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Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

November 7, 2001

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

RE: Comments on Docket No. 01D-0269
Draft Guidance for Industry on the Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format

Dear Sir or Madam:

Wyeth-Ayerst Laboratories, a Division of American Home Products Corporation, hereby submits comments to Docket No. 01D-0269, pertaining to the proposed guidance on the "Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format." The availability of this draft guidance was announced in the July 9, 2001 Federal Register, pp. 35797 – 35798.

Wyeth-Ayerst is a major research-oriented pharmaceutical company with leading products in the areas of women's health care, cardiovascular disease therapies, central nervous system drugs, anti-inflammatory agents, anti-infective agents, vaccines, and biopharmaceuticals. American Home Products Corporation is one of the world's leading research-based pharmaceutical and healthcare products companies, and is a leading developer, manufacturer, and marketer of prescription drugs and over-the-counter medications.

We acknowledge the Agency's efforts in proposing labeling guidance intended to improve the communication of product information to prescribing physicians and other healthcare professionals. We fully support the overall goal of enhancing safe and effective use of prescription medicines. However, we do have some concerns and comments on the draft guidance, as discussed below.

General Comments on the Guidance

Wyeth-Ayerst believes that it would be helpful for FDA to add examples in the guidance describing how a revised clinical studies section might look, and to clearly illustrate points that were made in the guidance regarding the amount of detail, concomitant therapy, comparative data, endpoints, etc. In the proposed rule on content and format ("Content and Format of Labeling for Human Prescription Drugs and Biologics" published in the Federal Register, Volume 65, Number 247, pages 81081-81131 [December 22, 2000]), the Agency provided a useful example of what the new labeling should look like. Unless FDA more definitively outlines its expectations for the Clinical Studies section, we are concerned the guidance could lead to substantial and undesirable increases in the

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length and complexity of the package insert which would not be consistent with the goal of improving usability. There are also likely to be inconsistencies in the labeling of products belonging to different therapeutic categories.

The following comments summarize our views on specific statements in the guidance.

Section III.A.2. General Principles - Amount of Detail
The guidance notes that less detail is needed when "the clinical endpoints measured in the study are not readily measurable or applicable in clinical practice". The term "less detail" is open to broad interpretation. More specific direction should be provided in the guidance regarding information to be included, and information not to be included. Wyeth-Ayerst also recommends that the guidance indicate that the sponsor can negotiate with the Agency on a case by case basis, to determine the appropriate amount of detail from a particular clinical trial to be included in labeling.

Section III.A.3. General Principles - Endpoints
Wyeth-Ayerst agrees with the first part of the first sentence of this section of the guidance, ie, "The CLINICAL STUDIES section should present those endpoints that are essential to establishing the effectiveness of the drug (or that show the limitations of effectiveness)..." We recommend that the next part of the sentence be reworded to read, "and sponsors have the option to describe additional endpoints that are scientifically valid and clinically meaningful (including pharmacoeconomic endpoints)."

Section III.A.4. General Principles - Comparative Data
In the first paragraph, second sentence, the guidance states "If, however, the results from an active comparator arm and identity of the active comparator contribute information that is essential to a clinician's understanding of the drug's effects, the results and identity should be included in labeling." Wyeth-Ayerst believes that the term "essential" is too restrictive. Discussion of all treatment arms, including active controls, provides a more complete and balanced presentation of the study results. In addition, the term "drug's effects" does not convey the overall usefulness of a presentation of the results from all treatment arms. We therefore recommend this sentence be reworded to indicate that "... the results and identity would be permitted when they contribute to the clinician's understanding of the drug's place in therapy when treating a particular patient."

In the second paragraph, the guidance notes that "... the name of the active control and the results from that arm should be omitted if those data are not adequate to support a comparative claim." However, since all study arms influence the analysis and interpretation of the study results, we believe sponsors should have the option to present data from all study arms when describing the results. As noted above, presentation of all treatment arms provides a more complete representation of the study design and results. Inclusion of the active treatment arm when describing study results is standard practice in the scientific community, and has been permissible under the current labeling regulations. Therefore, if it is the Agency's intent to restrict the inclusion of such information in labeling, this would represent a significant change from current standards that ought to be proposed through the notice and comment rulemaking procedure rather than through a guidance document.

In addition, the phrase "data do not support a comparative claim" is not meaningful to the prescribing physician and other healthcare professionals, and should not be included in approved labeling. This phrase is legal terminology used by the Agency and is understood by the pharmaceutical industry in the context of promotional messages, but has no relevance to labeling information provided for the benefit of healthcare professionals.

Section III.B.4. Describing the Study Design – Study Population
The guidance states the description should include important inclusion and exclusion criteria, demographic characteristics, baseline values, and other characteristics of the population that have implications for the extent to which results can be generalized. If interpreted literally, this will significantly add to the length of the labeling, resulting in much greater detail than most prescribers would find useful. In most cases, a concise description of the study design, study population and endpoints should suffice. We recommend this section be revised to clearly indicate that the suggested additional details should only be included when they are essential for understanding the study results.

Appendix II.C. Graphs - Features of a Good Graph
In the bullet regarding Uncertainty of Treatment Effect, the direction to use the appropriate measure of uncertainty (confidence interval or p-value [emphasis added]) is inconsistent with the guidance's position on not using p-values alone that was stated in section III.C.2. There are graphs where the inclusion of confidence intervals could prove problematic (eg, a display of several Kaplan-Meier survival curves). Wyeth-Ayerst recommends that the statement in **Appendix II.C** be modified to the following:

"Differences should be accompanied by the appropriate measure of uncertainty (confidence interval or p-value); although confidence intervals should be incorporated into the presentation of treatment effect, they may not be the most appropriate measure for a particular graph, such as a display of several Kaplan-Meier survival curves."

Conclusion
This letter is submitted in duplicate. Wyeth-Ayerst appreciates the opportunity to provide this constructive input to the guidance. Please contact the undersigned at (484) 865-3794 if there are any questions regarding the submitted comments.

Sincerely,

Roy J. Baranello, Jr.
Assistant Vice President
Worldwide Regulatory Affairs

Rjb91

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