American Medical Association
Physicians dedicated to the health of America

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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

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

The American Medical Association (AMA), representing approximately 300,000 physicians and physicians-in-training, is pleased to comment on the Food and Drug Administration's (FDA) Proposed Rule entitled, "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels," 65 Fed. Reg. 247, 81082-81131 (December 22, 2000).

General Comments

The AMA commends the FDA for undertaking its Professional Product Labeling initiative that we hope will result in more useful and user-friendly prescription drug product labeling (e.g., the package insert) for prescribing physicians. As you know, the AMA has been involved with this project for a number of years, both as a member of the FDA's Physician Labeling Project Advisory Group and as a participant at the Public Meeting on October 30, 1995.

The FDA's proposed "Prototype 4" for labeling, as described in the Proposed Rule, has evolved through a deliberative process that has transpired over the past decade. This process has included two physician focus groups, a physician survey, the development of two early prototypes for professional labeling, four additional physician focus groups, and the development of a third prototype that was subjected to public review and comment.

The AMA believes that "Prototype 4" improves upon the preceding prototype and is most likely very close to what most prescribing physicians seek in terms of revised professional labeling. The AMA generally is supportive of the format and content requirements of this revised professional labeling for prescription drugs and biologics. The AMA is especially pleased with the following specific characteristics of "Prototype 4":

- "Highlights of Prescribing Information." Physicians and the AMA have consistently been supportive of adding a short summary section to professional labeling which contains the most important information about a drug product. The FDA's proposal to

add a "Highlights" section and to limit this section to one-half page, as previously recommended by the AMA, will make professional labeling more useful and user-friendly for physicians as they care for their patients. The AMA commends the FDA for its superb work in designing the content and format requirements for this new section.

- Reordering of Prescribing Information. The AMA is pleased that the FDA has taken the advice of physicians and is proposing to reorder the information in professional labeling to give more prominence to those sections that are most important to and most commonly referenced by prescribing physicians. Moving sections, such as "Indications and Usage" and "Dosage and Administration," to the beginning of the "Comprehensive Prescribing Information" section will make the labeling more useful to physicians.

- "Index" and Standardized Numerical Identifiers. In previous communications to the FDA, the AMA expressed support for the inclusion of an "Index" for "Comprehensive Prescribing Information;" the use of standardized numerical identifiers for major headings (e.g., "Indications and Usage"); and cross-referencing of sections included in the "Highlights of Prescribing Information" with the corresponding sections in the "Comprehensive Prescribing Information." The AMA is pleased that the FDA has incorporated these elements into "Prototype 4." This should make the revised professional labeling easier to access and more amenable to searching by computer.

- "Drug Interactions" as a Major Section. The AMA continues to support the FDA's proposal to elevate "Drug Interactions" to major section status in the revised professional labeling. This change should be welcomed by physicians who frequently must care for patients who are on multiple medications and/or those individuals who also use dietary supplements for self-care.

- Addition of "Recent Labeling Changes." The AMA continues to support the inclusion of this new section in the "Highlights of Prescribing Information" with appropriate cross-referencing to the relevant sections in the "Comprehensive Prescribing Information." The content of this proposed new section should be very useful, especially if professional labeling is available on frequently updated (e.g., online) databases.

- "Contacts for ADR Reporting." The AMA, a MedWatch partner, supports the prominence given to telephone numbers that will enable physicians to contact the manufacturer or the FDA's MedWatch program if a serious drug-related adverse event is suspected. The AMA concurs with the FDA that these contacts should be prominently displayed in both the "Highlights of Prescribing Information" and in the "Comprehensive Prescribing Information."

Responses to Specific Questions

In its description of the proposed labeling requirements, the FDA has raised several questions for comment on specific issues (see p. 81086). The AMA is pleased to present its views on some of these questions.

In proposed Section 201.56(b)(1), the FDA lists those prescription drugs and biologics that would be subject to the revised labeling and format requirements. Only newly and more recently approved drug and biologic products (i.e., those approved up to five years prior to the effective date of the Final Rule) would have to comply with these new labeling requirements. Older drugs that were approved more than five years prior to the effective date of the Final Rule would be exempt unless a new efficacy supplement was subsequently approved. The FDA asks whether alternative application criteria should be used (see Question #15 on p. 81086).

The AMA strongly urges that the revised professional labeling eventually apply to all marketed prescription drug and biologic products, regardless of their date of FDA approval for marketing. The AMA believes that having two different regulatory requirements for the content/format of professional labeling is inappropriate for the following reasons. First, more useful and user-friendly labeling would not be available for a large number of (older) prescribed drugs and biologics. Second, two distinctly different sets of labeling requirements potentially could be confusing to physicians. Finally, it would be far more difficult to create easily searchable electronic databases of professional labeling if there were two very different formats for the information.

The FDA has raised several questions on p. 81086 about the proposed "Highlights of Prescribing Information" section. Question #1 asks whether there are circumstances where it may be inappropriate to include this section. Question #3 asks whether the full text (as opposed to the proposed 20-line limit) of any boxed warnings should be required in the "Highlights" section, regardless of length. Question #6 asks whether the "Indications and Usage" subsection should be presented verbatim from the "Comprehensive Prescribing Information" section (as opposed to the proposed concise summaries in bulleted format). Finally, Question #12 asks whether there are better alternatives to the proposed one-half page limit on the "Highlights of Prescribing Information" section (not including boxed warning(s) or contraindication(s)).

A consistent message from physicians to the FDA in the survey and focus group testing was to add a short summary section to the professional labeling so there would be easy access to the most important product information and a means to get to detailed information more efficiently. The AMA believes the FDA's proposed Section 201.57(a) satisfies the needs of prescribing physicians. Thus, the AMA recommends against elimination or lengthening of the "Highlights of Prescribing Information" section under certain circumstances. The AMA supports the one-half page length, the 20-line limit summary for lengthy boxed warnings, and the concise summaries of indications in bulleted format. However, in addition to the proposed standard "Highlights Limitation Statement" under Section 201.57(a)(15), the AMA encourages the FDA to require, on a case-by-case

basis, within specific subsections of the "Highlights" section (e.g., boxed warning or "Indications and Usage") any necessary disclaimers or qualifying statements to assure that the physician will know there is additional information and that the physician will be guided to the appropriate subsection of the "Comprehensive Prescribing Information."

Question #7 on p. 81086 asks whether it is necessary to include the proposed requirement for an "Index" section in revised professional labeling. As noted above, the AMA supports inclusion of an "Index" section as an efficient means for physicians to access information in the "Comprehensive Prescribing Information." The inclusion of an index also is recommended for the following reasons. Standardized numerical identifiers will only apply to major section headings (e.g., "Indications and Usage") and selected subsections (e.g., "Pregnancy"). However, professional labeling for most drug and biologic products will have many nonstandardized subheadings (e.g., see the Capoten^{R} example on p. 81125) and, an index will help physicians to quickly access this information. Also, the "Highlights of Prescribing Information" section will not contain information from all of the sections/subsections of the "Comprehensive Prescribing Information," and the "Highlights" section is being formatted differently than the "Comprehensive Prescribing Information" section (e.g., "Common Adverse Reactions" are listed under "Warnings/Precautions" in the "Highlights" section). Therefore, the "Highlights of Prescribing Information" section cannot be relied upon to serve as an index.

Question # 8 on p. 81086 asks whether standardized headings [for subsections] in the "Warnings/Precautions" section is appropriate. To the extent it can be achieved, the AMA supports uniformity in the formatting of revised professional labeling. This will be most useful and user-friendly to physicians who access the information, especially if this is done electronically. However, the AMA does not believe it is possible to standardize the headings of subsections in the "Warnings/Precautions" section because of the diversity of the information. The AMA does support the use of nonstandardized headings of subsections in the "Warnings/Precautions" section, as was done in "Prototype 4" (see the Capoten^{R} example on p. 81125 and pp. 81127-81128).

Question #9 on p. 81086 asks if it is necessary to include a contact number for reporting suspected serious adverse drug reactions in the proposed "Comprehensive Prescribing Information" as well as the proposed "Highlights of Prescribing Information." As discussed above, the AMA believes this information is especially important for physicians and should be prominently displayed in both sections of the revised professional labeling.

In response to Question #5 on p. 81086, the AMA supports the FDA's proposal in Section 201.57(a)(5) to place a one-year time limit on the information placed in the "Recent Labeling Changes" section of the "Highlights of Prescribing Information."

In response to Questions #4, #11, #13, and #14 about format on p. 81086, the AMA supports the FDA's proposals in Section 201.57(c)(1) [also, Section 257(a)(4)], Section 201.57(d)(5), Section 201.57(d)(9), and Section 201.57(d)(6) regarding the icon for boxed warnings, bolded information, a vertical line to identify new labeling information, and font size, respectively.

Additional Comments

The AMA supports the FDA's proposal in Section 201.57(c)(9) to revise the definition of adverse drug reaction to be consistent with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline. The AMA agrees with the FDA that this will result in a more focused "Adverse Reactions" section in the revised professional labeling and promote consistency in labeling worldwide. In particular, physicians will be pleased that the revised definition would clarify that at least a reasonably plausible causal relationship must exist between a drug and a noxious and unintended response for the response to be included as an adverse reaction in the "Adverse Reactions" section. This should eliminate some of the clinically meaningless adverse reactions that appear in professional labeling currently.

Under proposed Section 201.56(d)(4), the FDA states that the labeling under Section 201.57(c) may contain a "Product Title" section preceding any boxed warning or, in the absence of such warning, preceding the "Indications and Usage" section. The AMA recommends that the inclusion of a "Product Title" section at the beginning of the "Comprehensive Labeling Information" section be mandatory. The "Product Title" section is very short and repeating it will be useful to physicians and avoid confusion.

In parallel with the development of a Final Rule, the AMA recommends that the FDA also develop an education program for physicians about the revised professional labeling for drugs and biologics. In particular, physicians must understand how best to use the "Highlights of Prescribing Information" section and its limitations. The AMA would be pleased to work with the FDA in developing and implementing such an education program so that physicians use the revised labeling optimally for the care of their patients.

Conclusion

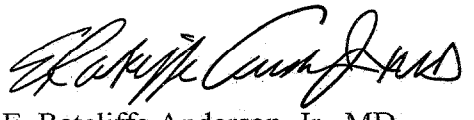
In conclusion, the AMA offers its strong support for the revised content and format of professional labeling for human prescription drugs and biologics, as described in the Proposed Rule. These revisions are consistent with what physicians are seeking in terms of professional labeling, and the changes should make the labeling more useful and user-friendly.

The AMA's primary concern with the Proposed Rule is that it exempts older drugs (i.e., drugs approved more than five years prior to the effective date of the Final Rule) from the revised labeling requirements. The AMA urges that the Final Rule require the revised professional labeling to apply to all marketed prescription drugs and biologics.

The AMA encourages the FDA to promulgate a Final Rule on revised professional labeling expeditiously and that a physician education program about the revised labeling also be developed. The AMA would be pleased to work with the FDA on such an education program.

The AMA appreciates the opportunity to comment on this important issue and would be pleased to discuss its views on revised professional labeling for human prescription drugs and biologics more fully with the FDA. Please direct any questions or comments to Carol Vargo in our Washington Office, at 202-789-7688.

Sincerely,



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