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Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

March 22, 2001

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

RE: Comments on Docket No. 00N-1269
Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; Proposed Rule

Dear Sirs:

Wyeth-Ayerst Laboratories, a Division of American Home Products Corporation, hereby submits comments to Docket No. 00N-1269, pertaining to the proposed rule on "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).

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 largest research-based pharmaceutical and healthcare products companies, and is a leading developer, manufacturer and marketer of prescription drugs and over-the-counter medications.

In general, we acknowledge the agency's efforts in proposing labeling regulations 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.

The following comments summarize our views on specific questions identified by FDA in the preamble to the proposed rule, and additional topics of concern relating to the Agency's proposal:

Highlights of Prescribing Information [proposed § 201.56(d) & § 201.57(a)]

According to the proposed rule, prescription labeling would begin with a new section entitled "Highlights of Prescribing Information" which would have a one-half page limit, not including boxed warning(s) or contraindication(s). Wyeth-Ayerst is concerned that use of a Highlights section may lead some prescribers to infer that the information in this section is the only information that is needed to prescribe the product. Therefore, the presence of a Highlights section may preclude a health care provider from reading the entire package insert, despite the fact that a statement to refer to the comprehensive prescribing information is proposed to be included at the end of the Highlights section. In fact, the comprehensive prescribing information contains the complete information that is relevant to the safe and effective use of the product.

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Due to these concerns, Wyeth-Ayerst proposes that the following measures be addressed if the "Highlights of Prescribing Information" section is ultimately retained:

- The disclaimer statement, *These highlights do not include all the information needed to prescribe (name of drug) safely and effectively. See comprehensive prescribing information for (name of drug) provided below*, should be placed at the top of the Highlights section immediately following the product name.

- The entire boxed warning should be placed in the Highlights section regardless of length, and should be repeated at the beginning of the "Warnings/Precautions" section of the comprehensive prescribing information. We do not believe any additional icons are needed to signal the presence of a boxed warning as the boxed format is well recognized by health care professionals to convey important safety information.

- The one-half page limit for the Highlights section should not be the required maximum. Rather, it should serve as a normal or default length. The manufacturer should determine the length of the Highlights section based on the amount of key information in the comprehensive prescribing information, and where the manufacturer offers reasonable justification for a longer highlights section it should be accepted by the Agency. Wyeth-Ayerst agrees that this section should be in bulleted format to facilitate readability.

Recent Labeling Changes: In section 201.57 (a)(5) FDA proposes, "This section must be retained in the labeling at least 1 year after the labeling change, and may be retained until such time that the labeling is reprinted for the first time following the change." We believe the intent of this language was to allow the information regarding labeling changes in the Highlight section to remain for a minimum of 1 year after a labeling change, and until the next labeling revision thereafter [see preamble p.81089, column 1, paragraph e]. However, the current proposed wording is confusing for products that have multiple labeling changes within a year because the language could be interpreted to mean that the reference to recent changes should be deleted every time the labeling is revised. We therefore propose the following wording to clarify this section: "This section must be retained in the labeling at least 1 year after the labeling change, and may be retained until *the next reprinting following the 1 year period.*"

In addition, we recommend the deletion of the term "recent" to describe the labeling changes because "recent" commonly connotes a timeframe of no more than several months. Therefore, we recommend that the wording be changed to "Changes Since..." or similar wording as an alternative to "recent."

In response to the agency's question on whether a time limit is needed for removing this section, Wyeth-Ayerst does not believe a maximum time limit is needed as this would result in frequent labeling changes unnecessarily adding to the cost of the product. However, the implementation time of the changes will be noted if our recommendation to call this section "Changes Since..." is adopted.

Indications and Usage: FDA requested comment regarding the method of presentation of information to be included under the subheading "Indications and Usage." Wyeth-Ayerst recommends that the "Indications and Usage" subsection should be summarized in a bulleted format to allow easier reading and understanding.

Warnings/Precautions: FDA inquired if specific standardized headings should be included in the "Warnings/Precautions" section. Wyeth-Ayerst believes that standardized headings should not be used because this section should be customized to appropriately reflect the characteristics of the product.

Contacts for ADR reporting: At the end of the "Warnings/Precautions" subsection, FDA is proposing the following statement: "To report SUSPECTED SERIOUS ADRs, call (manufacturer) at (phone #) or FDA's MedWatch at (current MedWatch 3)." Wyeth-Ayerst recommends including instruction for reporting all ADRs, not just serious ADRs, in this section. Therefore, the contact number for reporting suspected adverse drug reactions should be included and worded as follows: "To report SUSPECTED ADRs, call..." or "Telephone SUSPECTED ADRs to..."

Index [proposed § 201.56(d) & § 201.57(b)]

The Highlights section is to be followed by an index titled "Comprehensive Prescribing Information: Index." The Index would list each subheading appearing in the comprehensive portion of the labeling in accordance with a standardized numbering system. Wyeth-Ayerst believes the inclusion of an index is useful since it will enhance navigation through the product information, particularly in electronic format.

NEW FORMAT REQUIREMENTS [PROPOSED § 201.57(d)]

Font Size: It is proposed by FDA [(201.57(d)(6)]that all headings and text in the labeling must be in at least 8-point font type size. In response to the agency's question, Wyeth-Ayerst believes an 8-point font is acceptable and in certain cases a 6-point font may be acceptable from a readability standpoint. Changing current package inserts to 8-point font can result in a 75% increase in length, necessitating acquisition of new packaging machines. An increase to 10-point font would further increase paper size, adding to the overall cost without offering a significant improvement in readability.

Wyeth-Ayerst believes the agency underestimated the cost of increasing font size. Both large and small businesses will feel the impact. Added expenses will be incurred due to the need to change packaging machines at manufacturing sites, and resulting from the associated resources and time for installation and validation of the new equipment.

IMPLEMENTATION OF PROPOSED CONTENT REQUIREMENTS

The revised format and content requirements under the proposed rule would be applied to prescription products with an NDA, BLA or an efficacy supplement that is pending on the effective date of the final rule, submitted on or after the effective date of the final rule or that has been approved from 0 up to and including 5 years prior to the effective date of the final rule. "Older" products not subject to the new requirements would remain subject to the requirements currently in 21 CFR 201.57 which would be redesignated 21 CFR 201.80.

However, FDA proposes additional changes be made for all products, and the following changes would be required to be implemented within 1 year of the effective date of the final rule:

- In vitro or animal data not shown by adequate and well controlled studies to be pertinent to clinical use--including for anti-infective drugs--could only be included in the label if a waiver is granted.

- Indications or uses must not be implied or suggested in sections of labeling other than "Indications and Usage" if not included in that section.

- Any approved patient information or Medication Guide must be referenced in the "Precautions" section and reprinted immediately following the last section of the labeling.

- Dosing regimens must not be implied or suggested if not included in the "Dosage and Administration" section.

Wyeth-Ayerst maintains that antibiotic sensitivity information included within current labeling for anti-infective products provides clinically relevant information for physicians. The requirement for a waiver to retain this information should not apply.

Wyeth-Ayerst agrees that the content revisions being proposed in redesignated § 201.80 should be consistent with certain revisions in proposed § 201.57 for newer drugs to ensure that statements currently in the labeling of older drugs relating to effectiveness or dosage and administration are sufficiently supported. However, for large companies with broad product lines, this will require a comprehensive effort to review, assess and prepare supplements for all marketed products. It would be an extraordinary burden to complete the necessary labeling review, prepare revisions and submit CBE supplements within the proposed one-year time period. Alternatively, Wyeth-Ayerst proposes that the implementation period for these changes be 3 years from the effective date of the final rule. This would provide a more reasonable time period for achieving compliance, and would be more consistent with the implementation schedule for all other format changes.

This letter is submitted in duplicate. Wyeth-Ayerst appreciates the opportunity to provide this constructive input to the rulemaking process. Please contact me at 610-902-3794 if there are any questions regarding the submitted comments.

Sincerely,

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

RJB:cmj:82

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