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PhRMA

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

Re: Docket No. 01D-0269; Draft Guidance for Industry on the Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format; 66 Federal Register 35797, July 9, 2001

Dear Sir/Madam:

The following comments on the above Draft Guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members are investing over $30 billion in 2001 for the discovery and development of new medicines.

PhRMA welcomes this draft guidance that offers direction on the clinical studies section of the drug label. Last December, the FDA issued a proposed rule on the content and format of the drug label (65 Fed. Reg. 81082; December 22, 2000). That proposed rule, to which PhRMA filed extensive comments, reflected the considerable attention that FDA devoted to improving the readability and usefulness of the approved product labeling for prescribing physicians and other health care practitioners. PhRMA agrees with the agency's stated objectives of making labeling more "user friendly" and accessible. PhRMA's goal is to build upon FDA's proposed rule and make the label more useful without unduly lengthening the clinical studies section. In this proposed guidance, FDA has neglected to address the following critical issues.

1. The draft guidance does not specify whether sponsors will have to make retroactive changes to existing drug labels to meet certain specifications in the guidance. It is PhRMA's position that when this guidance is finalized, it should explicitly state that the guidance only applies to new products or efficacy supplements.

2. The big question is "how to present the information in a format that physicians will find more useful?" PhRMA believes that FDA focuses this guidance on its concern that companies might use the Clinical Studies Section for promotional purposes rather than the key issue at hand -- how to present the information in a format that physicians will find more useful. FDA must be aware that those factors that the company selects for promoting a given pharmaceutical are drawn from the entire NDA and not just the label that is, at best, a summary of all the data.

3. This section should include those significant safety benefits that have a direct bearing on the use of the drug, assuming that they are not redundant with other sections of the

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label. FDA should not ignore those parameters that contribute to patient compliance and that are clinically relevant.

Our comments to the specific sections of this Draft Guidance follow.

Section I, Introduction

FDA states "...in some cases, making the information in the CLINICAL STUDIES section of labeling more useful to prescribers could warrant significant departures from past labeling practices."

PhRMA requests that FDA clarify the meaning of this statement. Is it FDA's intent to refer back to the proposed rule on content and format?

Section II, Identifying Studies for Inclusion in the Clinical Studies Section

FDA states "...study results that are inconsistent with the overall conclusions (e.g., absence of a treatment effect) should be included when they provide important information about drug effectiveness that is not otherwise available (e.g., information about a population subset, dose response, or the limitations of effectiveness.)"

PhRMA believes that this statement requires further clarification with respect to meaning and scope. Is it FDA's intent that subsections A and B of this guidance list all of the possible examples of what should and should not be included in the Clinical Studies Section? If it is the FDA's intent to use these examples to limit the amount of information presented in the Clinical Studies Section, this would likely prevent health care providers from knowing the full spectrum of information about a drug's activities in various clinical situations. Certainly in the case of many antibiotics, information critical to the use of the product that falls outside the specifications included here would be useful to clinicians.

PhRMA believes that manufacturers should be able to discuss in this section a lack of prospectively identified adverse events. This could include safety information if confirmational studies are carried out (e.g., non-sedation). As FDA is aware, this is the only way that companies can make such information known to patients and health care providers. To accomplish this, PhRMA suggests establishing a new category under II.A., "Important Safety Benefits Based on Substantial Evidence." In addition, FDA should clarify Footnote 4, by including "safety" as one of the parameters to define effectiveness.

Only limitations of effectiveness based on pivotal studies that are not adequately addressed in other sections of the label should be incorporated into this section. Otherwise, the insert will be unnecessarily long.

PhRMA is puzzled by FDA's desire for concise, yet more detailed information if the study results are inconsistent. With anti-infectives, for example, multiple indications, with multiple studies, and possible inconsistent outcomes may result in a considerable discussion. Does FDA expect, and will they accept, this level of detail?

In subsection A, FDA identifies "...clinical studies that provide important information about the limitations of effectiveness" as an example of studies that should usually be included in the clinical studies section.

PhRMA believes that this statement is too far-reaching and lacks some necessary examples that would provide clarity as to the Agency's intent. Some of this information could be safety related and is better placed in another section of the label.

Section III, Describing Studies in the Clinical Studies Section

As PhRMA noted in our comments to Section II, FDA should revise language so that companies can incorporate important safety information in the Clinical Studies Section. PhRMA disagrees with FDA's assertion that it will be unusual for "safety" data to be described in the Clinical Studies Section. There is an important class of safety data that is beneficial for physicians to know when they are discussing potential therapies with patients, e.g., data demonstrating clinically relevant safety benefits. The final sentence in III.A.1 should be revised to read: "Critical safety data linked to benefits that is presented in the CLINICAL STUDIES section should be accompanied by the study description and efficacy data."

PhRMA believes that it would be useful for FDA to provide some meaningful examples about the amount of detail expected in the clinical studies section (III.A.2). In the proposed rule on content and format, the Agency provided a useful example of what the new label should look like. Unless FDA outlines its expectation with a little more certainty, this section of the drug label is likely to become much longer than is the case at present as sponsors attempt to interpret FDA's intent

FDA states "...ordinarily, less detail is needed in the following situation – the new drug appears to have effects that are typical of its class."

PhRMA believes that this statement is ambiguous. Furthermore, would the fact that less information is required for results that were typical of a class leave some drugs at a competitive disadvantage? For instance, would "me too" drugs not be allowed to include the same amount of details/results in the insert as compared to the first approved drug of the same class? PhRMA strongly believes that each label must rely on its own data set and not any inferences from other drugs in the same therapeutic class.

In subsection 3, FDA discusses the types of endpoints that should be described in the Clinical Studies Section. The Agency notes *"...when it would be informative, the CLINICAL STUDIES section can also discuss other endpoints that were shown to be affected by the drug and endpoints that would have been expected to be influenced by the drug but were not."*

PhRMA believes that the underlined language is speculative. While this statement appears to give the sponsor considerable flexibility in presenting clinical information, it is contradictory to statements in previous sections that argue for a more narrow scope. PhRMA is concerned that these contradictory statements might lead to prolonged labeling negotiations because of a lack of clarity and requests that FDA reexamine the Guidance to insure that there are no ambiguities.

PhRMA believes that composite endpoints should be explicitly defined and agrees with the draft guidance if the endpoints are irreversible morbidity/mortality composite endpoints. However, the current version may not be appropriate if the endpoint is the sum of rating scales (such as

the HAMD-17 scale used in depression studies). PhRMA recommends that FDA add language that clarifies the points made above.

PhRMA would like clarification as to why FDA combines primary and secondary endpoints in a single bullet. Both terms are in widespread use. It appears that the FDA is trying to reduce their use in drug labels. If so, PhRMA requests that the FDA explain its rationale.

PhRMA believes that it would be useful for FDA to expand the section on closely related endpoints and provide some illustrative examples.

Section III.A.4 Comparative Data

Comparative data often are used to validate a study design and inform the prescribing physician about this product in comparison to the "gold standard." FDA must acknowledge that there is a difference between comparators and active controls. The term "comparator" implies a claim of comparative safety/efficacy, whereas "active control" is a scientific term more appropriate for the Clinical Studies section. Information should be included on the active controls, but they should not be referred to as comparators. This will assist in providing clear information to physicians.

Furthermore, this section appears at odds with FDA's statement in subsection III.C.3 that *"... because the comparison between treatment groups is critical to an understanding of the treatment effect, results for both the study drug and comparator should be presented."* PhRMA believes that for clarity, all of the issues regarding the use of non-active comparators in clinical studies should be treated in the same section of the guidance so that there is no ambiguity.

In the past, sponsors have not been allowed to include data when the effectiveness is supported by one Adequate and Well Controlled Trial with a comparator arm (unless there is some form of replicate data), even if superiority is shown. Is this still the case?

Is it FDA's intent to leave the interpretation of "essential to clinicians" to each FDA division/FDA reviewer – without more definitive and global explanations with examples?

Section III.B.4 Study Population

PhRMA questions whether all of the information noted in III.B.4 is necessary for the Clinical Studies Section. In most cases a brief description of baseline parameters is sufficient. Some of this information deals with risk management and would be better suited for other sections of the label.

Section III.C Summarizing the Study Findings

FDA lists items that should be addressed (emphasis added). Collectively all of these requirements, even if summarized will provide excess detail and will make the label more complicated for clinicians. Again FDA should provide concrete examples regarding the necessity and how the data should be presented. In addition, the FDA requests information on dropouts, which is already dealt with in other sections of the label.

Are sponsors required to break down the requested data in III.C.1 by clinical trial phase? How about by arm? Are the reasons for patient withdrawal from the clinical study always relevant for every drug and each arm of the study? PhRMA requests clarification on each of these points.

FDA notes that the use of a p-value in addressing the uncertainty of treatment effects can be included with a confidence interval, but should not be used alone, as it is potentially misleading. This appears to contradict the statement in Appendix II.C, Uncertainty of Treatment Effect, unless it is the FDA's belief that graphs cannot stand alone in the presentation. PhRMA requests that FDA clarify this point.

Subsection III.C.4 appears to be redundant, as this issue is already handled in other sections of the package insert. Again, for clarity, FDA should group all proposals for how demographic information should be treated in the same subsection of the final guidance. Furthermore, PhRMA requests FDA clarify the following statement: *"compelling results from analyses of other subgroups of established interest should also be presented with a caution statement, where appropriate, about the inherent risks of unplanned subgroup analyses."* PhRMA believes that this should only be done if there is clinical significance and it should be handled in the precautions section of the label; is this FDA's interpretation?

Section III.D, Presenting Data for Different Types of Outcomes

In subsection III.D.1, FDA notes that information on categorical outcomes "...where informative, those patients whose outcome status is unknown can be further differentiated by including the number who dropped out due to adverse events, the number who were lost to follow-up, or any other pertinent distinction" should be shown. PhRMA believes that it is only useful to include data related to drop-outs because of adverse events. Other information is likely not relevant to the clinician. If this information must be included, relatedness to drug should be included. Additionally, if this information is located in another section of the label, e.g., the adverse events section, there should be flexibility to place this information in only one place so as not to increase the length of the PI. Finally, for anti-infectives, there is no longer "success," but rather "cure." Also FDA should clarify what is meant by "of clinical importance." Who determines whether it is important?

Section III.E, Advertising and Promotional Considerations

This section dealing with advertising and promotional consideration appears to be derived from the proposed rule on content and format that was published last December. Many of the terms that FDA questions in this section are already in common use and well understood by clinicians. PhRMA notes that FDA's suggestions in this subsection will lengthen the label.

Section III.F, Updating the Clinical Studies Section

Sponsors recognize their obligation to update the label whenever there is new, important information on a drug. The language in this in this section is somewhat ambiguous and PhRMA suspects that there is not a particular problem in this regard. PhRMA assures FDA that it is the sponsor has numerous incentives and the ultimate responsibility to determine what is new and important so that the label may be updated in a timely manner.

Section IV, Appendix

PhRMA notes that the graphs presented in the Appendix are of a print size /legibility that would normally not be acceptable to the FDA in a label, i.e., too small to be useful. Also, FDA has positioned them next to the text, rather than above or below. As FDA is aware, the current printed label is dense with important information for clinicians. PhRMA recommends that sponsors should be able to construct graphs of a defined size and position in a manner that maximizes their impact, while recognizing that they should be in close proximity to the associated text where possible.

PhRMA takes issue with the FDA's statement in subsection B that meta-analytic graphs are *"...useful for illustrating a lack of consistency across studies."* PhRMA believes that the converse is also true and that the use of such graphs should not be restricted.

Furthermore, it would be helpful if FDA can clarify if these rules will be applied to:

1) primary efficacy endpoints,
2) primary and secondary efficacy endpoints or
3) primary efficacy and safety endpoints (including lab data).

We would be pleased to discuss these and other issues about prescription drug labels.

Sincerely,

Alan Goldhammer