already developed and approved through ICH guidelines should be adopted.²

The logic of repeating very similar discussions in the WARNINGS and ADVERSE REACTIONS sections for certain events is not clear. We believe that multiplicity of discussion, in this case, leads to additional wording that is unnecessary and potentially confusing to prescribers. Additional comment on Section B, below, is related to this point. We would suggest as a guiding principle that the ADVERSE REACTIONS section be limited to the enumeration of reactions, with cross-referencing to other appropriate sections of the labeling if necessary. Issues relating to clinical management or prevention of such events should be discussed in PRECAUTIONS, WARNINGS, or other such sections of the labeling.

4. The term "most commonly occurring adverse reactions" should be defined as referring to the most commonly occurring confirmed adverse reactions from clinical trials, since the frequency of adverse events reported spontaneously cannot be accurately determined.
5. Presenting adverse reactions most frequently resulting in clinical intervention would theoretically be useful, but is unlikely to be routinely achievable because of practical limitations to the amount of information that can reliably be captured in clinical trials. This is even more difficult with spontaneous reports. Collecting this information would require significant re-write of the current adverse event collection and handling processes and procedures.

FDA proposes that the need for concomitant medication to treat an adverse reaction is an "important" element for inclusion in the Overview. This proposal is inconsistent with FDA's stated content of the Integrated Summary of Safety (ISS) in NDAs/BLAs, since the guidance for the ISS does not include an analysis of the frequency of such medication use. In addition, use of the word "concomitant" in this context is confusing, as most companies define concomitant medication as a drug/biologic the patient was already taking at the time the adverse reaction occurred.

² ICH Harmonized Tripartite Guidelines. Clinical Safety Data Management Definitions and Standards for Expedited Reporting, March 1995

In the last paragraph we suggest that the word "listed" be replaced (e.g., by "included"), as this word has a special meaning within the ICH E2C Periodic Safety Update Report (PSUR) guideline vis-à-vis a company's core safety information document, that does not appear to be intended here.

Section B - Discussion of Adverse Reactions Information - Content and Format

1. Statement Concerning the Significance of Adverse Reaction Data Obtained from Clinical Trials - The use of standard disclaimer language does not appear to add value. In fact, such language may detract from the adverse reactions information presented by casting doubt upon its validity, and would undoubtedly undermine the credibility of both PhRMA member companies and FDA in the eyes of patients and health care practitioners. The lack of utility of this paragraph is reinforced by the fact that there is no plan or prospect evident in the draft guidance to enable inclusion of more informative, practice-related adverse reactions in labeling. If the Agency feels it necessary to include a disclaimer in the guidance document, we recommend that its use in labeling be optional, and that it be revised to read as follows:

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of one drug cannot be directly compared to rates observed in clinical studies of another drug. In addition, adverse reaction rates recorded in clinical studies may differ from those observed during actual patient use because clinical studies occur in controlled environments. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that may possibly be related to drug use, and a basis for approximating rates of occurrence.

2. Description of Data Sources - Although potentially useful, a description of the database(s) may be confusing rather than helpful because the diverse clinical programs that support development of New Chemical Entities are increasingly complex.

Data sources are often described in detail in other sections of labeling, such as DESCRIPTION OF CLINICAL STUDIES or CLINICAL PHARMACOLOGY. This information should not be repeated.

The sample text suggests description of a database by a number of baseline characteristics (as does the bullet "Subpopulation and Risk Factor Data" under Point 5). If analysis of adverse reactions by certain baseline characteristics is desired for labeling, the specifics of the data cuts that are likely to be required for the ADVERSE REACTIONS section of labeling should be discussed at the End-of-Phase II meeting. Timing is important because the Sponsor must be in a position to collect the requested information in the Phase III program. FDA should ensure consistency between the requests made in this context and the requirements for the NDA/BLA ISS. In cases where ranges, medians, or means are required, they should be included to better describe the population.

The meaning of "significant differences," "critical exclusion," and "unusual components" should be clarified.

3. Tabular Presentation of Adverse Reaction Data - FDA anticipates that the main table of information on adverse reactions will come from controlled clinical trials. In view of FDA's emphasis on the "real world" applicability of adverse reaction data, we urge FDA to encourage inclusion of data from expanded access programs, treatment IND experience, and other such experiences in the ADVERSE REACTIONS section, especially if these data differ significantly from those observed in controlled clinical trials. Historically, FDA has largely excluded such sources of information from the ADVERSE REACTIONS section due to a strong preference for safety data from controlled clinical trials; however, in view of FDA's clear concern about the real world applicability of safety data, information from these sources merits routine inclusion in labeling if appropriate.

The draft guideline appears to require tables in all situations. PhRMA suggests that in some instances it might be more appropriate to present data for widely different indications in either tabular or narrative format.

Although mentioned later in the draft guidance, it might also be useful to include in this section a statement that, generally speaking, only those events occurring in >x% of treated patients and that could reasonably be considered as having a possible causal association with the use of the drug should be included in the tabular listings. Less frequent events that are serious, that are typical of drug-induced reactions, and/or that are particularly plausible in light of the drug's pharmacology should be discussed in the commentary section following the table.

The draft guidance document refers to active-controlled data as "less informative" and of "lower quality" than placebo-controlled data. Active-controlled trials performed under appropriately rigorous conditions provide valuable information and should be included in the label if the data are informative. Inclusion of these data in tabular form may be the best format for disclosure, and therefore, inclusion of this information should not be discouraged or denigrated, even in the presence of placebo-controlled data.

This section mentions that if "*lower quality data sources contribute a critical element not found in more rigorous trials (e.g., ... or important comparative data on a specific adverse reaction)*..." these data should be discussed in the commentary section. However, section IV states that comparative safety claims may be included only if the study is designed and powered to test a comparative safety hypothesis. PhRMA urges the FDA to clarify this apparent contradiction.

4. When Additional Tables May be Needed - The basis for the statement that differences in incidences between population subsets are "typically not important" should be documented. Further, an explanation should be provided to support the suggestion that there is value in doing extensive subgroup analyses if observed differences are dismissed by default.

As opposed to emphasizing that "multiple tables should be avoided in most cases," we propose alternate language to stress that "multiple tables should be included when the additional tables present important information that is best communicated in a tabular format."

Although it appears that additional tables are warranted only when all three criteria specified in the third sentence of this paragraph are met, there may be other circumstances where additional tables would be informative. For example, when the adverse reaction profile differs considerably in different populations or different disease settings, it may be informative to present information on the safety profile of the drug in each such different setting.

5. Commentary and Elaboration on Tabular Data - What are "clinically important adverse reactions" and who would make the decision? The draft document states that "*to the extent that they are not adequately discussed in other labeling sections...*" the commentary should provide additional information on certain adverse reactions. PhRMA suggests that perhaps the largest single improvement in safety-related labeling would be to provide all information on a specific adverse reaction in one location in the labeling, in contrast to the current practice of dividing such information across multiple sections. We propose that adverse reactions be discussed once in the labeling and cross-referenced, as appropriate, with other sections. A description of adverse reactions should not be duplicated. We believe that the ADVERSE REACTIONS section should generally only contain discussions relevant to the observed reactions, supplemented by appropriate incidence estimates if available from controlled clinical studies. Where discussion of a certain reaction is required from a pathophysiological or treatment perspective, we believe other sections of the labeling are more appropriate.

The Discussion of Clinically Important Adverse Reactions subsection states that "*the commentary should discuss the intervention that is indicated.*" PhRMA opposes routine inclusion of specific interventions in labeling, since consideration of possible interventions in labeling reduces the importance of the medical judgment of the treating physician and subjects the company to the liability consequences of alternative courses of action.

Providing dose response information on adverse reactions may be possible if clinical studies consistently examined two or more doses, but will be very difficult if a single dose was used in all or almost all studies.

The Duration of Treatment section is confusing as written. There is no standard method described for assessing rates of increase or decrease related to "continued" use, and no definition of "continued use" or "long-term use." Do these terms refer to chronic use in an individual patient or larger numbers of patients exposed over increasing lengths of time? Does this paragraph refer to data obtained in continuing or new post approval clinical trials or spontaneous data from post-marketing commercial use? One assumes that actual rates can only be obtained by use of data from controlled clinical trials, but this is not specified. It would seem that the intent of this paragraph is to provide a place for data gathered from clinical trials continued post approval to gather longer term exposure data. If so, then this should be clearly stated.

Under Subpopulation and Risk Factor Data, FDA should define "reliable negative information" and criteria for including such information in product labeling. The

subgroup analyses requirements in the draft labeling guidance should be consistent with existing guidance for the NDA/BLA ISS.

We suggest changing the text under Vital Signs to "If biologically and pharmacologically relevant, and not provided elsewhere..."

6. Presentation of Less Common Events - As stated earlier, terminology should be consistently applied throughout the guidance document (e.g., "events" vs. "reactions"). A clear, unambiguous definition of "significant adverse reactions" should be provided, to limit the number of judgment calls involved.

The guidance document states that events that would be expected in the observed or studied population at a similar frequency absent drug therapy should be omitted. We believe that there are several scenarios where including this type of event would be warranted. For example, the "FIAU crisis" of several years ago occurred at least in part because the drug was being investigated in patients with chronic hepatitis B who were prone to periodic flares of their underlying disease, with all the attendant symptoms of active hepatitis. Only after Phase III study subjects began to experience hepatic failure leading to liver transplantation or death was it recognized that the severe fatigue described by some patients in earlier studies and attributed to the underlying disease actually represented severe pathology occurring within mitochondria. In this case, it would not be prudent to suggest that because fatigue is a well-described symptom of the underlying disease, it should not be included in the Adverse Reaction section of the label for a drug to treat that disease. Another scenario involves instances where the similar rate between active drug and placebo-treated subjects turned out to be a balance of beneficial and detrimental drug effects (e.g., a paradoxical effect, in which the drug appears to aggravate a condition it is meant to treat). A third reason for including adverse events that are commonly observed in the absence of drug therapy relates to the role of labeling in determining expectedness for post-marketing regulatory reporting. In our experience, the reporting pattern of spontaneous adverse events tends to reflect the pattern of adverse events reported in clinical trials. If adverse events that occur commonly in clinical trials are eliminated from labeling, it will result in a marked increase in the number of adverse events that are considered unexpected. Serious adverse events that occur commonly in conditions such as diabetes, cancer, infections, heart failure, etc. would require expedited reporting if they were not included in the labeling of the products used to treat these conditions, greatly increasing the volume of irrelevant expedited reports, and potentially compromising the ability of sponsors and FDA to conduct appropriate pharmacovigilance by markedly decreasing the "signal to noise" ratio. Thus, we believe that this guidance should provide some leeway to allow for inclusion of this type of information if relevant. Also, it would be useful to have additional perspective on the comment that some adverse reactions, although rare, can be explainable from a drug's pharmacology. We would not ordinarily expect these reactions to be rare.

This section also describes inclusion of events "even if there are only one or two reports". Inclusion of post-marketing events should be based on an objective, evidence-based assessment of the safety data. PhRMA suggests that the focus should be on assessing the signal of a new adverse reaction compared to the noise (e.g., background

frequency of the event in the population), taking into account the completeness of information contained in the reports. Absent an approach based on this type of assessment, labeling will be based on subjective views of small numbers of individual case reports, rather than on objective assessment of the totality of evidence.

FDA should delete the sentence, "If numbers of reports are cited, the period of observation should be stated." This implies inclusion of time-dependent information from notoriously inaccurate and incomplete spontaneous adverse reaction reporting sources. We do not believe that this type of information, which might falsely be interpreted as trend information, should be included in the labeling.

7. Adverse Reaction Information from Spontaneous Reports - PhRMA is supportive of standard language to introduce this section of labeling, but wonders whether the language proposed in the draft guidance has been accepted by all the CDER and CBER Review Divisions. One member company has recently had very similar wording rejected by one of the CDER Review Divisions. If this paragraph is retained, we suggest changing the last sentence to "...or (3) relative strength of causal connection..."

III - Organizing and Presenting Adverse Reactions Data in a Table

A preferable title would be "TABULAR PRESENTATION OF ADVERSE REACTIONS DATA FROM THE NDA DATABASE."

Pooling data: We suggest the use of "more broad-based" rather than "more precise" adverse reaction rates; such data are rarely "precise." Current industry practice is to pool data unless obvious differences have been noted. Is FDA requesting a *priori* analysis that pooling is justified?

Body System Organization: FDA should expand on what is meant by the handling of adverse reactions "reported in more than one body system that represent a common pathophysiologic event." Where and how should these be reported? Also, the suggestion to organize adverse reactions according to frequency is unclear - does this term refer to "rate" or "incidence" of terms?

Frequency Cut-off: We agree that cut-offs should be appropriate for the size of the database. However, specific suggestions for cut-offs should be provided to guide sponsors in deciding what cut-off is appropriate for the database size (e.g., what minimum database size would ordinarily allow cut-offs of 1%, 2%, 5%, etc.) taking into account other parameters of the study, such as duration of the study, and the age and general health of the population treated. Also, it is not clear whether FDA will require inclusion of all adverse reactions that occur > 1% and are observed more frequently on drug than placebo. For some indications, this could lead to listings that are too long to be useful.

It should be noted that current experience with frequency cut-offs is based primarily on experience with coding terminologies with limited specificity at the preferred term level (e.g., COSTART, WHO-ART). The impact of more specific terminologies (e.g.,

MedDRA) that have multiple preferred terms for conditions such as headache and abdominal pain, will need to be considered in establishing frequency cut-off thresholds in the future.

Comparator Adverse Reaction Data: This section states that placebo "or other comparator arms" should be included in the table. Chapter II, however, suggests that only placebo-controlled data should be presented in the table. We would ask FDA to clarify and expand on this. We would also ask FDA to define when "such rates would constitute or imply an unfair or unsubstantiated comparative safety claim" and how comparative data should be included (or if necessary excluded) from the table in such a case. In addition, we would ask FDA to define "suboptimal or excessive." Is this inclusive of doses at the low or high end of the labeled range?

Quantitative Data: There is a need to include mean change, not just rates of the events above a certain level. This information is useful to physicians in understanding the magnitude of risk.

Subgroup rates: We suggest that the example intended in the last sentence should read "... (e.g., specific laboratory tests),..."

Percentages: This section should be expanded to provide additional detail. Is it intended that only signals at < 1% from a large single study would qualify, or could < 1% signals from the pooled data be equally meaningful? What size database would allow < 1% signals to be detected?

Adverse Reaction Rates \leq Placebo Rates: We are curious to know the rationale for removing from tables the adverse reactions where the placebo rate equals or exceeds the rate for drug. This information is often important for the prescriber as it helps to put the data into its overall context, and makes it clear that such events do occur as "background noise" in the population being studied. This information also helps to identify events associated with the disease that may be lowered by the drug treatment (e.g., in a study of a migraine drug the incidence of vomiting is lower in the treated group than in the comparator group).

A simple numeric cut-off of items separated by only one integer is not consistent with the published guidance for FDA reviewers which states that one should look for adverse events which occur at rates of at least 5% or which occur at double the placebo rate.³ We suggest that the labeling guidance be consistent with such internal reviewer guidance. We believe that the meaning of a 1% difference is highly dependent on the comparison: e.g., 0 vs. 1%, 10 vs. 11%, 99 vs. 100%. Such an absolute difference is not very meaningful or useful.

Significance Testing: Please provide examples of situations where the results of significance testing would meet FDA's concept of providing "critically useful information." Clinically meaningful, statistically significant differences in safety have been part of the basis of approval of certain new drugs; for this reason such information should be

³ Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review. Draft, November 22, 1996.

evident in labeling. For example, some drugs are explicitly indicated for treatment of patients who do not respond to or are intolerant of alternative drugs. Such data should be expressly presented in the appropriate sections of labeling. We suggest that this section be rewritten as follows: "Results of significance testing should be omitted unless they provide useful information or 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

Rare, Serious Events: PhRMA recommends that, for clinical trial data, rare serious events should be included only if these are suspected reactions (i.e., events that are not causally related to the drug should be excluded from this section of labeling). Additionally, specific laboratory findings or diagnoses should not be included as examples of such adverse reactions as it could be misinterpreted to assume these terms must be included whenever a report is received, regardless of relationship to drug.

Determining Adverse Reaction Rates: If the intent is for the labeling to focus only on adverse reactions from clinical trials that are possibly, likely or definitely related to drug, what is the rationale for quoting all-causality event rates?

Characterizing Adverse Reactions: Understanding FDA's intent to improve the ADVERSE REACTIONS section's usefulness to end-users, we urge FDA to reconsider this part of the draft guidance. Characterizing adverse reactions with terms that have accepted regulatory definitions should be allowed. We understand that survey results document the inconsistent interpretation of well-defined frequency terms by end-users and the public. However, this could be addressed by allowing the inclusion of the definition of the terms in the labeling [e.g., rarely (1 in 1000)]. FDA should consider use of terms identified and defined by CIOMS III to allow for appropriate characterization of the data presented.

Comparative Safety Claims: See the previous comment in section II.B.3 above. The footnote at the bottom of the page should be numbered "5" rather than "7."

V - Updating the Adverse Reactions Section of Labeling

Sources (and following section): What are "safety issue documents" from consulting divisions? Both controlled and uncontrolled clinical trials are conducted in postmarketing clinical programs and both types of studies can generate information relevant to the ADVERSE REACTIONS section of labeling. The word "controlled" should be deleted or the word "uncontrolled" should be added to these two sections of the guidance.

Inconsistent or Outdated Information: We suggest changing the title of this section to "Review of Safety Information," which is a more accurate description of what is requested. The meaning of the second sentence in this paragraph is unclear. It would

be useful to have further explanation and examples of the "defects" that may have accumulated with time (other than the required updating to ensure consistency with current product and drug class knowledge described in the first half of the sentence). It is not clear that the second part of the same sentence adds value.

PhRMA suggests that the last sentence in this section be deleted, for several reasons. First, by definition, FDA-approved labeling is not false or misleading. Second, this sentence puts the responsibility of updating the labeling on the sponsor only. However, FDA intervention would be necessary when it comes to class labeling. As the CIOMS III report points out, "known reactions to drugs of the same class should have the same statements in all CCSI (PI), within and among companies...the authorities are expected to ensure uniformity among different companies' labeling."

PhRMA also thinks it important that this section clearly state that one should not use post marketing spontaneous report data to refute data initially gathered from controlled clinical trials (i.e., it would not be appropriate to request deletion of an event noted in the clinical trials simply due to lack of reporting of such an event during the post marketing period). The term "outdated" should not be used, as it might imply that any change of data, no matter how insignificant, might require a change to the package insert. For example, if there has been an increase in the number of patients exposed via ongoing clinical trials, but the rates of adverse reaction reporting has not changed, it should not be necessary to simply "update" the numbers of patients and/or regenerate tables using the larger numbers. This paragraph should emphasize the need to add clinically significant NEW information, especially the identification of previously unknown reactions or significant increases in the rates of occurrence of known reactions based upon well-controlled clinical trial or observational study data. This section could also be linked to the use of PSURs (e.g., reference the six or twelve month cycle for which these are prepared) as the basis of labeling updates. Such cross-reference to PSURs would make for integrated compliance on an international level.

Glossary:

We note that the three definitions of Adverse Events and Reactions all refer to "association" with drug. These definitions should be corrected.

In footnotes 6 and 7, reference should be made to ICH E2A rather than ICH E8.

All of the terms mentioned in the previous comments as requiring definitions should be added to the Glossary; whenever possible, the terms should be based on previously established definitions and be consistent with internationally accepted terminology.

Closing Remarks:

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

Sincerely,





Pharmacia & Upjohn

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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.