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

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

TO WHOM IT MAY CONCERN:

The American Society of Health-System Pharmacists (ASHP) is pleased to provide comments on the Food and Drug Administration's December 22, 2000 *Federal Register* notice requesting comments on proposed revisions to FDA's regulatory requirements for prescription drug product labeling. ASHP is the 30,000-member national professional association that represents pharmacists who practice in hospitals, health maintenance organizations, long-term care facilities, home care agencies, and other components of health care systems.

In general, ASHP believes that the FDA has made a significant step in improving professional product labeling. The new prototype labeling included in the current proposed rule is far more user friendly than current labeling. In particular, the reorganization of sections of information and the concepts of highlighting, indexing, and moving more frequently-used or significant information to the beginning of the label are positive improvements that will facilitate the usefulness of prescription drug labeling.

ASHP has the following specific comments about the revisions to the professional labeling:

- ASHP believes that to fully inform health care practitioners (prescribers, pharmacists, and nurses), some brief statement of what the drug is (i.e., therapeutic/pharmacologic class) should appear early in both the "Highlights" section described in §201.57(a) and the "Comprehensive Prescribing Information" section described in §201. 57(c). As they are described in the proposed rule, this information is excluded from the "Highlights" section and is difficult to find -- and, therefore, could be overlooked -- within the "Comprehensive Prescribing Information" section.

- ASHP is concerned with the FDA's discussion beginning on page 81087 of the preamble to the proposed rule relating to the limitation of use information that will be permitted in the "Highlights" section. Proposed §201.57(a)(15) would require the following statement to be included in the "Highlights" section of the labeling: "These highlights do not include all the information needed to prescribe (*insert name of drug product*) safely and effectively...." ASHP believes that either the limitations themselves should be summarized in the "Highlights" section, or the language in §201.57(a)(15) should be revised to state: "These highlights are limited and do not include all the information needed to prescribe (*insert name of drug product*) safely and effectively...."

- Section 201.57(a)(5) requires that the "Highlights" section of the labeling contain a listing of those portions of the comprehensive prescribing information that have undergone substantive, FDA-approved changes; this listing must remain on the labeling for at least one year after the date of the labeling change. ASHP believes that it would be useful to have noted beside each such listing the month/year of the respective change, and not just the date of the most current revision as currently proposed in §201.57(a)(16). In addition, it would be useful if the changes could be listed chronologically, so that a clinician who periodically refers to the "Highlights" section would have a better sense of what might have changed since he/she last looked at the labeling.

- The preamble to the proposed rule (on page 81091) provides examples of headings that could be used in the boxed warnings section of the labeling under §201.57(c)(1). One of these examples is: "WARNING: USE IN PREGNANCY." This specific terminology could be interpreted as an imperative statement (confusing the word "use" as either a noun or a verb). ASHP suggests that the FDA consider other terminology (e.g., 'WARNING: DO NOT USE IN PREGNANCY") for warning professionals not to use the drug for pregnant women.

- The preamble to the proposed rule (see page 81091) states that the FDA is proposing to require in §201.57(c)(1) that the boxed warning be preceded by an exclamation point ("!") so that it would not be confused with the number one ("1"). ASHP believes, however, that typographically, the exclamation point could easily be misread as the number "1." The FDA's suggestion that another icon could be used instead seems preferable, and we would recommend the use of the octagonal, "stop sign" design -- which would alert practitioners to "stop" and read the boxed warning . This icon would not have to be in red, as the FDA indicates in the preamble; a black octagon would have the same effect.

- The proposed change in definition for "adverse reactions" in §201.57(c)(9) as explained on page 81093 of the preamble is an improvement over the current labeling requirements. The new definition should greatly help clinicians sort out what is reasonably associated with use of a drug from the myriad of effects that have been reported but are not reasonably associated causally with the drug. This has been a principal complaint of clinicians for years -- that too much clinically meaningless information on possible adverse effects is included in labeling simply because something was associated temporally with the use of a drug. The revision of the definition also fosters understanding that the sub-set of adverse drug events (which are defined as injuries) that we should classify as "adverse reactions" will be those ADEs that were not anticipated. ASHP thinks, however, that the word "unexpected" might be more accurate in that context than the word "unintended" in the proposed definition. Most practitioners would probably argue that no adverse drug reaction is ever "intended." Some are unavoidable, such as some side effects, but none are ever deliberately "intended" in the sense of being sought as an outcome. In that sense, every adverse event or reaction is "unintended." What seems important, especially for the purpose of postmarketing surveillance of newly-approved drug products, is that we need to gather information about the surprising, unexpected ADRs. We appreciate the FDA's desire to harmonize the agency's definition with that of the ICH's E2A guideline, but we would argue that the word "unintended" is equally imprecise in that guideline. However, even if the agency does not adopt the term "unexpected," the proposed revision of the definition for ADRs would be an improvement over the current definition.

- The FDA is on a good track in its discussion on page 81095 of the preamble to the proposed rule by suggesting that *in vitro* data not be included in the professional labeling. It is certainly the case that drugs sometimes behave very differently *in vitro* vs. *in vivo*. To the extent that *in vivo*, as opposed to *in vitro*, information helps clinicians make more logical therapeutic decisions, the removal of *in vitro* data from the labeling requirements seems reasonable.

- Section 201.57(a)(2) of the proposed rule (see page 81088 of the preamble) requires an inverted black triangle symbol "if the drug product has been approved for less than 3 years in the United States and contains a new molecular entity or new biological product, a new combination of active ingredients, is indicated for a new population, is administered by a new route, or uses a novel drug delivery system." ASHP is not convinced of the value of using an inverted black triangle, unless there will be a regularly updated and on-line source that everyone uses. This requirement assumes that the reader has the most current professional product label. In practice, drugs may be in stock for over a year. Perhaps a **BOLD** date of approval of the labeling in hand would provide practitioners with more useful information.

- Section 201.57(c)(2)(iv)(A), as discussed on page 81115 of the *Federal Register* notice, states that the labeling must describe the limitations and usefulness of the drug if there is evidence that supports its safety and effectiveness "only in selected subgroups of the larger population with a disease, syndrome, manifestation, or symptom under consideration." Some of the differentiating characteristics of such subgroups are noted (e.g., CD4 cell counts). Soon, however, we are likely to have the ability to identify subgroups on the basis of genetic characteristics as well. ASHP believes that this should perhaps also be included in the rule when it is finalized.

- Section 201.57(c)(9)(ii) of the proposed rule, relating to the Adverse Reactions section of the labeling, states (on page 81120 of the *Federal Register* notice) that "adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanisms, or by a combination of these, as appropriate." ASHP agrees that the prevalence of adverse reactions as listed in the labeling should be arranged in some logical order, but the labeling should be required to state exactly what categorization system is being used. This does not seem to be the case in the labeling examples that are provided in the *Federal Register*.

ASHP appreciates this opportunity to present its comments on prescription drug product labeling to the FDA. Feel free to contact me if you have any questions regarding our comments.

Sincerely,

Gary C. Stein, Ph.D.
Director, Federal Regulatory Affairs

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