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Federal Register

Friday,
December 22, 2000

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 201

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 00N–1269]

RIN 0910–AA94

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations governing the format and content of labeling for human prescription drug and biologic products. This proposal would revise current regulations to require that the labeling of new and recently approved products include a section containing highlights of prescribing information and a section containing an index to prescribing information, reorder currently required information and make minor changes to its content, and establish minimum graphical requirements. These revisions would make it easier for health care practitioners to access, read, and use information in prescription drug labeling and would enhance the safe and effective use of prescription drug products. This proposal would also amend prescription drug labeling requirements for older drugs to require that certain types of statements currently appearing in labeling be removed if they are not sufficiently supported. Finally, the proposal would eliminate certain unnecessary statements that are currently required to appear on prescription drug product labels and move other, less important information to labeling. These changes would simplify drug product labels and reduce the possibility of medication errors.

DATES: Submit written comments by March 22, 2001. Submit written comments on the information collection requirements by January 22, 2001.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Wendy Taylor.

FOR FURTHER INFORMATION CONTACT: *For information on drug product labeling:*

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I. Background

The part of a prescription drug product's approved labeling directed to health care practitioners (also known as its ''package insert,'' ''direction circular,'' or ''package circular'') is the primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals. This part of approved labeling is a compilation of information based on a thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. The regulations governing the format and content of labeling for prescription drugs and biologics appear at §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57).[1] Under § 201.100(d) (21 CFR 201.100(d)), any labeling, as defined in section 201(m) of the act (21 U.S.C. 321(m)), that is distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use of the drug, or that prescribes, recommends, or suggests a dosage for the use of the drug, must meet the content and format requirements contained in §§ 201.56 and 201.57. Thus, §§ 201.56 and 201.57 apply to the labeling for all prescription drugs approved under an NDA, abbreviated new drug application (ANDA), or BLA, including labeling on or within the package from which the drug is to be dispensed and ''promotional'' labeling described in § 202.1(l)(2) (21 CFR 202.1(l)(2)).

Regulations proposing §§ 201.56 and 201.57 were published in the **Federal Register** of April 7, 1975 (40 FR 15392). At the time of the proposal, agency regulations required that certain section headings appear in prescription drug labeling, but did not, for the most part, specify the type of information required under those headings. The purpose of the proposal was to improve prescription drug labeling by ensuring that it contained more specific, comprehensive, and accurate information. The agency determined

[1] Although current §§ 201.56 and 201.57 do not specifically refer to biologics, under the Federal Food, Drug, and Cosmetic Act (the act), most biologics are drugs that require a prescription and thus are subject to these regulations.

that the primary purpose of prescription drug labeling is to provide practitioners with the essential information they need to prescribe the drug safely and effectively for the care of patients, and that revision of labeling requirements was necessary to achieve this objective for all products. Among other things, the proposal set forth standards for the content of labeling information required under the then-existing section headings, provided for a new section in prescription drug labeling entitled ''Clinical Pharmacology,'' revised the format and expanded the content requirements for the ''Indications and Usage'' and ''Adverse Reactions'' sections of prescription drug labeling, and reformatted and expanded required information related to possible hazards of use in pregnant women and in children.

Regulations finalizing §§ 201.56 and 201.57 were published in the **Federal Register** of June 26, 1979 (44 FR 37434). These regulations were revised in 1994 by amending the requirements relating to the inclusion of data relevant to use in pediatric populations (59 FR 64240, December 13, 1994) and in 1997 by amending the requirements relating to the inclusion of data relevant to use in geriatric populations (62 FR 45313, August 27, 1997).

Current § 201.56 requires that prescription drug labeling contain the required information in the format specified in current § 201.57. Section 201.56 also sets forth general requirements for prescription drug labeling, including the requirement that labeling contain a summary of the essential scientific information needed for the safe and effective use of the drug, that it be informative and accurate and neither promotional in tone nor false or misleading, and that labeling be based whenever possible on data derived from human experience. In addition, § 201.56 sets forth required and optional section headings for prescription drug labeling and specifies the order in which those headings must appear. Required section headings include: ''Description,'' ''Clinical Pharmacology,'' ''Indications and Usage,'' ''Contraindications,'' ''Warnings,'' ''Precautions,'' ''Adverse Reactions,'' ''Drug Abuse and Dependence,'' ''Overdosage,'' ''Dosage and Administration,'' and ''How Supplied.'' Section headings that may be included under certain circumstances include: ''Animal Pharmacology and/or Animal Toxicology,'' ''Clinical Studies,'' and ''References.''

Current § 201.57 specifies the kind of information that is required to appear under each of the section headings set forth in § 201.56. This information is intended to help ensure that health care practitioners are provided with a complete and accurate explanation of prescription drugs to facilitate their safe and effective prescribing. Thus, the regulations require prescription drug labeling to contain detailed information on various topics that may be important to practitioners.

In addition to these regulations, the National Childhood Vaccine Injury Act (Public Law 103–66) requires FDA to monitor the adequacy of labeling for children's vaccines.

In addition to the requirements for prescription drug labeling discussed above, current §§ 201.55 (21 CFR 201.55) and 201.100(b) set forth certain requirements for prescription drug product labels. As discussed in section V of this document, the agency is proposing certain amendments to these requirements that would simplify prescription drug product labels and reduce the possibility of medication errors.

II. The Need for Revised Prescription Drug Labeling

Although the format and content requirements for prescription drug labeling in §§ 201.56 and 201.57 have enabled health care practitioners to prescribe drugs more safely and effectively, the requirements, together with various developments in recent years, have contributed to an increase in the amount, detail, and complexity of labeling information. This has made it harder for health care practitioners to find specific information and to discern the most critical information in product labeling.

Nonregulatory developments that have affected the length and complexity of drug labeling include technological advances in the drug products themselves and recognition of the importance of including new or additional labeling information, such as information on drug/drug interactions and information necessary to optimize use in various subpopulations. In addition, the use of labeling in product liability and medical malpractice lawsuits, together with increasing litigation costs, has caused manufacturers to become more cautious and include virtually all known adverse event information, regardless of its importance or its plausible relationship to the drug. Finally, accelerated approval of certain drugs for serious or life-threatening illnesses has resulted in the rapid availability of products for which expanded information about benefits and risks is necessary to help ensure safe and effective prescribing.

In response to the resulting increase in the length and complexity of prescription drug labeling and to anecdotal evidence suggesting that current prescription drug labeling does not optimally communicate its information (Ref. 1), FDA evaluated the usefulness of prescription drug labeling for its principal audience to determine whether, and how, its format and content can be improved. As discussed below, the agency conducted two initial focus groups and a national physician survey to ascertain how prescription drug labeling is used by health care practitioners, what labeling information is most important to practitioners, and how prescription drug labeling can be improved. Based on the results of the physician survey, FDA developed two prototype revisions to the format of prescription drug labeling (''Prototypes 1 and 2'') and examined the value of these prototypes in four physician focus groups. Based on these results, FDA developed a third prototype (''Prototype 3'') and held a public meeting to solicit public comments on Prototype 3. FDA revised the prototype (''Prototype 4'') based on the public meeting and written comments submitted to the agency on Prototype 3. Prototype 4 serves as the model for this proposal and is included as Appendix 1.[2]

A discussion follows of the agency's prescription drug labeling development efforts, including the focus groups, physician surveys, public meeting, and prototype development.

A. Initial Focus Groups

In February 1992, FDA conducted two physician focus groups (Ref. 2) to ascertain how practitioners use prescription drug labeling, which aspects of labeling are most important to practitioners, and how current labeling can be improved. The focus groups indicated that the Physicians' Desk Reference (PDR) was the most common source of labeling information. The practitioners expressed concern about the lack of ease in locating specific information among the extensive information presented. They stated that the most important information needed to make a confident decision about prescribing a particular drug for a particular individual is contraindications (especially when the patient is a member of a special population), side effects, drug interactions, dosage, comparative efficacy, and cost information. The

[2] All prototypes may be seen at the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday (see Docket No. 95N–0314).

focus groups' recommendations with regard to improving the format included: (1) Using graphical devices to highlight important information; (2) adding an abstract of important information; (3) placing packaging and dosing information earlier in labeling; (4) enlarging the type size; and (5) reducing or eliminating anecdotal, marginal information.

B. Physician Surveys

Between October 1993 and March 1994, FDA conducted a telephone interview survey of a national probability sample of office-based physicians to determine how physicians perceive and use drug product labeling and to ascertain how labeling (the drug package insert) could be made more useful (the DPI survey). FDA designed the DPI survey to examine specific issues, including what is the perceived importance of the various labeling sections and what formatting alterations could make labeling more useful to practicing physicians.

Results of the DPI survey demonstrated that office-based physicians use drug product labeling primarily to answer specific questions about patient care rather than as a general educational tool and that labeling (generally in its reprinted form in the PDR) is consulted after the physician has made a tentative prescribing decision. The DPI survey further demonstrated that:

(1) The labeling sections physicians read most often and perceive as most important are: Dosage and Administration, Contraindications, Warnings, Adverse Reactions, and Precautions;

(2) Overall, the Clinical Pharmacology section, and the Abuse and Dependence and Overdosage sections, are referred to relatively infrequently;

(3) Physicians are prompted to refer to labeling most often by negative product experiences and newness of the product; and

(4) Physicians believe that labeling overly stresses the occurrence of extremely rare events. They also asserted that although they can generally find the information they need, the usefulness of labeling could be improved by highlighting and providing an abstract of the most important information.

In addition to the DPI survey that addressed drug package inserts generally, the agency conducted a physician survey from October 1994 to October 1995 to obtain information specifically regarding physicians' use of and perceptions about vaccine package inserts (the VPI survey). The VPI survey was conducted by the agency's Center for Biologics Evaluation and Research (CBER) in an effort to improve the utility of vaccine package inserts in communicating the nature and extent of risks associated with vaccines. Among other things, the VPI survey was designed to examine whether changes can be made to vaccine package inserts to increase their usefulness.

Although the objectives of and the methodology used in the VPI survey were different than those used in the DPI survey, the VPI survey helped to confirm the findings of the DPI survey. For example, the VPI survey found that, overall, the vaccine package insert sections that are perceived as most useful by physicians include Dosage and Administration, Indications and Usage, Contraindications, Warnings, and Adverse Reactions. The Clinical Pharmacology and References sections were found to be among the least useful sections. Of the physicians surveyed, 71 percent indicated that they would increase their use of vaccine package inserts if a summary of prescribing information were used in the inserts. Eighty percent of physicians surveyed indicated that the summary should be no more than one-half page in length, 64 percent wanted the summary to have large print, and 56 percent wanted the summary to list serious reactions and be printed in bold type. The physicians also indicated that the following information (listed in order of preference) should be included in a summary: (1) Indications/usage, contraindications, and warnings; (2) adverse reactions, precautions, and dosage/administration; (3) a description of the vaccine; and (4) storage.

C. Initial Prototype Development

Based on the results of the DPI survey, FDA developed two prototypes of revised labeling formats for each of three prescription drug products (Prototypes 1 and 2). Both prototypes incorporated three major differences from the current labeling requirements. The first and most visible difference was the addition of a short section, entitled ''Summary of Prescribing Information,'' inserted at the very beginning of the labeling. It included brief excerpts from the content areas that physicians felt included the most important labeling information. The second major difference was the reordering and reorganization of the presentation of information topics in the current labeling. For example, one of the sections judged by survey participants to be most important and most often used, ''Dosage and Administration,'' is currently required to be placed toward the end of labeling. This section was placed more toward the beginning of labeling in the prototypes. The ''Clinical Pharmacology'' section, judged by physicians as one of the least frequently used and least important, is currently placed at the beginning of labeling. This section and other less highly rated sections were moved toward the end of the labeling in the prototypes.

The prototypes also combined the current ''Warnings'' and ''Precautions'' sections into a single section entitled ''Special Considerations'' because of anecdotal information that physicians do not make meaningful distinctions between these two categories. The prototypes also included the subheadings ''Hypersensitivity Reactions'' and ''Major Toxicities'' to distinguish potentially serious reactions from ''General Precautions,'' which included drug interactions. Subsections currently required to be included under the ''Precautions'' section concerning use of a drug in special populations (e.g., ''Pediatrics,'' ''Labor and Delivery,'' ''Nursing Mothers'') and the section entitled ''Information for Patients'' were reorganized in the prototype into separate headings entitled ''Use in Specific Populations'' and ''Patient Counseling Information.''

The third major difference between the prototypes and current labeling was the use of a paragraph identification system to make detailed information more accessible. This system was designed to be used together with a listing of the contents of the comprehensive information, inserted immediately before the comprehensive section. The system was also designed to provide ''pointers'' within the summary section that would refer readers desiring additional information to the proper place in the comprehensive section. The system is analogous to the hypertext linkage systems currently used on the Internet in which a user can select a particular word or phrase within other text to have more detailed information about the selected word or phrase automatically displayed.

The only difference between Prototypes 1 and 2 was the length of their ''summary'' sections. Prototype 1 included a two-column page-length summary while the summary of Prototype 2 was one and one-half pages in length.

D. Qualitative Testing of Initial Prototypes

FDA conducted qualitative testing of the revised labeling format prototypes (Prototypes 1 and 2) in four physician focus groups. The focus group results

showed that the physicians preferred the prototype with the one-page summary section (Prototype 1), but believed (consistent with the VPI survey results) that it was still too lengthy, which might discourage its use. The physicians stated that the availability of a short summary would not decrease the likelihood of reading the detailed labeling sections, but would direct them more efficiently to needed detailed information in the comprehensive section. The physicians also found the contents listing very helpful.

The focus group results confirmed the agency's belief that it is important to include the following sections prominently in the summary of prescription drug information: ''Indications and Usage,'' ''Dosage and Administration,'' and ''How Supplied.'' It is also important that the summary include information about the negative attributes of a drug product—its contraindications, warnings, precautions, and adverse drug reactions (ADR's), and that drug interactions be listed under a separate major heading.

The focus groups also recommended that summary information be presented in a short, bulleted format and include pointers indicating where in the labeling they should go for additional information. Many physicians preferred a table format, where possible, in place of narrative descriptions, and preferred the placement of patient counseling information toward the end of labeling.

E. The Public Meeting

Based on the results of the physician survey and focus group testing, FDA developed a revised prototype (Prototype 3). This prototype differed from the two initial prototypes in that it had a shorter ''Summary'' section and the organization of sections was changed. The paragraph identification system was modified such that the major information headings would be assigned the same index number, regardless of product, to help familiarize prescribers more rapidly with the new indexing system and facilitate ease of access to specific types of information across products. Finally, the combined warnings and precautions section was renamed ''Warnings/Precautions'' and information relating to drug interactions was removed from the combined section and placed under its own separate heading.

In the **Federal Register** of October 5, 1995, FDA published a notice (60 FR 52196) announcing an informal public meeting on October 30, 1995,[3] to present background information and research concerning how approved prescription drug product labeling could be revised to communicate important information more effectively to health care practitioners, and to solicit comments on Prototype 3. Several panelists, including representatives from the American Medical Association (AMA), United States Pharmacopeial Convention, Pharmaceutical Research and Manufacturers of America, Biometric Research Institute, Inc., American Pharmaceutical Association, American Academy of Physician Assistants, and the American Academy of Nurse Practitioners presented their comments on Prototype 3 at the meeting. Many panelists supported the prototype, stating, for example, that it would ''result in more useful and user-friendly professional labeling for the prescribing physician.''

FDA also received 10 written comments on Prototype 3 in response to the October 5, 1995, notice. Many of these comments supported the labeling prototype, stating, for example, that ''the proposed reorganization of the product labeling is a positive step that better reflects the manner in which the information is actually employed at the point of care.'' Another comment stated that ''[t]he prototype is well organized, and the information seems to be positioned to be more accessible and, therefore, more helpful to health-care practitioners.'' Other comments recommended that FDA conduct additional research on the prototype and that ''FDA thoroughly study any reformatting with a broad range of health care professionals who use labeling.''

The written comments submitted in response to the notice are discussed below.

III. A Description of the Proposed Labeling Requirements

In its effort to develop prototypes of drug labeling and obtain feedback on those prototypes, the agency has identified certain format elements that it believes would enhance the ability of practitioners to access, read, and use prescription drug labeling. The proposed rule would revise current §§ 201.56 and 201.57 to incorporate these format elements as requirements for new and more recently approved drugs. Older drugs would remain subject to the format requirements in current § 201.57, which would be redesignated as § 201.80. Certain requirements in current § 201.57 also would be modified to help ensure that statements appearing in the labeling of older drugs relating to effectiveness or dosage and administration are sufficiently supported. The categories of drugs that would be subject to the revised labeling format and content requirements are discussed below in conjunction with the description of proposed § 201.56. The implementation scheme for the proposed changes is discussed in detail in section IV of this document. As discussed in section IV, the agency believes that applying the revised format requirements only to more recently approved products is appropriate because, among other factors, physicians are more likely to refer to the labeling of recently approved products than the labeling of older products.

The format changes that would be required under the proposal for new and more recently approved drugs include the addition of an introductory section of prescribing information, entitled ''Highlights of Prescribing Information,'' to the comprehensive labeling information required under current § 201.57 (the comprehensive prescribing information).[4] The highlights section would consist of selected information that practitioners most commonly refer to and view as most important from specific sections in the comprehensive prescribing information. As discussed further in this section and in section IV of this document, sponsors would be responsible for proposing language to be used in the highlights section in their product applications (i.e., NDA's, BLA's, or efficacy supplements). As with all approved prescription drug labeling, review and approval of the language by FDA would be required. The proposal would also add an index to, reorder, and reorganize the comprehensive prescribing information to make it easier to use and read, and make minor changes to its content. The proposal would set minimum standards and requirements for certain critical graphic elements of the format of prescription drug labeling.

A detailed description of each section of the proposed rule is provided below. Comments received on those sections of Prototype 3 corresponding to the proposed requirements are also

[3] A transcript of the meeting may be seen at the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday (see Docket No. 95N–0314).

[4] The highlights section (''Highlights of Prescribing Information'') corresponds to the section entitled ''Summary of Prescribing Information'' in earlier prototypes. As discussed below, the agency has changed the title in response to industry comments that the section does not represent a true summary. To avoid confusion about which labeling section is being discussed, the term ''summary'' is used only in direct quotes of comments.

summarized and addressed.[5] In addition to requesting general comments on the proposal, the agency is seeking comment on the following specific issues (presented here for the convenience of the reader):

(1) Whether, and under what circumstances, it may be inappropriate to include the proposed ''Highlights of Prescribing Information'' section in the labeling of a particular drug or drug class;

(2) Does the inclusion of a highlights section have a significant effect on manufacturers' product liability concerns and, if so, is this concern adequately addressed by: (a) Titling this section ''highlights'' rather than ''summary,''; and (b) including the following statement, in bold, at the end of the highlights section: ''These highlights do not include all the information needed to prescribe (name of drug) safely and effectively. See (name of drug)'s comprehensive prescribing information provided below.'' If these are not sufficient, could the agency take different or additional measures to alleviate product liability concerns without eliminating the highlights section altogether or lengthening it to an extent that it would no longer serve its intended purpose;

(3) Whether the full text of any boxed warnings should be included in the proposed ''Highlights of Prescribing Information'' section, regardless of length;

(4) What different types of icons could be used to signal a boxed warning and what are their costs and benefits;

(5) Whether there should be a time limit by which the ''Recent Labeling Changes'' section must be removed;

(6) Whether the information required under the ''Indications and Usage'' subsection in the proposed ''Highlights of Prescribing Information'' section should be presented verbatim from the comprehensive labeling section or summarized in a bulleted format;

(7) Whether it is necessary to include the proposed requirement for an index section given the proposed requirement for a highlights section (i.e., do the additional purposes served by the index justify its inclusion?);

(8) Whether not including standardized headings in the ''Warnings/Precautions'' section is appropriate. If it is believed that specific standardized headings should be included, FDA requests comment about what they should be;

(9) Whether it is necessary to include a contact number for reporting suspected serious adverse drug reactions in the proposed ''Comprehensive Prescribing Information'' section as well as the proposed ''Highlights of Prescribing Information'' section;

(10) Whether the potential impact of the proposed rule on small entities has been accurately estimated by the agency, and whether small business concerns have been adequately addressed;

(11) Whether the proposed requirement to bold certain information in proposed § 201.57(d)(5) will serve its intended purpose of ensuring the visual prominence of the bolded information or whether different highlighting methods may be more effective;

(12) Whether the proposed one-half page limit on the ''Highlights of Prescribing Information'' section (not including boxed warning(s) or contraindication(s)) is adequate or whether there are alternatives that would be more appropriate and under what circumstances such alternatives should be considered;

(13) What means (other than the vertical line proposed in § 201.57(d)(9)) could be used to facilitate access to, and identification of, new labeling information in the proposed comprehensive prescribing information section;

(14) Whether the proposed minimum 8-point font size for labeling is sufficient or whether a minimum 10-point font size would be more appropriate; and

(15) Whether the revised format and content requirements should be applied to drug products with an NDA, BLA, or efficacy supplement that is pending at 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, or whether alternative application criteria should be used.

A. General Requirements on Content and Format of Labeling for Human Prescription Drugs (§ 201.56)

The proposal would revise current § 201.56 to set forth: (1) General labeling requirements applicable to all prescription drugs; (2) the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in proposed §§ 201.56(d) and 201.57; (3) the schedule for implementing the revised content and format requirements in proposed §§ 201.56(d) and 201.57; (4) the required and optional sections and subsections associated with the revised format in proposed § 201.57; and (5) the required and optional sections and subsections for the labeling of older prescription drugs not subject to the revised format and content requirements.

Proposed § 201.56(a) (''General Requirements'') would set forth general labeling requirements applicable to all prescription drugs. These are currently set forth at § 201.56(a) through (c), and include the requirements that labeling contain a summary of the essential scientific information needed for the safe and effective use of the drug, that labeling be informative and accurate and neither promotional in tone nor false or misleading, and that labeling be based whenever possible on data derived from human experience.

Proposed § 201.56(b) sets forth the categories of new and more recently approved prescription drugs and biologics subject to the revised format and content requirements in proposed §§ 201.56(d) and 201.57. These would include prescription drug products for which an NDA, BLA, or efficacy supplement has been approved in the 5 years before the effective date of the final rule, drug products for which an NDA, BLA, or efficacy supplement is pending at the effective date of the final rule, and drug products for which an NDA, BLA, or efficacy supplement is submitted on or after the effective date of the final rule. The revised content and format requirements in the proposed rule would not apply to drug products approved more than 5 years before the effective date of the final rule (provided that an efficacy supplement was not approved for such products in the 5 years before the effective date of the final rule, or submitted after the effective date of the final rule). As mentioned above, these products would remain subject to the labeling requirements in current § 201.57, which under the proposal would be redesignated as § 201.80.

Proposed § 201.56(c) sets forth the schedule for implementing the revised format and content requirements in proposed §§ 201.56(d) and 201.57. The implementation schedule is discussed in detail in section IV of this document. The implementation schedule would require that for products with certain applications (i.e., NDA's, BLA's, and efficacy supplements) submitted on or after the effective date of the final rule, revised labeling must be submitted with the application. For drugs and biological products approved in the 5 years before the effective date of the final rule, revised labeling must be submitted on a staggered basis beginning 3 years after the effective date of the final rule. The implementation schedule would require that labeling for the most recently

[5] As discussed above, the proposed rule is based on Prototype 4, which is very similar to Prototype 3.

approved drugs (i.e., those approved in the year immediately preceding the effective date of the final rule) be revised first.

Proposed § 201.56(d) would require that labeling for new and more recently approved prescription drugs contain the information required under proposed § 201.57 under specified headings and subheadings. This section sets forth required and optional headings for labeling under the revised format. Proposed § 201.57(d)(1) through (d)(4) is similar to current § 201.56(d), but reflects the revised headings and subheadings that are included under proposed § 201.57(a) (Highlights of Prescribing Information) and § 201.57(c) (Comprehensive Prescribing Information). The section also reflects the proposed reorganization and revisions of the comprehensive prescribing information. Proposed § 201.56(d)(5) would permit the use of additional subheadings where appropriate to emphasize specific topics within the text of required sections. For example, under the ''Warnings/Precautions'' section, additional subheadings could be used to set off each warning or precaution. The use of headings in this manner is consistent with current labeling formatting practice and would provide sponsors with a valuable tool in designing labeling that effectively communicates important information to prescribers.

Proposed § 201.56(e) would set forth the required section headings and subheadings for older drugs (i.e., drugs approved more than 5 years before the effective date of the final rule). The section incorporates current § 201.56(d) without change, except for the references to § 201.57, which would be changed to reflect the redesignation of current § 201.57 to § 201.80.

B. Revised Format and Content Requirements Applicable to Newer Drugs

1. Highlights of Prescribing Information

Proposed § 201.57(a) would require that the labeling of human prescription drugs, specified in § 201.56(b)(1), contain the heading ''Highlights of Prescribing Information'' followed by the specific information and subheadings listed in proposed § 201.57(a)(1) through (a)(17). As discussed below, information under these sections would be a concise extract of the most important information already required under current § 201.57, as well as certain additional information that the agency believes is important to prescribers (e.g., recent labeling changes). The agency is proposing to add this highlights section to prescription drug labeling because, based on the information discussed in section II of this document, the agency believes that the usefulness of labeling can be improved by highlighting at the beginning of labeling the information that is most often used and cited as most important by health care practitioners. FDA is requesting comment, however, about whether and under what circumstances it may be inappropriate to include a highlights section for a particular drug or drug class.

Inclusion of only a limited amount of information in the highlights section would not affect any of the regulations related to prescription drug promotion. Manufacturers still would be responsible for ensuring that claims in promotional labeling and advertisements are consistent with the comprehensive prescribing information. Thus, for example, if certain limitations of use contained in the comprehensive prescribing information regarding a drug's effectiveness, contraindications, or side effects is permitted to be excluded from the highlights section, a manufacturer still would be required to include information about those limitations in its promotional labeling and advertisements in accordance with applicable regulations. It is essential that promotional labeling and advertisements be consistent with the comprehensive prescribing information because the highlights section does not include all the information needed to prescribe a drug safely and effectively, and is thus not intended to act as a substitute for the comprehensive prescribing information. This responsibility is described in the introductory paragraph of proposed § 201.57(a) which provides that, in order to comply with §§ 202.1(e) and 201.100(d)(1), statements made in promotional labeling and advertisements must be consistent with all information included in labeling under proposed § 201.57(c) (i.e., the comprehensive prescribing information).

Several comments received on Prototype 3 strongly supported inclusion of a highlights section in the labeling. One comment stated that the section ''would impart key information of most common interest to prescribers'' and ''would be a concise and clear means of displaying information.'' Another comment stated that the highlights section serves ''as an excellent vehicle for drawing the practitioner's attention to the most important facts and precautions associated with a product'' and that ''[c]ross-referencing each point in the summary to the underlying complete prescribing information further enhanced the summary's value.''

Other comments on Prototype 3 opposed inclusion of a highlights section. Several comments contended that practitioners might rely solely on this section and fail to read the comprehensive prescribing information. One comment stated that ''it is difficult, if not impossible, for summary information to adequately deliver the complete message regarding complicated prescribing information'' and ''the mere availability of a summary, even if it is followed by the complete information, discourages a time-pressured human being from reviewing the pertinent sections of the complete prescribing information.''

It is unrealistic to expect practitioners to read every word of product labeling each time they reference it, regardless of how desirable it may be for them to do so. Therefore, FDA is proposing to add the highlights section to prescription drug labeling to draw attention to those sections of the labeling that are most important, and to do so in a way that readily facilitates and encourages more detailed followup. For example, certain kinds of information that are now potentially lost in a long list of topics under ''Precautions'' would be identified and described at least briefly in the highlights section.

Other comments expressed concern about the inclusion of a highlights section because of its potential effect on product liability. The comments stated that including a highlights section would force manufacturers to pick and choose only certain parts of the warning information listed in the comprehensive information. One comment stated that this ''would allow an expert witness testifying on behalf of a patient who suffered an adverse reaction that was listed in the full prescribing information to argue that a manufacturer's warning was inadequate or ''buried'' because that specific adverse reaction was not also highlighted in the Summary.''

The agency recognizes that prescription drug labeling may be used as evidence in product liability cases and other types of civil actions to determine, among other things, whether a manufacturer has adequately disclosed information about risks associated with its drug. However, the agency believes that it is highly speculative to assert that, because certain risk information has been summarized in or omitted from the highlights section of prescription drug labeling (but included in its entirety in the comprehensive prescribing information), a manufacturer may be found liable in a

product liability action based on a theory that the warning is ''buried.''

Moreover, although the highlights section would not include all information about risks associated with a drug, the agency believes that, as described in this proposal, the highlights section would include the most important information regarding drug-related risks. As discussed below in section III.B.1.j. of this document, the ''Warnings/Precautions'' section of the highlights would include those ADR's that are most relevant to clinical prescribing situations. This would include both rare but life-threatening drug reactions and less serious but more common reactions that may be important from a clinical standpoint when prescribing a drug. Additionally, this section of the highlights would include, under its own subheading, the most common or frequently occurring ADR's that are reasonably associated with the use of the drug, which for most drugs would be those ADR's with an incidence of greater than 1 percent.

Nevertheless, the highlights section is not intended to act as a substitute for the comprehensive prescribing information, and it is extremely important for practitioners to be aware of this and to review all relevant sections of the comprehensive prescribing information before making prescribing decisions. Thus, in response to the comments' concerns, to generally aid in avoiding misunderstandings about the purpose of the highlights section by health care practitioners and others, and to encourage practitioners to review the relevant sections of the comprehensive prescribing information, the agency is proposing two modifications to Prototype 3. First, FDA is proposing that the introductory section be entitled ''Highlights of Prescribing Information.'' This title more appropriately acknowledges that the section does not comprehensively summarize all sections of product labeling. Second, the following statement would be required to be presented in bold print, at the end of the highlights section: ''These highlights do not include all the information needed to prescribe (*insert name of drug product*) safely and effectively. See (*insert name of drug product*)'s comprehensive prescribing information provided below.'' The agency is seeking comment on whether the inclusion of a highlights section would have a significant effect on manufacturers' product liability concerns and, if so, whether this concern has been adequately addressed in this proposal. If it is believed that product liability concerns have not been adequately addressed, the agency seeks comment on whether it could take different or additional measures to alleviate product liability concerns without eliminating the highlights section altogether, or lengthening it to an extent that it would no longer serve its intended purpose.

a. *Product names and other basic information.* Proposed § 201.57(a)(1) would require that information necessary to identify a drug product—the proprietary name and the established name or, for biologics, the proper name (as defined in § 600.3 (21 CFR 600.3)) and any informative descriptors—be the first information that appears in the highlights section. This information would be followed by the product's dosage form and route of administration. For drugs that are controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must also be included in this section. In accordance with § 1302.04 (21 CFR 1302.4), the symbol must be clear and large enough to afford prompt identification of the controlled substance.

b. *Inverted black triangle.* Proposed § 201.57(a)(2) would require placement of the ''▼'' symbol if the drug has been approved in the United States for less than 3 years and contains a new molecular entity (NME) 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. It is well recognized that many important ADR's are not discovered until several years of marketing have elapsed. FDA believes that providing an easily recognizable symbol to serve as a signal for increased vigilance and reporting of suspected adverse reactions will facilitate faster recognition of rare but serious side effects that may be associated with newly marketed products and help ensure that drugs are used with particular care during their initial years of marketing. The inverted black triangle symbol is currently used in the United Kingdom to alert prescribers to the fact that a product contains a new active ingredient or is indicated for a new route of administration, among other things. FDA recognizes that U.S. prescribers' experience with the ▼ symbol is limited and that it will take time and an educational program to familiarize them with it. FDA believes that efforts to educate the public about this symbol, as well as general education concerning revisions to the labeling format, can be largely accomplished through the agency's routine outreach and education programs.

c. *Prescription drug symbol.* Proposed § 201.57(a)(3) would require placement of the ''R_x '' symbol to indicate that the drug is a prescription drug.

d. *Highlighted boxed warning.* Proposed § 201.57(a)(4) would require that the full text of boxed warning(s) or contraindication(s) required by proposed § 201.57(c)(1) be included in the highlights section, provided that the text does not exceed 20 lines. For boxed warnings longer than 20 lines, the proposed section would require a statement, not to exceed 20 lines, summarizing the contents of the boxed warning. The agency has tentatively concluded that the proposed limit of 20 lines of text, together with a ''pointer'' to the full boxed warning (discussed below) and any other pertinent information in the comprehensive prescribing information, is sufficient to disclose the most important aspects of the warning for the purposes of the highlights section. However, because of the importance of the information in the boxed warning, the agency requests comment on whether the full text of any boxed warning should be included in the highlights, regardless of the length of its text.

The agency is proposing to require that the text of all boxed warnings in the highlights section be preceded by an appropriate heading, in uppercase letters, that contains the signal word ''WARNING'' and describes the subject of the warning. For example, an appropriate heading for a boxed warning regarding use of the drug product during pregnancy could be entitled ''WARNING REGARDING USE IN PREGNANCY'' or a warning about agranulocytosis could be entitled ''WARNING: AGRANULOCYTOSIS.'' When the agency determines that a contraindication must be placed inside a box, the heading should reflect that the information inside the box is a contraindication. For example, an appropriate heading for a contraindication against use in pregnant women could be ''WARNING: DO NOT USE IN PREGNANT WOMEN.'' Research on the effectiveness of warning labels has consistently shown that the use of a signal word to attract attention increases the effectiveness of warnings (Ref. 3). Both the text of the summary statement and the heading would be required to be contained within a box and bolded. The signal word and title would be required to be in uppercase letters to provide for additional prominence.

In addition to the requirements discussed above, proposed § 201.57(a)(4) would require that, for boxed warning(s) or contraindication(s)

that must be summarized because it exceeds 20 lines of text, a statement be placed immediately under the heading that states: ''See for full boxed warning.'' This statement would alert practitioners to the fact that the boxed warning statement appearing in the ''Highlights'' section does not constitute the full boxed warning.

e. *Recent labeling changes.* Proposed § 201.57(a)(5) would require the subheading title ''Recent Labeling Changes'' (instead of the title ''New Information'' in Prototype 3) to indicate that this section of the labeling includes recent FDA approved or authorized substantive labeling changes, not other kinds of new information, such as information that is in the scientific literature, but not approved or authorized by FDA for inclusion in labeling. Minor or nonsubstantive changes, such as changes in an address, correction of typographical errors, or grammatical changes, would not be required to be included under this section. The agency is proposing to require that the ''Recent Labeling Changes'' section remain for at least 1 year after the date of the labeling change. In response to the comments, the section would be permitted to be retained, after the expiration of the 1-year period, until the next labeling revision. FDA is requesting comments, however, concerning whether there should be a time limit by which the section must be removed. To ensure that practitioners are aware of the date of the most recent labeling revision, FDA is proposing, under § 201.57(a)(16), that the highlights section prominently include the date of the most recent labeling revision.

f. *Indications and usage.* Proposed § 201.57(a)(6) would require the heading ''Indications and Usage,'' followed by a concise statement of each of the product's indications, as specified in proposed § 201.57(c)(2), with any appropriate subheadings. This information must include major limitations of use (e.g., particular subsets of the population, second line therapy status, antimicrobials limited to certain microorganisms). At the public meeting, the agency requested public comment about whether the information required under this heading should be presented verbatim from the comprehensive labeling section or summarized in a bulleted format. Although FDA received strong support for the latter, it remains interested in receiving further comment on this subject.

g. *Dosage and administration.* Proposed § 201.57(a)(7) would require the heading ''Dosage and Administration,'' followed by highlights of the comprehensive prescribing information proposed under § 201.57(c)(3), with any appropriate subheadings. Information under this heading would consist of the most common dosage regimen(s) and the most important moderating information, such as different doses for population subsets, critical monitoring requirements, and other therapeutically important information. If different dosage regimens are associated with different indications or patient populations, this information should be summarized as succinctly as possible. As discussed above, many physicians in the initial focus groups stated that tabular presentation of dosage and administration information is useful. The agency encourages development of such a format and provides in Prototype 4 one example of a tabular presentation of different dosage regimens for different indications.

h. *How supplied.* Proposed § 201.57(a)(8) would require the heading ''How Supplied,'' followed by a concise summary of information concerning the product's dosage form(s) under proposed § 201.57(c)(4). This would ordinarily include the metric strength or strengths of the dosage form and whether the tablets are scored. If appropriate, the information in this section heading could include subheadings to specify different dosage forms (e.g., tablets, capsules, suspension).

i. *Contraindications.* Proposed § 201.57(a)(9) would require the heading ''Contraindications,'' followed by a concise summary of the comprehensive prescribing information in proposed § 201.57(c)(5), and any appropriate subheadings.

j. *Warnings/precautions.* Proposed § 201.57(a)(10) would require the heading ''Warnings/Precautions,'' followed by a concise summary of the most clinically significant aspects of the comprehensive prescribing information in proposed § 201.57(c)(6), with any appropriate subheadings. The cautionary information chosen from the comprehensive prescribing information for inclusion in this section should be that which is most relevant to clinical prescribing situations. Rare but life-threatening drug reactions must be included, especially when the likelihood of occurrence can be reduced by taking recommended steps (e.g., by monitoring, by checking the patient's history or current medication use, or through informing patients which symptoms to look for and report immediately). However, seriousness of reaction should not be the only criterion. It may be just as, if not more, important from a clinical standpoint for a prescriber to know about a less serious, but common and irritating adverse reaction likely to reduce compliance with drug therapy in many patients. Thus, in determining whether specific cautionary information should be included in the highlights section, consideration should be given to a combination of factors, including the seriousness of an adverse reaction and its frequency of occurrence, whether steps can be taken to avoid the adverse reaction or identify and treat it at an early stage, and the likelihood that the reaction could affect patient compliance or continuation of therapy. These factors should be assessed in light of how they would affect a health care practitioner's decision to prescribe the particular drug in a clinical setting and how the practitioner would use and monitor the drug.

The agency is also proposing that the ''Warnings/Precautions'' heading in the highlights section include the subheading ''Most Common Adverse Reactions (≥ n/100).'' This subheading would typically list the most common or frequently occurring ADR's that are reasonably associated with the use of the drug from the adverse reactions section under proposed § 201.57(c)(9). As stated in the report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group III report entitled ''Guidelines for Preparing Core Clinical-Safety Information on Drugs'' (Ref. 4), common ADR's include those with an incidence of greater than 1 in 100 (i.e., 1 percent). Therefore, the agency believes that, for most drugs, it would be appropriate to report ADR's with an incidence of greater than 1 percent. However, for those drugs that are associated with a very large number of ADR's, and/or for which many of the ADR's occur at an incidence rate of more than 1 percent, it may be appropriate to report in the highlights section only those ADR's associated with incidences of 2, 3, 4, or 5 percent, or more. The incidence rate that is used to determine inclusion in this subsection would be required to be disclosed in parentheses together with this subheading.

k. *Contacts for ADR reporting.* Proposed § 201.57(a)(11) would require, for drug products other than vaccines, the following statement be placed in the highlights section following ''Warnings/Precautions'': ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA's MedWatch at (*insert the current FDA MedWatch number*).'' For vaccines, the following

statement would be required: ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS number*).'' In partnership with many professional associations and private sector groups, FDA has consistently encouraged the reporting of suspected serious adverse drug reactions. The proposed section would alert practitioners to the importance of reporting suspected serious ADR's and provide convenient reporting contacts.

l. *Drug interactions.* Proposed § 201.57(a)(12) would require the heading ''Drug Interactions,'' followed by a concise summary from the comprehensive prescribing information in proposed § 201.57(c)(7) of other prescription or over-the-counter drugs or foods that interact in clinically significant ways with the product, with any appropriate subheadings.

m. *Use in specific populations.* Proposed § 201.57(a)(13) would require the heading ''Use in Specific Populations,'' followed by a concise listing of any clinically important differences in response to or use of the drug in specific populations from the comprehensive prescribing information in proposed § 201.57(c)(8), with any appropriate subheadings. With respect to pregnancy categories, the agency does not believe that prescribers would find it helpful to include in the highlights section the category for the drug or selected animal data related to use of the drug during pregnancy. Thus, manufacturers should include under this heading only that information concerning use of the drug during pregnancy that is provided under the ''Contraindications'' or ''Warnings/Precautions'' sections of the highlights. In the absence of such information, the availability of human data regarding use during pregnancy should be briefly noted.

n. *Referral to patient counseling information.* Proposed § 201.57(a)(14) would require, where applicable, the verbatim statement ''See P for Patient Counseling Information.'' This statement would inform practitioners of the existence of patient counseling information and allow them to easily access the information. As discussed below in the description of § 201.57(c)(17), patient counseling information is intended to help practitioners communicate important drug information to patients. For drugs that have approved patient labeling or Medication Guides, the following statement would be required: ''See P for Patient Counseling Information, followed by (*insert name of drug*)'s (*insert either* approved patient labeling or Medication Guide).''

o. *Highlights reminder.* Proposed § 201.57(a)(15) would require that the labeling include the statement: ''These highlights do not include all the information needed to prescribe (*insert name of drug product*) safely and effectively. See (*insert name of drug product*)'s comprehensive prescribing information provided below.'' As discussed previously, this statement would be a prominent reminder to practitioners that the highlights section is not intended to be an all-inclusive source of drug prescribing information.

p. *Labeling revision date.* As discussed previously, proposed § 201.57(a)(16) would require that the highlights section include the date of the most recent labeling revision, identified as such. The inclusion of this date in the highlights section would indicate to practitioners precisely when the ''recent labeling changes'' identified under § 201.57(a)(5) were incorporated into the labeling.

q. *Index numbers in the highlights section.* Proposed § 201.57(a)(17) would require that any subheadings required by paragraphs (a)(4) through (a)(10), (a)(12), and (a)(13), as well as additional subheadings included in the highlights under § 201.56(d)(5), be followed in parentheses by their corresponding index number (i.e., the number appearing before required subheadings under § 201.56(d)(1) or assigned to optional subheadings in accordance with § 201.56(d)(5)). The agency is proposing the use of a numbering system to facilitate the cross-referencing of specific topics between the highlights section, the index, and the comprehensive prescribing information. As discussed in the following section III.B.2, several comments supported this numbering system.

2. Comprehensive Prescribing Information: Index

Proposed § 201.57(b) would require the heading ''Comprehensive Prescribing Information: Index'' followed by a list that contains each subheading required under § 201.56(d)(1), if not omitted under § 201.56(d)(3), and each optional subheading included in the comprehensive prescribing information under § 201.56(d)(5). Each subheading would be required to be preceded by its corresponding index number or identifier. The agency is proposing to require this indexing system to make it easier for practitioners to access specific topics included in the comprehensive prescribing information and to facilitate hypertext links in electronic labeling that will be available in the near future.

In general, the comments on Prototype 3 supported the indexing system. For example, one comment stated that when standardized across all approved drug product labeling, this system will provide a useful mechanism for facilitating electronic retrieval of information by subject area and will enable practitioners to more quickly and easily locate needed data. Some comments stated that the index should be used in place of the highlights section because the index alone is sufficient to direct the reader to the appropriate information. In contrast, one comment asserted that the use of index numbers in the highlights section that cross-reference the comprehensive prescribing information would be sufficient without inclusion of an index.

As discussed above, the purpose of the highlights section is to highlight only the labeling information that practitioners considered to be most important. The index, in contrast, is intended to make it easier for the practitioner to access any details in the comprehensive prescribing information, regardless of the perceived importance of the information. Although both sections contribute to enabling practitioners to more easily access, read, and use prescription drug labeling information, the highlights section and the index serve separate and distinct purposes. Therefore, FDA is proposing to include both sections in prescription drug labeling. However, FDA requests comment on whether the additional purposes served by the index are sufficient to justify its inclusion in labeling.

3. Comprehensive Prescribing Information

The agency is proposing to revise the content and format of the comprehensive prescribing information contained in current § 201.57 to make it easier for health care practitioners to access, read, and use the labeling information. The proposal would reorder the information to place more prominently those sections that the agency found, based on the physician surveys, focus groups, public comments, and its own experience, to be most important and most commonly referenced by practitioners. In most cases, this would require moving the information closer to the beginning of the comprehensive section. The agency is also proposing to reorganize certain sections of the labeling, to require standardized index numbers for each subheading, and certain other format and content changes.

a. *Proposed § 201.57(c)(1)—boxed warning.* Under the current ''Warnings'' section (§ 201.57(e)), labeling must describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The section provides that, ''Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box.'' If a boxed warning is required, ''its location will be specified by the Food and Drug Administration.'' Under the current regulation, boxed warnings have frequently been placed at or near the beginning of labeling to increase their prominence and accessability. However, this has not always been the case.

The proposal would move the language describing when boxed warnings may be required from § 201.57(e) to § 201.57(c)(1). The agency is proposing to move this requirement out of the ''Warnings'' section because, in the past, information required to be placed within a box has consisted of contraindications information as well as warnings information. Proposed § 201.57(c)(1) would revise the language in current § 201.57(e) to specify that a box is appropriate for contraindications information as well as warnings information. Additionally, because of the importance of the information contained in boxed warnings, the agency believes that boxed warnings should always be placed before other labeling information. Accordingly, proposed § 201.57(c)(1) would require that any boxed warning(s) be the first substantive information to appear in the comprehensive prescribing information section of prescription drug labeling. As with the boxed warning in the highlights section, the agency is proposing to require that the boxed warning in the comprehensive labeling section be preceded by an appropriately descriptive heading, placed within the box, that contains the signal word ''WARNING,'' and a brief descriptive title in uppercase letters. The heading may be general (*e.g.,* ''WARNING: USE IN PREGNANCY'') or specific (*e.g.,* ''WARNING: INTERACTION WITH CYP3A4 INHIBITORS'').

The agency is proposing to require that, for indexing purposes, the boxed warning be preceded by an exclamation point ''!'' instead of the number ''1.'' This is appropriate because index numbers will be standardized across all products, yet many products do not have a boxed warning. Therefore, if the number ''1'' were to be used in conjunction with boxed warnings for the relatively few products that have a boxed warning, the highlights and comprehensive prescribing information for the many products without a boxed warning would begin with the index number ''2,'' which might be confusing. In addition, the agency believes that the exclamation point is an appropriate icon to help alert prescribers to the importance of the information contained in the boxed warning. However, other icons could be considered, such as an open hand that signals ''stop'' or, if labeling is in color, a red octagon that signals ''stop.'' The agency requests comments on the relative benefits and costs of different icons that could be associated with a boxed warning.

b. *Proposed § 201.57(c)(2)—indications and usage.* Under current § 201.57(c), a drug product's indications must be included after the ''Description'' and ''Clinical Pharmacology'' sections of labeling. The section requires, among other things, that indications be supported by substantial evidence of effectiveness based on adequate and well-controlled studies, unless the requirement is waived under § 201.58 (21 CFR 201.58) or § 314.126(c) (21 CFR 314.126(c)). [6]

Under proposed § 201.57(c)(2), the ''Indications and Usage'' section would be placed more prominently toward the beginning of the comprehensive prescribing section than it is currently. Proposed § 201.57(c)(2)(i) would modify current § 201.57(c)(1) to remove certain examples of indications that have become outdated. Section 201.57(c)(2)(ii) would modify current § 201.57(c)(2) to clarify that indications or uses not included in the ''Indications and Usage'' section may not be implied or suggested in other sections of labeling.

Proposed § 201.57(c)(2)(iii) would be added to address biological drug products subject to licensing under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). The proposed section would make clear that substantial evidence of effectiveness must support indications for biological drug products. Under section 351 of the PHS Act, FDA approves BLA's on, among other things, a demonstration that the biological product that is the subject of the application is safe, pure, and potent. Potency has long been interpreted to include effectiveness (§ 600.3(s)).

In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for ''adequate and well controlled studies'' for new drugs, § 314.126, unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (§ 601.25(d)(2) (21 CFR 601.25(d)(2) (the biologics efficacy review)). One example of such an adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists.

Although the biologics efficacy review regulation, § 601.25, references § 314.126, and the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) directs FDA to take measures to minimize differences between the review and approval of BLA's and NDA's, § 314.126 does not expressly apply to BLA's. However, FDA believes that it is appropriate to take the characteristics of an adequate and well-controlled clinical investigation, as described in § 314.126, into account in evaluating the sufficiency of evidence of effectiveness that sponsors submit in BLA's to satisfy the licensure standards in section 351 of the PHS Act. (See FDA's guidance for industry entitled ''Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products,'' May 1998.)

Proposed § 201.57(c)(2)(iv)(A) would modify current § 201.57(c)(3) to specify that if evidence is available to support the safety and effectiveness of the drug or biologic only in selected subgroups of the larger population with the disease or condition, or if evidence to support the indication is based on surrogate endpoints, the limitations in the usefulness of the drug (or, in the case of surrogate endpoints, the limitations of the supporting efficacy data) must be described succinctly. Reference should be made to the ''Clinical Studies'' section (proposed § 201.57(c)(15)) for a detailed discussion of the specific methodology and clinical data relevant to the limitation. The agency anticipates that this change would facilitate a more focused ''Indications and Usage'' section for the practitioner seeking basic information. For those practitioners seeking more detailed information, the reference to the ''Clinical Studies'' section should be sufficient to signal that additional information is available.

Current § 201.57(c)(3)(iv) permits the agency to require a statement that there is a lack of evidence supporting a drug's

[6] Current §§ 201.57(c) and 201.58 inadvertently refer to waiver under § 314.126(b) instead of (c). The agency is proposing to correct these references in the current rulemaking.

effectiveness for a use or condition if there is a common belief that a drug may be effective for a certain use, or if there is a common use of the drug for a condition, but the preponderance of evidence shows that the drug is ineffective. Proposed § 201.57(c)(2)(iv)(D) would modify the current section to permit the agency to require a statement that there is a lack of evidence that a drug is *safe* for a use or condition when the preponderance of the evidence shows that the therapeutic benefits of the product do not generally outweigh its risks. The agency believes that the current language is too limiting in that it only addresses products that are shown to be ineffective for a particular use or condition. This fails to address products that may be effective, but pose an unacceptable safety risk for the condition or use.

c. *Proposed § 201.57(c)(3)—dosage and administration; proposed § 201.57(c)(4)—how supplied/storage and handling.* Under current § 201.57, the ''Dosage and Administration'' and ''How Supplied'' headings appear toward the end of prescription drug labeling. Under ''Dosage and Administration,'' labeling must state the usual dose and dosage range, the recommended intervals between doses, duration of treatment, and any modification of doses needed in special patient populations, among other information. Under ''How Supplied,'' labeling must include the strength of the dosage form, units in which the dosage form is ordinarily available, information appropriate to the identification of the dosage form, and special handling and storage conditions.

Based on the DPI survey and focus groups conducted by FDA, the agency has determined that the information contained in these sections is important to practitioners and frequently referenced by them. Accordingly, the agency is proposing to move both sections closer to the beginning of the comprehensive prescribing section to facilitate access to them. In addition, the agency is proposing that the current heading ''How Supplied'' be changed to ''How Supplied/Storage and Handling'' to emphasize the placement of storage and handling information in the section, which may otherwise be overlooked by practitioners. The proposal would add a provision to the current dosage and administration section stating that, where established and when clinically important, efficacious and/or toxic drug and/or metabolite concentration ranges and therapeutic concentration windows for drug and/or metabolite(s) must be stated in this section. The proposed section would also require information on therapeutic drug concentration monitoring (TDM) when TDM is clinically necessary. Finally, the current dosage and administration section would be revised to specify that dosing regimens must not be implied or suggested in other sections of labeling if not included in this section.

d. *Proposed § 201.57(c)(5)—contraindications.* Current § 201.57(d) requires contraindications to be placed immediately following indications. The section requires labeling to describe those situations in which a drug should not be used because the risk of use clearly outweighs any possible benefit. Proposed § 201.57(c)(5) would incorporate the current section without substantive change.

e. *Proposed § 201.57(c)(6)—warnings/precautions.* Warning and precautionary information currently appears under two separate headings in accordance with § 201.57(e) and (f), respectively. Under ''Warnings,'' labeling must describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. Under the heading ''Precautions,'' labeling must contain, among other things, information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (current § 201.57(f)(1)) and information on laboratory tests that may be helpful in following a patient's response or in identifying possible adverse reactions (current § 201.57(f)(3)).

To make this information easier to use, the agency is proposing to combine the ''Warnings'' information required by current § 201.57(e) with the ''Precautions'' information required by current § 201.57(f)(1) and (f)(3) into one heading entitled ''Warnings/Precautions.'' As discussed below, the remaining information covered in current § 201.57(f) would be presented under new proposed section headings.

Observations and suggestions from the physician focus groups discussed in section II of this document, combined with FDA's experience, have convinced the agency that the distinction between warnings and precautions is perceived by prescribers as being relatively arbitrary and frequently not clinically meaningful. FDA first attempted to address these concerns by combining the Warnings and Precautions sections in the labeling prototype presented at the public hearing (i.e., Prototype 3). That prototype, however, continued to account for differences in the types of information required in the current Warnings and Precautions sections by creating subsections that distinguished more specifically between ''Hypersensitivity Reactions,'' ''Major Toxicities,'' and ''General Precautions.''

After further consideration, FDA believes that the clinical relevance of an adverse reaction is not always related to the seriousness of the reaction. For example, if a drug is associated with two adverse reactions (one serious, but very rare, and another less serious, but extremely common), it may be as important from a clinical standpoint, if not more so, for a prescriber to know about the less serious reaction as it is to know about the serious reaction. This is especially true where the less serious reaction may affect compliance with drug therapy for many patients. In addition, for certain products, a warning about a serious but nonpredictable ADR may be less clinically meaningful than the recommendation for routine monitoring to detect a relatively less serious but predictable ADR. Accordingly, the proposed ''Warnings/Precautions'' section would substitute the terminology ''clinically significant adverse reaction'' for the terminology ''serious adverse reactions'' in the current ''Warnings'' section to clarify that clinically significant adverse reactions must be included under the section. In addition, the proposed rule would not require adverse reactions selected for inclusion in the ''Warnings/Precautions'' section to be distinguished by specific standardized headings on the basis of seriousness or other criteria. However, certain adverse reactions (including those that result in contraindications) may be serious enough to warrant being placed inside a box under proposed § 201.57(c)(1). FDA requests comment about whether the lack of standardized headings in the ''Warnings/Precautions'' section is appropriate. If it is believed that specific standardized headings are appropriate, FDA requests comment about what they should be.

Proposed § 201.57(c)(6)(iv) would require, where applicable, a brief notation of the information that is currently required under § 201.57(f)(4)(ii) (i.e., information on known interference of a drug with laboratory tests) and a reference to the detailed labeling information. As discussed below, under the proposal the detailed labeling information would be moved from its present location under ''Precautions'' to a separate ''Drug Interactions'' section. The agency is proposing this requirement to alert practitioners to the existence of important laboratory test interference information without making the ''Warnings/Precautions'' section unnecessarily lengthy.

Proposed § 201.57(c)(6)(v) would require, for drug products other than vaccines, the inclusion of the statement ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA's MedWatch at (*insert the current FDA MedWatch number*).'' For vaccines, the following statement would be required: ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS number*).'' As discussed above, inclusion of these statements would also be required in the highlights section. The agency believes that inclusion of these statements in both places would contribute to the communication of this important information. FDA is requesting comments, however, concerning whether this additional requirement constitutes unnecessary repetition.

As discussed in further detail below, the remaining information currently required to appear under the ''Precautions'' section would be reorganized into new section headings. The agency believes that this is appropriate because some of the information currently included under ''Precautions'' is in fact not cautionary (e.g., a negative carcinogenicity study or lack of drug interactions). Other information currently included may be cautionary, but was deemed to be sufficiently important to be included under its own section heading to provide greater emphasis and ease of access. The proposal would move the information required by current § 201.57(f)(2) (''Information for patients'') to proposed § 201.57(c)(17); move the information required by current § 201.57(f)(4) (''Drug interactions'') to proposed § 201.57(c)(7); move the information required by current § 201.57(f)(5) (''Carcinogenesis, mutagenesis, impairment of fertility'') to proposed § 201.57(c)(14); and move the information required by current § 201.57(f)(6) through (f)(10) (''Pregnancy,'' ''Labor and delivery,'' ''Nursing mothers,'' ''Pediatric use,'' and ''Geriatric use'') to proposed § 201.57(c)(8).

f. *Proposed § 201.57(c)(7)—drug interactions.* Under current § 201.57(f)(4), ''Drug interactions'' is a subsection under ''Precautions.'' The subsection requires the inclusion of practical guidance for the practitioner on preventing clinically significant drug/drug and drug/food interactions that may occur in patients taking the drug. Specific drugs with which the labeled drug interacts in vivo must be identified, and the mechanisms of action briefly noted.

Proposed § 201.57(c)(7) would move ''Drug interactions'' from current § 201.57(f)(4) to create a separate section with the same heading. The agency believes that placing this information in a separate section under its own heading would draw attention to this area of increasingly recognized importance. This change was supported both by focus group participants and by comments received on the prototype.

g. *Proposed § 201.57(c)(8)—use in specific populations.* Under current § 201.57(f)(6) through (f)(10), information on specific populations (i.e., ''Pregnancy,'' ''Labor and Delivery,'' ''Nursing mothers,'' ''Pediatric use,'' and ''Geriatric use'') is placed under ''Precautions.'' The agency is proposing to move this information to its own section entitled ''Use in Specific Populations.'' FDA believes that by establishing a more descriptive heading for this information, and separating the information from other types of information currently required to appear under the precautions section, the information would be easier to find and use.

Current § 201.57(f)(6)(i)(*d*) and (f)(6)(i)(*e*) require the labeling of drug products in Pregnancy Categories D and X to contain the statement ''* * * If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.'' Proposed § 201.57(c)(8)(i)(A)(*4*) and (c)(8)(i)(A)(*5*) would modify this statement to read: ''If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.'' The agency is proposing this revision to alert practitioners to the risk of prescribing the drug to any woman of child bearing age, since such a woman can be in the first trimester of pregnancy and be unaware that she is pregnant. This caution would highlight to prescribers the importance of considering the pregnancy-related effects of drugs, especially those used on a chronic basis, for women who may become pregnant as well as those who are already pregnant. The agency is also currently considering other initiatives to revise pregnancy labeling that may be proposed in the future. However, because of the importance of the current revision, the agency believes that it is appropriate to propose it immediately.

Proposed § 201.57(c)(8)(iii) would change the subheading ''Nursing mothers'' to ''Lactating Women'' to recognize the role of women who may nurse an infant but are not the mother, as well as women who produce breast milk for others' use. Proposed § 201.57(c)(8)(iii)(B) and (c)(8)(iii)(C) would substitute the terminology ''clinically significant adverse reactions'' for the ''serious adverse reaction'' terminology in current § 201.57(f)(8)(i) and (f)(8)(ii) to clarify that all clinically significant adverse reactions, not just those that are classified as serious, must be taken into consideration when placing the required precautionary statements in labeling. Minor conforming changes would also be made to the section.

Under proposed § 201.57(c)(8)(vi), the agency would permit additional subsections representing other types of patient subpopulations to be included under the ''Use in Specific Populations'' section if sufficient data are available concerning the use of the drug in the subpopulations (e.g., hepatically or renally impaired or immunocompromised populations).

h. *Proposed § 201.57(c)(9)—adverse reactions.* Current § 201.57(g) defines adverse reaction as an ''undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.'' Proposed § 201.57(c)(9) would revise the definition of adverse drug reaction to read: ''An adverse reaction is a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response.''

The revised definition of ''adverse reaction'' in proposed § 201.57(c)(9) is consistent with the definition of ''adverse drug reaction'' developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in a final ICH guideline entitled ''Clinical Safety Data Management: Definitions and Standards for Expedited Reporting'' (60 FR 11284, March 1, 1995) (the ICH E2A guideline). The ICH E2A guideline defines an adverse drug reaction as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase 'response to medicinal products' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

ICH was formed to facilitate international consideration of issues, particularly safety issues, concerning the use of global data in the

development and use of drugs and biological products. ICH has worked to promote the harmonization of technical requirements for products among three regions: The European Union (EU), Japan, and the United States. As discussed in further detail below, FDA believes that adoption of the proposed definition of ''adverse reaction'' will result in a more focused ''Adverse Reactions'' section and will promote consistency in labeling worldwide. Moreover, the agency is currently in the process of developing a proposed rule revising its adverse event reporting regulations for drugs and biological products, and the revised definition of ''adverse reaction'' in proposed § 201.57(c)(9) is consistent with definitions being considered by the agency for inclusion in that rulemaking. FDA will ensure that the term is consistently defined in both regulations.

The definition of ''adverse reaction'' in proposed § 201.57 would change the current definition in two respects. It would substitute the terminology ''a noxious and unintended response to any dose of a drug product'' for ''an undesirable effect.'' This change in terminology would clarify that only those responses that are noxious (i.e., injurious to health) and unintended, rather than all effects that are undesirable (which does not necessarily imply either that the effect is injurious or unintended) may be included in the ''Adverse Reaction'' section of labeling. In addition, the proposed definition would substitute the terminology ''for which there is a reasonable possibility that the product caused the response'' for ''reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.'' The agency is proposing this change in terminology because the ''reasonably associated'' language in the current definition can be and in many cases has been interpreted as meaning that a reaction should be included merely if there is a temporal association, rather than a reasonable causal association, between a response and a drug. This has resulted in the inclusion of information in the ''Adverse Reactions'' section of labeling that is not meaningful to prescribers and which dilutes the usefulness of the clinically meaningful information. 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 of labeling.

i. *Proposed § 201.57(c)(10)—drug abuse and dependence; proposed § 201.57(c)(11)—overdosage.* Labeling sections ''Drug Abuse and Dependence'' and ''Overdosage'' are currently required to appear in labeling under § 201.57(h) and (i), respectively. Proposed § 201.57(c)(10) and (c)(11) would incorporate the current sections without change.

j. *Proposed § 201.57(c)(12)—description.* Under current § 201.57(a), the ''Description'' section appears at the beginning of prescription drug labeling and requires certain basic information about the drug such as the proprietary and established name of the drug and its dosage form and route of administration.

Under proposed § 201.57(c)(12), the information would be moved toward the end of product labeling, but retain its current placement in relation to the ''Clinical Pharmacology'' section. Movement of the description section reflects the findings of the focus group studies and physician surveys that the information in the section is less important than other labeling information that would be required under proposed § 201.57(c)(1) through (c)(11). In addition, the most important information prescribers need from the description section, the proprietary or established name of the drug (or, for biologics, the proper name), is required to appear at the beginning of the highlights section under proposed § 201.57(a)(1).

k. *Proposed § 201.57(c)(13)—clinical pharmacology.* Under current § 201.57(b), the ''Clinical Pharmacology'' section appears near the beginning of prescription drug labeling, immediately following the ''Description'' section. The section requires a concise factual summary of the product's clinical pharmacology and actions. The section includes absorption, distribution, metabolism, excretion, elimination, pharmacokinetic, and pharmacodynamic (i.e., concentration in body fluids associated with therapeutic and/or toxic effects) information important for safe and effective use of the drug, if known. The section may include information based on in vitro or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Under current § 201.57(b)(2), in vitro or animal data related to the activity or efficacy of a drug that have not been shown to be pertinent to clinical use by adequate and well-controlled clinical studies are generally prohibited except in two specific circumstances: (1) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement: ''The following in vitro data are available but their clinical significance is unknown''; and (2) in vitro and animal data for classes of drugs other than anti-infectives may be included if a waiver is granted under § 201.58 or § 314.126(c).

Under proposed § 201.57(c)(13), the section would be moved toward the end of product labeling. Movement of the section reflects prescribing physicians' reports, as demonstrated in the physician surveys, that the clinical pharmacology information appearing in this section is used less often than other labeling information. In addition, the current positioning of this sometimes lengthy section, just before the ''Indications and Usage'' section, may make it more difficult and time consuming to find the latter section, which is more commonly referred to by practitioners. This revised placement of the clinical pharmacology section would also be consistent with the practice of the EU, which requires this information be placed toward the end of its Summary of Product Characteristics (the EU's equivalent of approved product labeling). Clinical pharmacology information that is relevant to other labeling sections and affects practitioners' prescribing concerns may be placed in other sections of the comprehensive prescribing information and/or highlights. For example, clinically important information related to special populations or drug interactions may appear under ''Special Populations'' or ''Drug Interactions.'' Similarly, clinically important information related to efficacious and/or toxic drug concentration ranges may appear under ''Dosage and Administration.'' Therefore, the agency does not believe that the placement toward the end of product labeling of clinical pharmacology information that is less likely to be used is objectionable to the majority of prescribers.

The proposal would revise current § 201.57(b)(1) to require that the information currently required under that section be presented under three separate subsections entitled ''Mechanism of action,'' ''Pharmacodynamics,'' and ''Pharmacokinetics.'' Where a category of information is not available for a specific drug, the labeling would be required to contain a statement about the lack of information. The information required under these subsections is substantially similar to currently required information. The changes are

intended primarily to enhance the clinical pharmacology section's organization and clarity. In addition, an optional subsection entitled ''Other clinical pharmacology information'' has been added to permit the presentation of information that is not covered by the three required subsections but is helpful to optimal use and understanding of the clinical pharmacology of the drug or biological product. Information within this section could include information related to the clinical pharmacology of drug/drug interactions or use in specific populations. The agency also is proposing that, if specific data on alternative dosing regimens (e.g., for hepatically or renally impaired patients) appears in the ''Clinical Pharmacology'' section, it must also appear in the ''Dosage and Administration'' section.

The proposal also would revise current § 201.57(b)(2) such that in vitro data related to the activity or efficacy for all drugs, including anti-infective drugs, could be included only if a waiver is granted under § 201.58 or 314.126(c). Since issuing the current regulations, extensive in vitro data has been included for nearly all anti-infective drugs. The agency believes that, despite the disclaimer concerning their lack of clinical relevance, inclusion of these data in approved product labeling creates the misleading impression that a product's in vitro action represents sufficient information to treat infections with the listed pathogens in humans. In vitro data alone do not provide information about factors critical to effective therapy, including tissue levels of the product necessary to cure the treated infection, and appropriate length of treatment. Such information is often essential to help ensure safe and effective use and avoid the development of antimicrobial resistance. More specifically, using anti-infectives at subtherapeutic levels for the wrong time period facilitates the development of antimicrobial resistance. Consequently, FDA believes that ''in vitro only'' labeling information, in contributing to the inappropriate prescribing of anti-infectives, may also be contributing to the further development of antimicrobial resistance for many drugs. Therefore, the proposal would treat the inclusion of in vitro data for anti-infective drugs in labeling the same as other data that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use (i.e., such data may be included only if a waiver is granted under § 201.58 or § 314.126(c)).

l. *Proposed § 201.57(c)(14)—nonclinical toxicology.* Current § 201.57(f)(5) requires a subsection entitled ''Carcinogenesis, mutagenesis, impairment of fertility'' to appear in the labeling under ''Precautions.'' The subsection must state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results of the studies. The section also requires a description of reproduction studies or other animal data, if any, revealing a problem or potential problem concerning mutagenesis or impairment of fertility. Under current § 201.57(l), a section entitled ''Animal Pharmacology and/or Animal Toxicology'' may be placed near the end of labeling to include animal data related to the safety or efficacy of a drug, if the data cannot be appropriately incorporated into other labeling sections.

Proposed § 201.57(c)(14) would move current § 201.57(f)(5) and (l) under a new section heading entitled ''Nonclinical Toxicology.'' The agency believes that the proposed title for the section accurately describes the nature and purpose of the animal data commonly included under both of these sections. Movement of the information under current § 201.57(f)(5) toward the end of the comprehensive labeling section reflects the agency's findings that this section is less important than other labeling information that would be required before it.

m. *Proposed § 201.57(c)(15)—clinical studies.* Current § 201.57(m) permits, but does not require, that a ''Clinical Studies'' section appear near the end of prescription labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. The section also permits a reference to be made to a clinical study in any labeling section if the study is essential to understanding the available information.

Proposed § 201.57(c)(15) would revise current § 201.57(m) to require a separate heading entitled ''Clinical Studies.'' The section would be required to contain a discussion of clinical study results that are important to a prescriber's understanding of the basis for approval of the drug product, including the extent of the product's benefits, how the drug was used in clinical trials, who was studied, and critical parameters that were monitored. The agency is proposing to require inclusion of this information to provide practitioners with more accurate and specific information about a drug's efficacy that could help them to make informed prescribing decisions. The proposed section would revise current § 201.57(m) to specify that a *brief* reference to a specific important clinical study or studies may be placed in any labeling section, but any detailed discussion of the study's methodology and results must be included in the ''Clinical Studies'' section, to which the reader would be directed. This change is being proposed to make it easier for practitioners to find clinical studies information, which has typically (although not invariably) been included in either the ''Indications and Usage'' or ''Clinical Pharmacology'' sections. Language has also been added to this section to reinforce the prohibition in proposed § 201.57(c)(2) against implying or suggesting uses or dosing regimens for a product that are not included in its ''Indications and Usage'' or ''Dosing and Administration'' sections.

n. *Proposed § 201.57(c)(16)—references.* Proposed § 201.57(c)(16)(i) would state that if the reference is cited in labeling in the place of a detailed discussion of data and information concerning an indication for or use of a drug or biological product, the reference must be based upon an adequate and well-controlled clinical investigation under § 314.126(b) or, for a biological product, upon substantial evidence of effectiveness. This section incorporates current § 201.57(m), as it relates to the use of references, without substantive change except for the addition of the language for biologics. The section would be assigned the letter ''R'' as an identifier for indexing purposes instead of the index number ''15.'' This would permit, where appropriate, the insertion of nonstandardized headings between the ''Nonclinical Toxicology'' and ''References'' sections without affecting the standard index numbering system (i.e., additional nonstandardized headings would be assigned the index number ''15,'' ''16,'' and so on).

o. *Proposed § 201.57(c)(17)—patient counseling information.* Current § 201.57(f)(2) requires a subsection entitled ''Information for Patients'' to appear in labeling under ''Precautions.'' The subsection requires labeling to include information to be given to patients for the safe and effective use of a drug. In addition, the subsection requires that any printed patient information required to be distributed to a patient be referenced under the ''Precautions'' section and its full text printed at the end of labeling.

Based on the results of the physician survey and the comments received on Prototype 3, proposed § 201.57(c)(17) would retitle the heading of the information required under current § 201.57(f)(2) from ''Information for Patients'' to ''Patient Counseling Information.'' The proposed change would clarify that the information under this section is not intended to be

distributed to patients, but is intended to facilitate practitioner counseling of patients. To further clarify this, the phrase ''to be given to patients'' in current § 201.57(f)(2) would be changed to ''useful for patients to know.'' The agency is proposing to use the letter ''P'' to identify the section for indexing purposes, rather than an index number, for the same reasons that the letter ''R'' has been used as an identifier for the references section (see the previous discussion of the ''References'' section). Finally, the agency is proposing that the section be moved from its current location under ''Precautions'' to a separate section at the end of the comprehensive prescribing information. This would ensure that patient counseling information would immediately precede any approved patient labeling or Medication Guide, which would be required to be reprinted immediately following it. Under the proposal, all approved printed patient information or Medication Guides would be required to be referenced in this section and reprinted following the ''Patient Counseling Information'' section, regardless of whether the information is required by regulation to be distributed to the patient.

4. Format Requirements

Although current §§ 201.56 and 201.57 set forth required headings and a required order for prescription drug labeling information, they do not contain requirements for a minimum type size or other graphical elements.

FDA has determined, based on the focus group and survey results described in section II of this document, that the typically lengthy and undifferentiated format of prescription drug labeling makes it difficult to locate and read specific information. Proposed § 201.57(d) would set forth new minimum standards and requirements for the format of prescription drug labeling to improve its legibility, readability, and usability.

The agency believes that optimum labeling formats can be created only by permitting the flexible application of graphical techniques. However, the agency has also determined that it is necessary to establish minimum standards and requirements for certain key graphic elements to ensure an acceptable base level of readability for prescription drug labeling. Type size, letter and line spacing, contrast, print and background color, and type style are all factors that may affect the readability of labeling information (Ref. 5). Accordingly, the proposal would establish minimum standards and requirements for many of these key graphic elements while leaving manufacturers extensive flexibility to implement their own ideas in labeling design.

Proposed § 201.57(d)(1) would require that all headings and subheadings be highlighted by bold type that prominently distinguishes the headings and subheadings from other information.

Proposed § 201.57(d)(2) would require that a horizontal line separate the three major sections of information proposed in § 201.57(a), (b), and (c). The agency believes that horizontal lines will distinctively separate each section of important information to make it more conspicuous and easier to read.

The agency is proposing to require in § 201.57(d)(3) that the headings specified in paragraphs (a)(4) through (a)(10), (a)(12), (a)(13), and (a)(14) of § 201.57 be highlighted in two ways. First, these headings must be presented in bold type. Second, these headings must be presented in the center of a horizontal line that provides a visual demarcation from the preceding section. For example, the heading ''Recent Labeling Changes'' could be presented as follows:

''———Recent Labeling Changes———''

To maintain flexibility in the application of graphical techniques, the agency would permit the horizontal line to consist of a series of horizontal icons (see, e.g., Prototype 4). The agency believes that a visual separation of each section of important information would facilitate search and readability.

Proposed § 201.57(d)(4) would require the use of bullet points to distinguish multiple subheadings listed under proposed § 201.56(d)(5) in paragraphs (a)(4) through (a)(10), (a)(12), and (a)(13) of § 201.57. For example, if there is more than one subheading listed under the ''Indications and Usage'' heading, these subheadings would be preceded by a bullet point. The agency is not proposing to specify a graphical icon for bulleted points.

Proposed § 201.57(d)(5) would require that the labeling information required by paragraphs (a)(1) through (a)(4), (a)(11), and (a)(15) of § 201.57 be highlighted by bold print. The agency requests comment on whether the proposed use of bolding in all of these sections will serve its intended purpose of ensuring visual prominence, or if different highlighting methods, such as the use of different colors, may be equally or more effective.

Proposed § 201.57(d)(6) would require that the letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section be a minimum of 8 points. FDA believes that this minimum type size would make it easier for practitioners to read labeling information and thus help to ensure the safe and effective use of prescription drug products. The rationale for the use of 8-point type size is discussed below.

There are no clear recommendations in the literature with regard to minimum type size for medical practitioners or other ''experts'' in a field. Type size can affect visibility and reading speed (Ref. 6). Early studies of how type size affects the speed of reading suggest that 8-point type is read significantly more slowly than 10-point type (Ref. 7). Newspapers, which are targeted to the general public, are usually printed in 8-point type (Ref. 8). However, the smallest recommended font size for the general public typically is 10-point, while larger font sizes are recommended for populations where low-literacy, age, or impaired vision are significant factors (Refs. 9, 10, and 11). A recent guidance document issued by a national collaborative group recommending format parameters for written patient prescription medicine materials recommended that 10- or 12-point type be used for this information, also noting that 12-point type is generally recommended for older persons. Because many prescribers are older and subject to the same limitations as others in reading print materials, this would suggest the use of a minimum of 10- or perhaps even 12-point type for prescription drug labeling. FDA performed a cost analysis, discussed in section X of this document, comparing the cost of requiring 10- versus 8-point type in prescription drug labeling. The analysis shows that there would be significant additional costs associated with producing and packaging 10-point type size labeling versus 8-point. Thus, although 10-point type size would clearly be better than 8-point with regard to its legibility, FDA is proposing to require the use of 8-point type to minimize the economic impacts on industry. However, the agency solicits

comments on minimum type size requirements, and in particular on whether the benefits of 10-point type justify its additional costs and should therefore be required.

Proposed § 201.57(d)(7) would require that the index numbers required by paragraphs (c)(1) through (c)(17) of § 201.57 be presented in bold print and precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter ''m'' in 8-point type).

Proposed § 201.57(d)(8) would limit the length of the highlights section by requiring that the information under proposed § 201.57(a), except for any boxed warning information required under § 201.57(a)(4), be limited in length to an amount that, if printed in 2 columns on one side of a standard size piece of typing paper (8½ by 11 inches), single spaced, in 8-point type with ½-inch margins on all sides and between columns, would fit on one-half of the page. The length restriction is being proposed in response to certain comments and the agency's concerns that, without setting a definitive limit on the amount of information that may be included in the highlights section, there will not be sufficient incentive to make the difficult, but necessary decisions about inclusion of specific information. As discussed above, the purpose of the highlights section is to provide a concise extract of the most important information from the comprehensive prescribing information. If too much information is included, the section would no longer serve its intended purpose. However, the agency recognizes that there may be circumstances under which this limited amount of information may be inadequate to communicate appropriately even the highlights of a product's labeling. Therefore, the agency requests comments on whether the proposed space limitation is adequate or whether there are alternatives that would be more appropriate and under what circumstances such alternatives should be considered.

Proposed § 201.57(d)(9) would require that labeling sections in the comprehensive prescribing information containing recent changes identified in § 201.57(a)(5) be highlighted by a vertical line on the left edge of the new or modified text. Given the extensive amount of information in the comprehensive prescribing information section, this additional graphic emphasis should make it easier for practitioners to identify modified labeling information. In addition, this graphic device will allow those practitioners who are reading the comprehensive information thoroughly to identify new labeling information without referring back to the highlights section. Nonetheless, FDA invites comments on other means that could be used to facilitate access to, and identification of, new labeling information for both casual and indepth readings.

C. Revisions to Labeling for Older Drugs

As discussed in sections II and IV of this document, older drugs not subject to the revised labeling content and format requirements would remain subject to the requirements in current § 201.57. Under the proposed rule, current § 201.57 would be redesignated as § 201.80 to permit the revised content and format requirements for new drugs to be designated as § 201.57. In addition to the redesignation of the current section, the proposed rule would make certain revisions to the content of current § 201.57. The content revisions being proposed in redesignated § 201.80 are consistent with certain revisions in proposed § 201.57 for newer drugs and would help to ensure that statements currently appearing in the labeling of older drugs relating to effectiveness or dosage and administration are sufficiently supported. As discussed in section IV of this document, these content changes would be required to be made within 1 year of the effective date of the final rule.

Proposed § 201.80(b)(2) would replace current § 201.57(b)(2). Under the proposed section, in vitro or animal data related to the activity or efficacy for all drugs, including anti-infective drugs, that have not been shown by adequate and well-controlled studies to be pertinent to clinical use, could be included in the labeling only if a waiver is granted under § 201.58 or § 314.126(c). The agency is proposing this limitation because the inclusion of data showing that a drug product is effective against certain pathogens in vitro may lead practitioners to believe that the drug product is effective for treatment of infections or other illnesses in humans involving those pathogens. However, in vitro action alone is generally not sufficient to demonstrate effectiveness in humans. Therefore, under the proposal, in vitro data that does not meet the revised requirements would be required to be removed from the ''Clinical Pharmacology'' labeling section of older approved drug products.

Proposed § 201.80(c)(2)(i) and (c)(2)(ii) would replace current § 201.57(c)(2). Proposed § 201.80(c)(2)(i) would incorporate current § 201.57(c)(2) and modify it to include the requirement that indications or uses must not be implied or suggested in sections of labeling other than ''Indications and Usage'' if not included in that section. This change is consistent with the change in proposed § 201.57(c)(2)(ii). Proposed § 201.80(c)(2)(ii) is the same as proposed § 201.57(c)(2)(iii), and would be added to address biological drug products subject to licensing under section 351 of the PHS Act. As discussed in section III of this document, the proposed section would make clear that substantial evidence of effectiveness must support indications for biological drug products.

Proposed § 201.80(f)(2) would replace the current ''Information for Patients'' section. The proposed section would modify the current section to require that any approved patient information or Medication Guide, not just those that are required by regulation to be distributed to patients, be referenced in the ''Precautions'' section and reprinted immediately following the last section of labeling. The agency believes that including this information in professional labeling will facilitate practitioner access to the information and improve their ability to communicate to patients information that the agency and sponsor believe is important.

Proposed § 201.80(j) would modify current § 201.57(j) (''Dosage and Administration'') to clarify that dosing regimens must not be implied or suggested in other sections of labeling if not included in this section.

Proposed § 201.80(m)(1) would modify current § 201.57(m)(1) to state that, for biological products, references do not have to be based upon, and clinical studies do not have to constitute, adequate and well-controlled studies. This change is being made to address biological products subject to licensing under section 351 of the PHS Act. In addition, the section would be modified to clarify that clinical studies and references must not imply or suggest indications, uses, or dosing regimens not stated in the ''Indications and Usage'' or ''Dosage and Administration'' sections.

IV. Proposed Implementation Plan

A. General Implementation Scheme for the Revised Format and Content Requirements

The proposed implementation plan for the revised labeling format and content requirements in proposed §§ 201.56(d) and 201.57 is summarized in table 1.

TABLE 1.—IMPLEMENTATION PLAN

Applications (NDA's, BLA's, and Efficacy Supplements) Required to Conform to New Labeling Requirements	Time by Which Conforming Labeling Must Be Submitted to the Agency for Approval
Applications submitted on or after the effective date of the final rule	Time of submission
Applications pending at the time of the effective date of the final rule and applications approved 0 to 1 year before the effective date of the final rule.	3 years after the effective date of the final rule.
Applications approved 1 to 2 years before the effective date of the final rule	4 years after the effective date of the final rule.
Applications approved 2 to 3 years before the effective date of the final rule	5 years after the effective date of the final rule.
Applications approved 3 to 4 years before the effective date of the final rule	6 years after the effective date of the final rule.
Applications approved 4 to 5 years before the effective date of the final rule	7 years after the effective date of the final rule.

As discussed in section III of this document, the agency is proposing that, with the exception of the requirements discussed in section IV.C and IV.D of this document, the content and format revisions apply only to products with applications (i.e., NDA's, BLA's, and efficacy supplements) pending at the time of the effective date of the final rule, products for which such applications are submitted on or after the effective date of the final rule, and products with such applications that were approved up to and including 5 years before the effective date of the final rule. Thus, the proposed content and format requirements would not apply to products with applications that were approved more than 5 years before the effective date of the final rule, unless an efficacy supplement was approved for such products in the 5 years before the effective date of the final rule or is submitted after the effective date of the final rule. As discussed in section III of this document, these older products would remain subject to the labeling requirements in current § 201.57, which under the proposal would be redesignated as § 201.80.

The agency believes that applying the requirements only to more recently approved products is appropriate because, as discussed previously in section II of this document, physicians are more likely to refer to the labeling of recently approved products than the labeling of older products. Additionally, the labeling of recently approved products is likely to be longer and more complex than that of older products and thus more in need of the proposed format revisions. Finally, even though certain older products will remain subject to the current format and content requirements (as revised by the proposal), many products not initially covered by the revised format and content requirements will at some point submit efficacy supplements, and thus will be required to revise their labeling to conform to the revised format and content requirements.

The agency intends to make the final rule based on this proposal effective 120 days after the date of its publication in the **Federal Register**. As indicated in table 1, the time by which revised labeling for products with applications would be required to be submitted would depend on when the application was approved. Applications (NDA's, BLA's, and efficacy supplements) submitted for review on or after the effective date of the final rule would be required to include labeling in the new format as part of the application. Sponsors of products with applications pending at the time the final rule becomes effective and applications approved before the effective date of the final rule would be required to submit labeling supplements for approval on a staggered basis beginning 3 years after the effective date of the final rule. The proposed implementation scheme would require revised labeling to be submitted for newer products first, followed by older products. This plan is intended to minimize the rule's economic impact by providing manufacturers with sufficient time to design and print new labeling and deplete existing stocks of products with old labeling. At the same time, newer products for which revised labeling is most essential will either have revised labeling or will revise labeling at the earliest possible date.

B. Implementation of Proposed Content and Format Revisions to Products Approved or Submitted for Approval Under an ANDA

Under section 505(j)(2) of the act (21 U.S.C. 355(j)(2)) and §§ 314.94(a)(8) and 314.127(a)(7) (21 CFR 314.94(a)(8) and 314.127(a)(7)) of the agency's regulations, the labeling of a drug product submitted for approval under an ANDA must be the same as the labeling of the listed drug referenced in the ANDA, except for changes required because of differences approved under a suitability petition (see 21 CFR 314.93) or because the generic and innovator products are manufactured by different manufacturers. Thus, whether a prescription drug product that was approved under an ANDA before the effective date of the final rule, or that is submitted for approval under an ANDA after the effective date of the final rule, will be required to have labeling that complies with the final rule will depend on the status of the labeling of the listed drug referenced in the ANDA. Where a reference listed product's labeling conforms to the requirements of the final rule (i.e., where the NDA for the product was submitted after the effective date of the final rule, the NDA for the product was pending on or submitted within 5 years before the effective date of the final rule and the labeling has been required to be revised under the implementation scheme, or the labeling for the product was revised by the sponsor to comply with the final rule voluntarily), the generic product that references the listed drug in its ANDA would be required to have labeling that is the same as the listed product and would therefore be required to comply with the final rule. On the other hand, where a reference listed product's labeling does not conform to the requirements of the final rule (i.e., the product was approved more than 5 years before the effective date of the final rule, or the final rule applies to the product but the product's labeling is not yet required to be revised under the implementation scheme), a generic product that references the product in its ANDA would not be required to have labeling that complies with the final rule.

C. Implementation of Proposed Content Requirements Applicable to Newer and Older Drugs

The agency is proposing that the revised content requirements for newer drugs in proposed § 201.57(c)(2)(ii), (c)(2)(iii), (c)(3), (c)(13)(ii), and (c)(15)(i), and the revised content requirements for older drugs at proposed § 201.80(b)(2), (c)(2)(i) and (c)(2)(ii), (j), and (m)(1), be implemented no later than 1 year after the effective date of the final rule. The agency believes that the changes necessary for existing product labeling

to comply with these sections could be made without prior FDA approval, that is, with a supplement explaining the changes at the time the applicant makes them under § 314.70(c) (21 CFR 314.70(c)) or § 601.12(f) (21 CFR 601.12(f)) (i.e., a ''Changes Being Effected'' supplement). FDA is proposing a broad and prompt implementation of these sections because the agency believes that the requirements proposed in the sections are necessary to help ensure that the information in labeling regarding a drug product's indications or uses is not misleading, and to help ensure that the staggered implementation scheme does not give a marketing advantage to certain products.

In accordance with the discussion above, the proposed sections would be implemented as follows. Proposed § 201.57(c)(2)(ii) and (c)(2)(iii) and proposed § 201.80(c)(2)(i) and (c)(2)(ii) would require that indications or uses not included in the ''Indications and Usage'' section not be implied or suggested in other sections of labeling. Thus, any implied or suggested indication or use for a drug not included in the ''Indications and Usage'' section would have to be removed from the labeling by 1 year after the effective date of the final rule. Similarly, proposed § 201.57(c)(3) and proposed § 201.80(j) would require that dosing regimens not included in the ''Dosage and Administration'' section be removed from other sections of labeling. Proposed § 201.57(c)(15)(i) and proposed § 201.80(m)(1) would require that any clinical study that is discussed that relates to an indication for or use of a drug be adequate and well-controlled as described in § 314.126(b), except for biological products, and relate only to indications, uses, or dosing regimens stated in the ''Indications and Usage'' or ''Dosage and Administration'' sections. Thus, any discussion of a clinical study or studies related to indications, uses, or dosing regimens not included in the ''Indications and Usage'' or ''Dosage and Administration'' sections would have to be removed. Finally, under proposed § 201.57(c)(13)(ii) and proposed § 201.80(b)(2), in vitro or animal data related to the activity or efficacy of a drug that have not been shown by adequate and well controlled studies to be pertinent to clinical use would be required to be removed by 1 year after the effective date of the final rule unless a waiver is granted to permit inclusion of the data.

D. Implementation of Proposed § 201.57(c)(17) and Proposed § 201.80(f)(2)

Proposed § 201.57(c)(17) would require that any approved printed patient information or Medication Guide be reprinted immediately following ''Patient Counseling Information.'' Proposed § 201.80(f)(2) would require that any approved printed patient information or Medication Guide be reprinted immediately following the last section of labeling. The agency is proposing that these requirements be implemented by 1 year after the effective date of the final rule. Sponsors of newer products subject to the revised format and content requirements in proposed § 201.57 would have to comply with the requirement in proposed § 201.57(c)(17) before revising other sections of labeling. These sponsors would be required to reprint the approved patient labeling or Medication Guide following the last section of labeling (e.g., generally after ''How Supplied'' or ''References''). The agency is proposing this broad and prompt implementation to help ensure that practitioners have access to printed patient information or Medication Guides.

E. Voluntary Submission of Labeling Conforming to Proposed Content and Format Requirements

Sponsors of drug products that are not required under the proposed rule to comply with the revised format and content requirements may voluntarily submit revised labeling for approval by the agency.

F. Relationship of Proposed Requirements to Other Prescription Drug Labeling Initiatives

The format and content revisions discussed in this proposal are the most extensive of many prescription drug labeling revision initiatives that are being considered by the agency. The agency will provide information on additional labeling initiatives, and how the agency intends to coordinate their implementation, at a later date.

V. Revisions to Prescription Drug Labels [7]

In addition to revising its regulations governing the format and content of labeling for prescription drugs, the agency is proposing minor revisions to the information required to appear on prescription drug product labels.[8] The proposed changes are intended to lessen overcrowding of prescription drug product labels by eliminating unnecessary statements and moving to the package insert less critical information that is currently required to appear on the product label. The agency believes that overcrowding of drug product labels makes reading critical information on these labels more difficult and may be one possible cause of medication errors by health care practitioners.[9] Thus, the agency hopes that by reducing the amount of required information on product labels and simplifying them, the number of medication errors will be reduced. It is estimated that at least one death every day is attributable to a medication error (Ref. 12). From January 1992 to May 1997, FDA's Center for Drug Evaluation and Research (CDER) has received approximately 6,000 reports of errors (actual or potential). Approximately 50 percent or 3,000 of these reports were attributable to the labeling, packaging, and/or design of the drug product.

The proposed changes are consistent with the recommendations of the joint United States Pharmacopeia (USP)–FDA Advisory Panel on Simplification and Improvement of Injection Labeling, which was formed to explore ways to avoid medication errors associated with overcrowded product labels.[10] The proposed changes are also consistent with the recommendations of an independent task force, the Committee to Reduce Medication Errors, which studied ways to reduce medication errors by improving label legibility.[11] Although the recommendations of the joint USP–FDA advisory panel and the committee were targeted primarily at labels for injection products, the agency believes that they will help to reduce medication errors for all dosage forms. Thus, the proposed changes would apply to all types of drug products. A

[7] The proposed changes would not affect the label requirements, set forth in parts 600 through 680 (21 CFR parts 600 through 680), for most biological products. As specified in § 601.2(c)(3), the label requirements described in § 610.62 do not apply to those biological products listed in § 601.2(c)(1). However, CBER is currently evaluating how it can best address the concerns regarding drug product labels discussed under section V of this document.

[8] Under section 201(k) of the act, the term label means a display of written, printed, or graphic matter upon the immediate container of an article.

[9] The term ''medication error'' is a general term used to refer to many types of errors associated with medication use including improper dosage, wrong strength or concentration, wrong drug or dosage form, use of the drug for an improper duration, or use on the wrong patient.

[10] The recommendations were published in the *Pharmacopeial Forum* (Ref. 13).

[11] The Committee to Reduce Medication Errors was assembled by the State of Washington and included individuals from pharmaceutical associations, industry, and health care practitioners.

detailed description of the proposed changes follows.

Current § 201.100(b)(2) requires that the label of a prescription drug bear a statement of the recommended or usual dosage. Current § 201.55 explains that, because the dosage may vary widely for treatment of different conditions, it may not be possible to present an informative or useful statement of the recommended or usual dosage in the space available on the label. Section 201.55 states that, in this case, the requirements of § 201.100(b)(2) may be met by including on the label a statement such as ''See package insert for dosage information,'' provided that detailed dosage information is contained in the package insert. The proposal would revise §§ 201.55 and 201.100(b)(2) such that, if it is not possible to place an informative and useful statement of the recommended or usual dosage on the label, the statement on the label would not be required. In these cases, the dosage information would appear in the comprehensive prescribing information section of the labeling without a statement on the label referencing the information.

Current § 201.100(b)(5) states that the label of a prescription drug for other than oral use must bear the names of all inactive ingredients, with some exceptions. Under current § 201.57(a)(iii), this information must also appear under the ''Description'' section in the package insert. The proposal would eliminate current § 201.100(b)(5) so that inactive ingredient information would not have to appear on the label. Instead, proposed § 201.57(c)(12)(i)(D) would require the information to appear in the package insert under the section entitled ''Description.''

Current § 201.100(b)(7) requires that the label of a prescription drug bear a statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity. The proposal would eliminate the requirement that this information appear on the label and instead under proposed § 201.57(c)(4)(v) require the information to appear in the package insert under the section entitled ''How Supplied/Storage and Handling.''

In addition to these changes to drug product labels, the agency recently proposed a change to § 201.100(b)(1) to require that the label of prescription drugs bear the ''R_x only'' symbol, rather than the statement: ''Caution, Federal law prohibits dispensing without prescription.'' (See 65 FR 18934, April 10, 2000.) This change was proposed in accordance with section 126 of the Modernization Act, which required that the ''R_x only'' symbol replace the longer statement. The change, when finalized in the other rulemaking, will eliminate unnecessary verbiage in the drug product label and thus should also contribute to the reduction of medication errors.

The proposed changes described in this section V, if finalized, would be implemented for all new NDA's as soon as the final rule takes effect. For products with approved or pending NDA's at the time the final rule takes effect, the changes would be implemented as follows. Changes affecting the labeling of a prescription drug product (i.e., changes made to the package insert in accordance with proposed § 201.57(c)(12)(i)(D) and (c)(4)(v)) would not be required to be made until the first time that labeling is revised for reasons other than to comply with the proposed requirements or 7 years after the final rule takes effect, whichever occurs first. The proposed changes to the container label (i.e., changes made to remove currently required statements from the container label) should not be made until the changes to the package insert are made. This would ensure that the information that currently is required to appear on the container label appears on the package insert before it is removed from the label. Once changes to the package insert are made, the changes to the container label would not be required until the first time the label is revised for reasons other than to comply with the proposed requirements. Thus, no additional printing costs would be associated with the proposed changes and, as discussed in section X of this document, economic impacts associated with the proposed changes would be minimal.

VI. Revisions to §§ 201.58 and 201.100(d)(3), Rescission of § 201.59 (21 CFR 201.59)

The agency is proposing to revise §§ 201.58 and 201.100(d)(3) to be consistent with revisions to proposed § 201.57 and the addition of proposed § 201.80 (proposed redesignated § 201.57).

The agency is also proposing to rescind § 201.59. Section 201.59(a) sets forth the effective date, December 26, 1979, for current §§ 201.56, 201.57, and 201.100(d)(3). Section 201.59(b) sets forth the effective date, April 10, 1981, for § 201.100(e). Section 201.59(a)(1), (a)(2), and (a)(3) set forth exceptions to the December 26, 1979, effective date for current §§ 201.56, 201.57, and 201.100(d)(3) for certain categories of drugs. Section 201.59(a)(1) sets forth an effective date of April 10, 1981, for prescription drugs that are not biologics and not subject to section 505 of the act and that were not subject to former section 507 of the act (21 U.S.C. 357, repealed 1997). Section 201.59(a)(2) sets forth different effective dates, and a schedule for submitting revised labeling, for certain classes of prescription drugs (e.g., anticonvulsants and progestins) that as of December 26, 1979, were: (1) A licensed biologic, (2) a new drug subject to an approved NDA or ANDA, or (3) an antibiotic drug subject to an approved antibiotic form. Section 201.59(a)(3) applies the same effective dates and schedule for submitting revised labeling in § 201.59(a)(2) to drugs that are approved after December 26, 1979, that are duplicates of drugs approved on or before December 26, 1979. Because all of the effective dates and dates for submission of revised labeling set forth in § 201.59 have passed and current §§ 201.56, 201.57, 201.100(d)(3), and 201.100(e) have been implemented for all categories of drugs and drug classes identified in § 201.59, § 201.59 is no longer necessary and the agency is proposing that it be removed from the regulations.

VII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of informaiton.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics;

Requirements for Prescription Drug Product Labels.

Description: FDA is proposing to amend its regulations governing the format and content of labeling for human prescription drug and biologic products. The proposal would revise current regulations to require that the labeling of new and recently approved products include a section containing highlights of prescribing information and a section containing an index to prescribing information, reorder currently required information and make minor changes to its content, and establish minimum graphical requirements. These revisions would make it easier for health care practitioners to access, read, and use information in prescription drug labeling and would enhance the safe and effective use of prescription drug products. The proposal would also amend prescription drug labeling requirements for older drugs to require that certain types of labeling statements currently appearing in labeling be removed if they are not sufficiently supported. Finally, the proposal would eliminate certain unnecessary statements that are currently required to appear on prescription drug product labels and move other, less important information to labeling. These changes would simplify drug product labels and reduce the possibility of medication errors.

FDA's legal authority to amend its regulations governing the content and format of labeling for human prescription drug and biologic products and to amend its regulations governing the requirements for prescription drug product labels derives from sections 201, 301, 501, 502, 503, 505, and 701 of the act (21 U.S.C. 321, 331, 351, 352, 353, 355, and 371) and section 351 of the PHS Act (42 U.S.C. 262).

A. Summary of Provisions in Proposed Rule That Contain Collections of Information

1. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics (Proposed § 201.56)

Current FDA regulations at § 201.56 require that prescription drug labeling contain certain information in the format specified in current § 201.57. Current § 201.56 also sets forth general requirements for prescription drug labeling, including the requirement that labeling contain a summary of the essential scientific information needed for the safe and effective use of the drug, that it be informative and accurate without being promotional in tone or false or misleading, and that labeling be based whenever possible on data derived from human experience. In addition, current § 201.56 sets forth required and optional section headings for prescription drug labeling and specifies the order in which those headings must appear.

The proposal would revise current § 201.56 to set forth: (1) General labeling requirements applicable to all prescription drugs; (2) the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in proposed §§ 201.56(d) and 201.57; (3) the schedule for implementing the revised content and format requirements in proposed §§ 201.56(d) and 201.57; (4) the required and optional sections and subsections associated with the revised format in proposed § 201.57; and (5) the required and optional sections and subsections for the labeling of older prescription drugs not subject to the revised format and content requirements.

2. Specific Requirements on Content and Format (Proposed § 201.57)

Current § 201.57 specifies the kind of information that is required to appear under each of the section headings set forth in § 201.56. This information is intended to help ensure that health care practitioners are provided with a complete and accurate explanation of prescription drugs to facilitate safe and effective prescribing. Thus, current FDA regulations already require prescription drug labeling to contain detailed information on various topics that may be important to practitioners.

The proposed regulations would require that prescription drug labeling for newer products include a new section entitled ''Highlights of Prescribing Information'' (proposed § 201.57(a)) and a new section containing an index to prescribing information (entitled ''Comprehensive Prescribing Information: Index''; proposed § 201.57(b)). The proposal would also reorder currently required information (current § 201.57, proposed as § 201.57(c) ''Comprehensive Prescribing Information''), make minor content changes, and establish minimum graphical requirements.

Proposed § 201.57(a) would require that the labeling of newer human prescription drugs contain a new section entitled ''Highlights of Prescribing Information.'' Information under this section would be a concise extract of the most important information already required under current § 201.57, as well as certain additional information that the agency believes is important to prescribers.

Proposed § 201.57(b) would require that the labeling of newer human prescription drugs contain a new section entitled ''Comprehensive Prescribing Information: Index'' and would consist of a list of all the sections of the labeling required in the Comprehensive Prescribing Information (proposed § 201.57(c); current § 201.57), preceded by a corresponding index number or identifier.

Proposed § 201.57(c) would require that the labeling of newer human prescription drugs contain a section entitled ''Comprehensive Prescribing Information'' and would revise the content and format of the labeling requirements contained in current § 201.57 to make it easier for health care practitioners to access, read, and use the labeling information. The proposal would reorder the information to place more prominently those sections found to be most important and most commonly referenced by practitioners. In most cases, this would require moving the information closer to the beginning of the comprehensive section. The proposal would also reorganize sections of the labeling, require standardized index numbers for each subheading, and make certain other format and content changes.

Although current §§ 201.56 and 201.57 set forth required headings and a required order for prescription drug labeling information, they do not contain requirements for a minimum type size or other graphical elements. Proposed § 201.57(d) would set forth new minimum requirements for the format of prescription drug labeling to improve its legibility, readability, and usability. The proposal would establish minimum requirements for key graphic elements such as bold type, bullet points, type size, spacing, and other highlighting techniques.

Older drugs not subject to the revised labeling content and format requirements in proposed § 201.57 would remain subject to the requirements in current § 201.57 which would be redesignated as § 201.80. In addition to the redesignation of current § 201.57, the proposed rule would make certain revisions to its content. The content revisions being proposed are consistent with certain revisions for newer drugs in proposed § 201.57. These revisions are designed to help ensure that labeling statements related to effectiveness or dosage and administration are sufficiently supported.

In addition to revising the regulations governing the format and content of labeling for prescription drugs, proposed § 201.100(b) would make

minor revisions to the information required to appear on prescription drug product labels. The proposed changes are intended to lessen overcrowding of drug product labels by eliminating unnecessary statements and moving to the package insert less critical information that currently must appear on the product label.

B. Estimates of Reporting Burden

1. Labeling Design, Testing, and Submission to FDA for New Applications (§§ 201.56 and 201.57)

Current § 201.56 requires that prescription drug labeling contain certain information in the format specified in current § 201.57, and also sets forth general requirements for prescription drug labeling. Current § 201.57 specifies the kind of information that is required to appear under each of the section headings set forth in § 201.56. As a result of these regulations, applicants must design drug product labeling, test the designed labeling, and prepare and submit the labeling to FDA for approval. Based on information received from the pharmaceutical industry, FDA estimates that it takes applicants approximately 3,200 hours to design, test (e.g., to ensure that the redesigned labeling will still fit into carton-enclosed products), and submit prescription drug product labeling to FDA as part of a new drug application. Annually, FDA receives (on average) 137 new applications containing such labeling from approximately 101 applicants.

2. The Reporting Burdens for the General Requirements (Proposed § 201.56)

The reporting burdens for the general requirements in proposed § 201.56(a) are the same as those for current § 201.56(a) through (c), and are estimated in table 2 under current §§ 201.56 and 201.57. Proposed § 201.56(b) and (c) set forth the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in proposed §§ 201.56(d) and 201.57 and the schedule for implementing the revised content and format requirements. No reporting burdens are directly associated with these requirements. Proposed § 201.56(d) sets forth the required and optional sections and subsections associated with the revised format in proposed § 201.57. The reporting burdens for this paragraph are estimated in table 2 under the requirements for proposed § 201.57.

Proposed §§ 201.56(e) and 201.80 set forth the labeling requirements for older prescription drugs. These are the same as the requirements in current §§ 201.56 and 201.57, with one exception. The exception is that provisions have been added in proposed § 201.80(b), (c), (f), (j), and (m) that would require certain statements to be removed from labeling or modified within 1 year of the effective date of the final rule. Therefore, the reporting burden associated with proposed §§ 201.56(e) and 201.80 will generally be the same as that for current §§ 201.56 and 201.57, which has been estimated in table 2. The reporting burden for proposed § 201.80(b), (c), (f), (j), and (m) is estimated in table 2 under proposed § 201.80, and has been combined with the reporting burden for the corresponding requirements for newer drugs in proposed § 201.57(c).

3. Labeling Redesign, Testing, and Submission to FDA for Approved Applications (Proposed § 201.57(a), (b), (c), and (d))

Proposed § 201.57(a) would require a new section in prescription drug product labeling entitled ''Highlights of Prescribing Information''; proposed § 201.57(b) would require a new section in the labeling entitled ''Comprehensive Prescribing Information: Index''; proposed § 201.57(c) would require a revision of the content and format requirements in current § 201.57 and a new title ''Comprehensive Prescribing Information''; and proposed § 201.57(d) would establish new requirements for type size and other graphical elements. For applications approved during the 5 years before the effective date of these new prescription drug labeling requirements, and for applications pending on the effective date, applicants must redesign drug product labeling, test the redesigned labeling (e.g., to ensure that the larger labeling will still fit in carton-enclosed products), and prepare and submit that labeling to FDA for approval. Based on the data and information provided in the ''Analysis of Economic Impacts'' (section X of this document), approximately 366 labeling supplements would be submitted to FDA during the period 3 to 7 years after the effective date. Approximately 145 applicants would submit these labeling supplements, and the time required for redesigning, testing, and submitting the labeling to FDA would be approximately 190 hours.

4. Labeling Revision and Submission to FDA Within 1 Year for Approved Applications (Proposed § 201.57(c) and Proposed § 201.80(b), (c), (f), (j), and (m))

Under the ''Proposed Implementation Plan'' (see section IV of this document), certain provisions under proposed § 201.57(c) and proposed § 201.80 would be implemented within 1 year after the effective date. Based on the data and information provided in the analysis of economic impacts, approximately 1,888 labeling supplements would be submitted to FDA during the first year after the effective date. Approximately 145 applicants would submit these labeling supplements, and the time required for revising and submitting the labeling for these supplements would be approximately 38 hours.

5. Labeling Design and Testing for New Applications (Proposed § 201.57(a), (b), (c), and (d))

Under the proposed implementation plan, prescription drug labeling in new applications submitted after the effective date must include new sections entitled ''Highlights of Prescribing Information'' and ''Comprehensive Prescribing Information: Index,'' as well as other new information and features not currently required in prescription drug labeling. Based on the data and information provided in the economic analysis, approximately 1,421 new applications would be submitted to FDA over a 10-year period after the effective date. Approximately 145 applicants would submit these applications, and the time required for the new labeling design and testing for each application would be approximately 149 hours.

6. Label Revisions (Proposed § 201.100(b))

In addition to revising the regulations governing the format and content of labeling for prescription drugs, the proposal, as explained above, would make minor revisions to the information required to appear on prescription drug product container labels. Neither the economic analysis nor this Paper Reduction Act analysis include burden estimates for these label revisions because, under the proposed rule, these changes do not have to be made until the next label revision. Thus, no new burdens would result from these proposed label revisions.

C. Capital Costs

A small number of carton-enclosed products may require new packaging to accommodate the longer insert. The economic analysis estimates that 1

percent of both the products with new efficacy supplement changes and the products approved in the 5 years before the effective date of the rule would incur costs of $200,000 each for needed packaging changes. Products approved after the effective date of the final rule would not incur added equipment costs because their labeling and packaging are not yet established. The estimated present costs for equipment changes over 10 years totals $1 million.

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

TABLE 2.—ESTIMATED REPORTING BURDEN [1]

21 CFR section	Number of respondents	Number of responses per respondent	Total responses	Hours per response	Total hours
Current 201.56 and 201.57: Labeling design, testing, and submission to FDA for new applications	101	1.36	137	3,200	438,400
Proposed 201.57(a),(b),(c), (d): Labeling redesign, testing, and submission to FDA for approved applications	145	2.52	366	190	69,540
Proposed 201.57(c) and 201.80: Labeling revision and submission to FDA within 1 year for approved applications	145	13.02	1,888	38	71,744
Proposed 201.57(a),(b),(c), (d): Labeling design and testing for new applications	145	9.80	1,421	149	211,729
Total					791,413

[1] There is no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507)(d), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding collection of information by January 22, 2001, to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Wendy Taylor.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Executive Order 13132: Federalism

FDA has analyzed this proposed rule in accordance with Executive Order 13132: Federalism. The Order requires Federal agencies to carefully examine actions to determine if they contain policies that have federalism implications or that preempt State law. As defined in the Order, ''policies that have federalism implications'' refers to regulations, legislative comments or proposed legislation, and other policy statements or actions that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government.

FDA is publishing this proposed rule to revise its regulations governing the format and content of labeling for human prescription drug products. The proposal would revise current regulations to require that labeling include a section containing highlights of prescribing information and a section containing an index to prescribing information. The proposal would also reorder currently required labeling information and make minor changes to its content. Finally, the proposal would establish minimum graphical requirements for labeling. This proposal would also eliminate certain unnecessary statements on prescription drug product labels and move other, less important information to labeling. Because enforcement of these labeling provisions is a Federal responsibility, there should be little, if any, impact from this rule, if finalized, on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of Government. In addition, this proposed rule does not preempt State law.

Accordingly, FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law.

X. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule may have a significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize the economic impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million in any one year (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. The proposed rule would amend current requirements for the format and content of labeling for human prescription drug and biologic products.

Based on the analysis following, as summarized in table 3, FDA projects that the present value of the quantifiable benefits of the proposed rule could exceed $296 million over 10 years. Direct costs resulting from the proposed changes are projected to range from approximately $8 million to $16.9 million in any one year, for a total present value of approximately $94.5 million over 10 years at 7 percent. The agency thus concludes that the benefits of this proposal substantially outweigh

the costs. Furthermore, the agency has determined that the proposed rule is not an economically significant rule as described in the Executive Order, because annual impacts on the economy are substantially below $100 million.

The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for the proposed rule because the proposed rule is not expected to result in any one-year expenditure that would exceed $100 million adjusted annually for inflation. The current inflation-adjusted statutory threshold is $110 million.

This rule may affect a substantial number of small entities, as defined by the Regulatory Flexibility Act. About half of the costs associated with relabeling are directly proportional to sales volume; thus, products with fewer sales would be associated with relatively lower relabeling costs. Nonetheless, it is possible that some small firms that produce small amounts of affected drugs, or small firms that might be required to undertake packaging modifications, may be significantly affected by this proposed rule. The following analysis constitutes the agency's initial regulatory flexibility analysis as required by the Regulatory Flexibility Act.

TABLE 3.—SUMMARY OF PROJECTED QUANTIFIABLE BENEFITS AND COSTS OVER 10 YEARS

Benefits and costs	Total ($ million)	Present value ($ million)
Benefits:		
Physician time saved	102.09	62.76
Adverse drug events avoided	345.58	233.80
Total benefits	447.67	296.56
Costs:		
Reformatting, revising, and FDA approval	14.68	11.62
Producing prescription drug labeling	81.43	54.37
PDR costs	43.96	28.54
Total costs	140.07	94.53

A. Purpose

The objective of the proposed rule is to make it easier for health care practitioners to find, read, and use information important to the safe and effective prescribing of prescription pharmaceuticals (drugs and biologics) for patient treatment. The agency has found that the current format, while effective, can be improved to more optimally communicate important drug information. The proposed rule is designed to achieve this objective by amending the current format for the labeling of human prescription drug and biological products to, among other things, highlight frequently accessed and new information, include an indexing system, and reorder certain information.

B. Benefits of Regulation

The expected economic benefits of this proposed rule are the sum of the present values of: (1) The reduced time needed by health professionals to read or review prescription drug labeling for desired information; (2) the increased effectiveness of treatment; and (3) the decreased number of adverse events resulting from avoidable drug-related errors.

1. Decreased Health Professional Time

The proposed new format for prescription drug labeling (*i.e.,* package inserts or professional labeling) would reduce the time physicians, pharmacists, and other health professionals must spend reading prescription drug labeling by highlighting frequently used information, by including an indexing system to direct readers to more detailed material in other sections of the labeling, and by reordering and reorganizing the detailed material to facilitate access to information deemed to be most important to prescribers. Although FDA is unaware of any data estimating the total time health professionals spend reading the labeling of prescription drugs, a 1994 FDA survey of physicians found that 42 percent referred to labeling at least once a day, 33 percent less often than once a day but more often than once a week, and 25 percent once a week or less. Even if physicians spend, on average, only 30 seconds referring to labeling (once the labeling is at hand), these findings imply that the cumulative amount of time spent referring to labeling by the nation's approximately 599,000 physicians active in patient care equals about 1.1 million hours per year (Ref. 14). If the new format reduced by 15 seconds the amount of time physicians needed to find information on prescription drug labeling, implementing that format for all prescription drug products would save approximately 525,000 hours per year.

Although the proposed rule initially applies to only a small percentage of all prescription drug labeling, its focus on the most recently approved products includes the labeling that health professionals are most likely to consult frequently. In FDA's survey of physicians, newness of the product was the factor most often rated by physicians as ''very likely'' to trigger referral to prescription drug labeling. This analysis assumes that the rule will begin affecting labeling consultations in the second year of implementation and that it will affect 5 percent of all consultations in that year. The percentage of reformatted labeling consulted by physicians is assumed to increase to 10, 15, and 25 percent in years 3, 4, and 5 respectively. Thereafter, it is assumed to increase an additional 5 percent each year, until reaching 50 percent in year 10. Thus, in year 10, the time savings for physicians is projected to equal about 264,000 hours per year. FDA has not attempted to project impacts beyond 10 years, due to the uncertainty of the longer term technological changes that would affect these estimates. Table 4 shows the annual value of physician time saved and indicates that the present value over 10 years equals approximately $62.8 million.[12] Savings in pharmacist time

[12] Hourly income for physicians was calculated using AMA data for the 1996 average net income of all non-Federal physicians (exclusing residents) and average weekly workload (Jacob, J., 1998, ''Income Data Spark Debate Among Delegates,'' *American Medical News,* July 13, 1998, http://www.ama–assn.org/sci–pubs/amnews/pick_98/anna0713.htm.) FDA's analysis assumes, on

could also be substantial, although they were not estimated.

TABLE 4.—ANNUAL BENEFITS OF REGULATION

Year	Physician time Saved ($ million)		Adverse Drug Events Avoided ($ million)		Total Benefits ($ million)	
	Current value	Present value	Current value	Present value	Current value	Present value
1	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
2	2.00	1.75	38.40	33.54	40.40	35.29
3	4.00	3.27	38.40	31.34	42.40	34.61
4	6.01	4.58	38.40	29.29	44.40	33.87
5	10.01	7.14	38.40	27.38	48.41	34.51
6	12.01	8.00	38.40	25.59	50.41	33.59
7	14.01	8.73	38.40	23.91	52.41	32.64
8	16.01	9.32	38.40	22.35	54.41	31.67
9	18.02	9.80	38.40	20.89	56.41	30.69
10	20.02	10.18	38.40	19.52	58.41	29.70
Total	$102.09	$62.76	$345.60	$233.81	$447.66	$296.57

2. Improved Effectiveness of Treatment

Under the proposed rule, the highlights section would emphasize the drug information that physicians report is the most important for decisionmaking. In addition, any patient information or Medication Guide approved by FDA would be printed at the end of the labeling regardless of when the product was approved. Moreover, certain information will be removed from existing professional labeling because the rule only allows inclusion of data that are pertinent to the clinical uses specified in the indications section. Consequently, this proposed rule would improve the ability of physicians to select the most safe and effective pharmaceutical treatments for their patients and to administer those treatments in the most safe and effective manner. In addition, the proposal may enhance the likelihood that physicians will communicate important information to patients, which could improve patient understanding and compliance with treatment. FDA is unable to quantify the magnitude of these expected improvements in treatment effectiveness and health outcomes, but the agency believes they could be significant.

3. Decrease in Avoidable Adverse Events

Because it will highlight important information about dosage, side effects, and contraindications, the proposed new prescription drug labeling format would decrease the number of adverse drug events (ADE's) caused by incorrect product use. Many ADE's result from poor or incorrectly applied information (*e.g.*, prescribing too high a dose for a patient with poor kidney function, or prescribing a drug to a patient with known contraindications) and are potentially preventable. Studies of hospitalized patients in the early 1990's suggest that the rate of preventable ADE's that occur during hospitalization is approximately 1.2 to 1.8 ADE's per 100 patients admitted (Refs. 15 and 16). Moreover, the latter study found that a majority of preventable ADE's (about 1 ADE per 100 hospital admissions) were related to errors or miscalculations in physician ordering, the stage most likely to be affected by improved prescription drug labeling information. Given the approximately 35 million hospitalizations annually in the United States, [13] these data suggest that about 350,000 ADE's among hospitalized patients are potentially preventable with better labeling for health professionals. Studies show that the occurrence of an ADE in a hospitalized patient increased the costs of caring for the patient by an average of $2,262 to $2,595 (Refs. 15 and 17). Costs associated with preventable ADE's were even higher, averaging about $4,685 per patient (Ref. 17). If other hospitals incur similar costs for preventable ADE's, the potentially preventable annual costs from this source could total $1.6 billion nationally.

In addition, many outpatients are hospitalized as a result of preventable adverse events associated with outpatient drugs. FDA previously estimated that the costs associated with these hospitalizations total $4.4 billion per year [14] (60 FR 44232, August 24, 1995). If half of these adverse events also are related to physician ordering errors, about $2.2 billion per year additional hospital costs result from this source of error. Thus, combining both inpatient and outpatient adverse drug events, about $3.8 billion per year in hospital costs may be potentially preventable through better prescription drug labeling.

The actual proportion of the ADE costs that would be prevented under the proposed rule cannot be predicted with certainty. If these costs were reduced by even 1 percent, however, the proposed rule would reduce hospitalization costs by $38.4 million per year. Over 10 years, the present value of these benefits would total $233.8 million (table 4). Furthermore, if additional averted costs (*e.g.,* physician visits, additional outpatient costs, patient time, lost productivity) were included, the savings from the ADE's avoided would be substantially higher.

C. Costs of Regulation

The proposed rule mandates two broad types of changes to the labeling of

average, that physicians work 56 hours per week for 47 weeks per year and that physician employee benefits are 20 percent of annual income. Thus, the hourly income of about $75 was calculated as follows: ($166,000 × 1.2) (47 × 56). A 7 percent discount rate was used to derive the present value of the benefit stream.

[13] 1997 hospital discharges, Heathcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample, 1997, Agency for Healthcare Research and Quality (AURQ), April 2000. Http://www.ahrq.gov/data/hcupnet.htm.

[14] 60 FR 44232, August 24, 1995. An estimated 498, 750 patients are hospitalized annually for a preventable adverse drug reaction to a prescription drug product, costing $4.4 billion in hospital charges. ($4.4 billion = 498,750 patients x $8,890 average hospiotal charges per patient; 498,740 patients = 35 million discharges x 3% treated for adverse drug events x 95% of adverse drug events from prescription drug products x 50% of adverse drug events that are preventable.)

prescription drug products. First, the professional labeling of recently approved and future products must follow format and content requirements proposed in the rule. Second, some labeling of products already approved for marketing must be revised to: (1) Delete information not pertinent to the approved indication, and (2) add previously approved printed patient information or a Medication Guide. Therefore, direct costs incurred to change professional labeling include the costs of: (1) Designing or revising prescription drug labeling and submitting the new labeling to FDA for approval, (2) the costs of producing longer labeling, and (3) printing a longer PDR.

1. Labeling Changes for Recently Approved and Future Prescription Drug Products

a. *Affected products.* The proposed rule would require that prescription drug labeling conform to format and content requirements for two categories of products: (1) All NDA's, BLA's, and efficacy supplements submitted to FDA on or after the effective date of the final rule: and (2) all NDA's, BLA's, and efficacy supplements pending at the time of the effective date of the final rule or approved over the 5 years preceding the effective date of the final rule. For the first category of products, the labeling requirements would apply when a sponsor files an NDA or BLA (new applications) or efficacy supplement. Products in the second category must file supplemental applications within 3 to 7 years after the effective date of the final rule according to the implementation plan provided in table 1. Labeling for nonprescription products (including nonprescription products approved under NDA's) is not covered by this rule.

Estimates of the number of new applications that would be affected by the rule over a 10-year period are shown in table 5 and are based on the number of application approvals since 1990.

TABLE 5.—NUMBER OF AFFECTED NEW DRUG AND BIOLOGICAL APPLICATIONS AND ESTIMATED LABELING DESIGN COSTS

Year	Number of affected applications by type				Cost for prescription drug labeling design ($ mil)				
	New NDA's/ BLA's	ES's*	Before—5**	Total	New NDA's/ BLA's	ES's*	Before—5**	Total	Present value
1	85	59	0	144	$0.43	$0.30	$0.00	$0.72	$0.67
2	134	73	0	207	0.67	0.37	0.00	1.04	0.90
3	121	57	74	252	0.61	0.29	0.56	1.45	1.18
4	113	38	74	225	0.57	0.19	0.56	1.31	1.00
5	113	20	73	206	0.57	0.10	0.55	1.21	0.86
6	113	14	73	200	0.57	0.07	0.55	1.18	0.79
7	113	10	72	195	0.57	0.05	0.54	1.16	0.72
8	113	8	0	121	0.57	0.04	0.00	0.61	0.35
9	113	6	0	119	0.57	0.03	0.00	0.60	0.32
10	113	5	0	118	0.57	0.03	0.00	0.59	0.30
Total	1,131	290	366	1,787	$5.66	1.47	2.76	9.87	7.09

* Efficacy supplements
** Approvals 5 years before effective date.

For this analysis, January 1, 1995, was used as a proxy for the effective date of the proposed rule. The number of covered application approvals for the 3 consecutive years beginning in 1995 were 85, 134, and 121, an average of 113 each year. FDA assumes that this average rate will continue. During this same 3-year period, 59, 73, and 57 efficacy supplements were approved for applications that initially had been approved prior to 1995. FDA estimates, therefore, that if this rule had become effective on January 1, 1995, as many as 144 products (*i.e.,* 85 covered applications and 59 efficacy supplements) would have incurred design costs in the first year. Most efficacy supplements are filed and approved within 5 years of the approval date of their original application. Therefore, beginning in 1997, an increasing number of efficacy supplements would not have required changes to the labeling format because these changes would have been made in the original application. As the annual number of affected efficacy supplements declined over time, the annual number of affected total applications would likewise diminish, as projected in table 5. Furthermore, between 1990 and 1994 (*i.e.,* the 5-year period before the proxy effective date), an additional 366 applications were approved. Thus, an average of 73 additional applications would have been received annually in years 3 through 7.

b. *Prescription drug labeling design costs.* The cost of designing prescription drug labeling that conforms to the proposed format and content requirements will depend heavily on when, during a product's life cycle, labeling design occurs. Costs will be highest for products already marketed with approved labeling that would otherwise not be changed. Conversely, design costs will be lowest for products that are closely related to a prior product application that has already had its labeling changed to the new format. Costs for currently marketed products undergoing relabeling for other reasons (*e.g.,* related to an efficacy supplement) will be intermediate between these extremes.

FDA has estimated the cost of designing novel patient labeling (for the first prescription drug in a therapeutic class) at about $12,000.[15] The estimated costs of redesigning patient labeling for products that could use previously developed prototypes (*i.e.,* generic drugs or innovator drugs in the same therapeutic class for which patient labeling was already developed) ranged from $500 to $1,500 per product. Although the design of prescription drug labeling under the proposed rule will primarily follow a format specified by FDA, detailed discussion and drug-specific decisions (*e.g.,* regarding exactly which adverse reactions should be listed in the highlights section) will be necessary. Consequently, this analysis estimates $7,500 as the average cost to a firm that needs to redesign the labeling of an existing innovator drug, to

[15] 60 FR 44232. $11,667 for 2 months full-time effort of professional/technical employees with annual compensation, including 40 percent benefits of $70,000 ($11,667 = $50,000 × 1.4 × 2/12).

test the redesigned labeling (*e.g.*, to ensure that the larger labeling will still fit in carton-enclosed products), and to prepare and submit that labeling to FDA for approval. Additional costs for the latter task, however, would be incurred only for those drugs approved in the 5 years before the effective date of the rule. Although sponsors of new applications and efficacy supplements would incur many of the same design costs, they would experience no additional testing and application costs. Thus, the design of labels for new applications and efficacy supplements is estimated to cost $5,000 on average.

In the first year after the final rule becomes effective, an estimated 144 affected products would incur an additional cost per drug of $5,000 to comply with the proposed rule. As shown in table 5, the total first-year costs would amount to $720,000, increasing in the second year to $1.04 million. Costs increase in year 3 to a high of $1.45 million as sponsors of recently approved products begin submitting FDA supplemental applications, at $7,500 per application, to comply with the new labeling format and content. After the seventh year, when all products approved within 5 years before the rule's effective date or pending approval at that time have redesigned labeling, the costs decline to about $0.6 million per year. As a result, the estimated present value of the costs of redesigning prescription drug labeling over 10 years is about $7.1 million.

c. *Costs associated with producing labeling*. Under the proposed rule, labeling for each affected product would be expanded to include a highlights section, an index, and additional formatting and font size requirements (if the labeling does not already meet these requirements). Consequently, all affected labeling will be longer than at present, with current shorter labeling affected proportionately more than current longer labeling (due to the fact that the highlights section will add nearly the same amount of absolute length to every affected product with prescription drug labeling). Longer labeling increases the cost of paper, ink, and other ongoing incremental printing costs. These costs apply both to the labeling that physically accompanies the product and to the labeling that accompanies promotional materials. Also, some products packaged in cartons containing package inserts will require a product-by-product review to assess whether the carton can still accommodate the longer labeling. It is possible that a few products would require equipment changes (*e.g.*, different insert-folding machinery).

i. *Incremental printing costs*. Based on quotes from industry consultants, FDA estimates that the cost of printing larger prescription drug labeling is approximately $0.0086 for each additional 100 square inches. The agency estimates that the proposed rule would increase the average size of labeling by about 93 square inches [16] adding $.008 to the per label printing cost, or $7,960 per million package inserts printed. The new highlights and index sections account for about 37 percent of the additional printing cost, whereas the larger font size imposes the remaining 63 percent of the incremental printing cost.

U.S. retail pharmacies dispense about 2.3 billion prescriptions per year, of which an estimated 560 million are for unit-of-use products, which often include labeling within the package.[17] If the remaining 1.7 billion pharmacy-prepared prescriptions average one insert per 3.33 prescriptions (assumes an average of 100 units per container and 30 units dispensed per prescription), the total number of inserts accompanying retail products equals roughly 1.1 billion. Adding hospital pharmaceutical volume, estimated at approximately 38 percent of retail volume, yields an annual total of 1.5 billion package inserts accompanying prescribed products. Allowing 10 percent for wastage indicates that pharmaceutical companies distribute roughly 1.65 billion package inserts with prescribed products each year. Over time, an increasing number of these inserts would have to be revised. Because the rule initially affects only innovator products and about 60 percent of all prescriptions are for branded products, FDA calculated that about 1 billion of these inserts are currently provided with about 2,287 branded products.[18] Thus, on average, about 435,000 inserts (1 billion ÷ 2,287) may be shipped annually for each affected product. Table 6 shows the estimated number of revised inserts that would accompany the prescribed products. Multiplying these numbers by the estimated incremental printing cost of $.008 per label indicates that the annual costs for package inserts would rise to about $6.2 million by the 10th year.

TABLE 6.—INCREMENTAL PRINTING COSTS FOR REFORMATTED PROFESSIONAL LABELING YEAR

Year	Number of approvals	Number printed per year (million)		Incremental printing costs ($ million)			
		Package inserts	Promotional labeling	Package inserts	Promotional labeling	Total	Present value
1	144	62.6	250.5	$0.50	$1.99	$2.49	$2.33
2	207	152.7	416.1	1.22	3.31	4.53	3.95
3	252	262.3	616.0	2.09	4.90	6.99	5.71
4	225	360.2	677.8	2.87	5.40	8.26	6.30
5	206	449.8	675.9	3.58	5.38	8.96	6.39
6	200	536.8	634.9	4.27	5.05	9.33	6.21

[16] The length of professional labeling from a random sample of approximately 5 percent of the listings printed in the PDR averaged 2.67 pages with a font size of 6.5 point. Twenty-four percent of the sample had at least one boxed warning with an average length of about 5.6 square inches in 6.5-point font or 6.25 square inches in 8-point font. Increasing the font size from 6.5 point to 8 point (*i.e.*, the minimum font size specified in the proposed rule) would increase the average length by an estimated 59 percent, or approximately 1.6 pages. Moreover, the agency estimates that the new highlights section, including any boxed warnings, and indexing system may add up to 90 percent of a page to professional labeling. Therefore, the proposed rule would increase the length of the average professional labeling by about 2.5 pages. Because package inserts are printed on both sides, the average package insert would increase in size by 92.6 square inches.

[17] Unpublished FDA analysis based on survey results from nine pharmacists and applied to IMS data.

[18] Derived from the 1998 *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book), CDER, FDA. The estimate is a count of all branded products marketed under an NDA and differentiated by active ingredient, dosage form, or manufacturer, not including multiple dosage strengths. Although biologics were not counted, adding biologics would not significantly alter results.

TABLE 6.—INCREMENTAL PRINTING COSTS FOR REFORMATTED PROFESSIONAL LABELING YEAR—Continued

Year	Number of approvals	Number printed per year (million)		Incremental printing costs ($ million)			
		Package inserts	Promotional labeling	Package inserts	Promotional labeling	Total	Present value
7	195	621.6	611.1	4.95	4.86	9.81	6.11
8	121	674.3	540.3	5.37	4.30	9.67	5.63
9	119	726.0	476.8	5.78	3.80	9.57	5.21
10	118	777.3	416.4	6.19	3.31	9.50	4.83
Total	1,787	4,623.6	5,315.8	$36.82	$42.30	$79.11	$52.67

To calculate the amount of labeling printed for promotional purposes, FDA assumed that the 23.7 million office and hospital calls per year made by pharmaceutical representatives [19] involved an average of 2 printed pieces of labeling per visit, or a total of 47.4 million per year. In addition, sales representatives made 8.2 million sample calls, distributing an estimated 82 million package inserts per year, or an average of 10 samples per call. Since most promotional visits involve relatively new products—the products most affected by this rule—FDA assumed that all of this labeling would incur additional printing costs, amounting to about $1.0 million annually.

Finally, FDA estimated that about 800,000 pieces of labeling per approval would be distributed each year by mail or at conferences to physicians, other health care professionals, consumers, retail pharmacy outlets and hospital pharmacies for 3 years following approval of a new drug.[20] As shown in table 6, annual total promotional labeling costs peak at $5.4 million in year 4. Over 10 years, the present value of the incremental printing costs for all types of longer prescription drug labeling would be about $52.7 million.

Some companies may incur additional costs associated with maintaining the labeling posted on their web sites. The agency did not estimate these related costs but believes they would be minimal and a routine cost of doing business. Nonetheless, the agency requests comment.

ii. *Equipment costs.* Agency consultants with expertise in pharmaceutical labeling operations estimate that only a small number of carton-enclosed products may require new packaging to accommodate the longer insert. This analysis assumes that 1 percent of both the products with new efficacy supplement changes and the products approved in the 5 years before the effective date of the rule would incur costs of $200,000 each for needed packaging changes. Products approved subsequent to the effective date of the final rule would not incur added equipment costs because their labeling and packaging are not yet established. The estimated present value of equipment changes totals $1.0 million over 10 years.

d. *PDR costs.* FDA estimates that the new highlights section, including any boxed warnings, and index would add about one-half pages to each affected labeling printed in the PDR.[21]

Conversations with Medical Economics (the publisher of the PDR) on the cost per printed page imply that the annual publishing costs of the extra space required for printing the expanded labeling would be about $4,300 for each affected product, plus an additional cost if the product was included in one of two annual supplements. FDA assumed that these costs would be incurred by the pharmaceutical industry via publishing fees paid to Medical Economics. The agency assumed that 75 percent of the new drugs and efficacy supplements would be published in the PDR (some smaller firms decline to publish labeling in the PDR). It was further assumed that 90 percent of the new drugs published would be included in the PDR supplements and 33 percent of the published efficacy supplements would be included in the PDR supplements (about half are actually included, but only two-thirds of these include full prescription drug labeling—the remainder include only the added indication). FDA also assumed that the labeling changes made as a result of the 5-year rule (applications approved in the 5 years preceding the effective date of the final rule) would not be included in the PDR supplements. Based on these assumptions, the estimated cost of publishing the extended labeling in the PDR would be about $0.75 million for year 1. These costs would continue to increase over time as all drug approvals after the effective date of the rule would have longer PDR listings. The estimated annual and total cost of printing longer PDR listings are shown in table 7.

[19] Data from IMS, 1997, as presented at FDA on June 3, 1998. Data include an estimated 17.8 million office calls, 8.2 million sample calls, and 5.9 million hospital calls made in 1997.

[20] For each approval, it was assumed that all physicians involved in primary care and 25 percent of physicians practicing a medical specialty would receive 2 mailings per year, or an estimated 711,535 pieces (*i.e.*, = (274,726 × 2) + (0.25 × 324,198 × 2)), for 3 years following product launch. An additional 10 percent or 71,153 pieces are estimated to be distributed annually for 3 years to other health professionals or consumers. Furthermore, FDA assumes that 50,829 retail pharmacy outlets and 7,120 hospital pharmacies would receive one mailing to announce the launch of a new product in the year of approval.

[21] The new highlights section could add up to one-half page when printed in 8-point size. Because the PDR is printed in a 6.5-point New Century Schoolbook Roman font, the highlights section would require less than one-half page in the PDR. The agency estimates 37 percent less space is required to print information in the smaller PDR font, reducing the size required for the new highlights section to 0.3 pages (*i.e.,* 0.5 × (1—0.37) = 0.315 pages). A sample of labeling printed in the PDR found that about 24 percent of the products may be required to print a boxed warning averaging 5.6 square inches. Therefore, the agency estimates an additional 0.02 pages for these warnings (*i.e.*, 23.9 percent × 5.6 square inches / 75 square inches per page = 0.02 pages). Furthermore, the new indexing system is estimated to add approximately 60 column lines to a PDR listing, equaling approximately 0.2 pages (*i.e.*, (60 lines / 96 lines per column) / 3 columns per page = .21 pages). In total, up to .54 pages may be added to the professional labeling printed in the PDR.

TABLE 7.—COST FOR LONGER LISTINGS IN THE PDR

Year	PDR printing costs ($ million)			
	PDR bound	Supplement	Total	Present value
1	$0.47	$0.31	$0.78	$0.73
2	1.13	0.47	1.60	1.40
3	1.95	0.41	2.36	1.93
4	2.68	0.37	3.05	2.32
5	3.34	0.35	3.69	2.63
6	3.99	0.34	4.33	2.89
7	4.62	0.34	4.96	3.09
8	5.01	0.34	5.35	3.11
9	5.39	0.34	5.73	3.12
10	5.78	0.33	6.11	3.11
Total	$34.36	$3.60	$37.96	$24.33

2. Labeling Changes for All Approved Prescription Drug Products

The agency is also proposing several new retrictions for the labeling of all prescription drug products. These changes can be made, without prior FDA approval, upon submission of a ''changes being effected'' supplement. Labeling for all prescription drug products must comply with the proposed content requirements within 1 year after the effective date of the final rule.

a. *Affected products*. The proposed rule will no longer allow certain information that is sometimes now included in professional labeling (*e.g.*, discussion of studies not supporting approved indications, suggestion of uses or indications not included in the ''Indications and Uses'' section, or discussion of in vitro and animal studies on drug action or efficacy that have not been shown to be pertinent to clinical use by adequate and well-controlled studies). FDA does not know how much product labeling would be affected, but because labeling of most antibiotics currently contains data from in vitro studies, the agency estimates that the proposed rule could affect 90 percent of all antibiotics. Of the approximately 5,300 marketed products in the United States, there are an estimated 789 antibiotics products.[22] Moreover, up to 25 percent of all other marketed products could have labeling containing information that would be prohibited. In the first year, therefore, as many as 1,838 products might have to delete some material from their professional labeling.

In addition, any existing prescription drug product with approved printed patient information or Medication Guide must reprint this information following the last section of the professional labeling. The agency estimates that about 50 approved products, or approximately 1 percent of the existing products, could be affected by this requirement.

b. *Professional labeling design costs*. Industry consultants estimate that, on average, prescription drug manufacturers would incur about $2,000 per product in design and implementation costs for a major revision in the content of professional labeling. Industry consultants with expertise in pharmaceutical labeling estimate that professional labeling inventories represent approximately 3 months worth of production. If given an adequate lead time, companies should be able to minimize inventory losses. This proposed rule would require changes within 1 year of the effective date. Assuming that not all affected firms would have sufficient time to deplete their inventories, consultants estimate the per product professional labeling inventory losses are $570 for a 12 month lead time. Thus, including excess inventory losses, the cost to change professional labeling is estimated at $2,600 per product. In the first year, therefore, firms may incur one-time costs of $4.7 million and $0.1 million, respectively, to remove prohibited material from labeling and to add printed patient information to labeling for all affected products (table 8).

c. *Incremental printing costs for professional labeling*. FDA estimates that an average of 310,000 package inserts may be printed annually for each prescription drug product marketed in the United States.[23] The removal of prohibited information from professional labeling may reduce the size of current packageinserts by about 3 percent or 3 square inches. With such a small change in the length of professional labeling, it is unlikely that the package insert would actually change size. Therefore, the agency assumed no cost savings for shorter professional labeling.

In contrast, printed patient information would add an estimated 2 pages or about 75 square inches to the length of professional labeling. For each of the affected products, manufacturers would incur additional incremental printing costs of about $2,000 for longer labeling.[24] For all 50 affected products, annual incremental printing costs would increase by $0.1 million (table 8).

[22] Derived from the 1998 *Approved Drug Products With Therapeutic Equivalence Evalutaion* (Orange Book), CDER, FDA. Products with NDA numbers in the 50,000 or 60,000 series (*i.e.*, antibiotics), with a distinct dosage form or manufacturer were counted. This number, however, probably overestimates the number of antibiotic products with distinct labeling.

[23] 310,000 inserts per product = 1.65 billion inserts printed annually/5,300 products.

[24] $2,000 per product = 75 square inches/insert × 0.000086 square inches × 310,000 inserts per product.

TABLE 8.—COSTS TO REVISE PROFESSIONAL LABELING OF EXISTING PRESCRIPTION PRODUCT

Changes to Labeling	Number of affected products	One-Time labeling revision costs ($ million)	Annual incremental printing costs ($ million)	Annual PDR costs ($ million)
Removal of prohibited material	1,838	$4.70	$0.00	$0.00
Addition of approved printed patient information or Medication Guide	50	0.13	0.10	0.60
Total	1,888	4.83	0.10	0.60

d. *PDR costs*. The agency assumes that 75 percent of prescription drug products have labeling already printed in the PDR. In accord with the rationale described above, the annual printing costs for the PDR are estimated to be unchanged for products that remove information and to increase for products that add patient information. The per product annual cost to print two additional pages in the PDR is about $16,000.[25] For all affected products, the annual PDR costs would increase by $0.6 million (table 8).

3. Changes to Drug Product Labels

The proposed rule also specifies minor changes to prescription drug product labels to remove excess information from the label to help reduce medication errors. To reduce the burden on industry, changes to labels are not required until the first time labeling is revised after the effective date of the final rule. Therefore, no additional compliance costs are estimated for these changes.

Table 9 displays the estimated compliance costs for the three major cost categories over a 10-year period.

TABLE 9.—COMPLIANCE COST OVER 10-YEAR PERIOD

Year	Cost Category ($ million)			
	Labeling design and FDA approval	Producing professional labeling (including equipment costs)	Printing PDR	Total costs ($ million)
1	$5.55	$2.71	$1.38	$9.64
2	1.04	4.77	2.20	8.01
3	1.45	7.35	2.96	11.76
4	1.31	8.59	3.65	13.54
5	1.21	9.25	4.29	14.75
6	1.18	9.60	4.93	15.72
7	1.16	10.08	5.56	16.79
8	0.61	9.78	5.95	16.34
9	0.60	9.69	6.33	16.61
10	0.59	9.61	6.71	16.91
Total current value	14.68	81.43	43.96	140.07
Total present value	11.62	54.37	28.54	94.52

D. Impacts on Small Entities

1. The Need for and the Objectives of the Rule

As discussed in detail in section II of this document, various developments in recent years have contributed to an increase in the length and complexity of prescription drug product labeling, and made it more difficult for health care practitioners to find specific information and discern the most critical information in labeling. The objective of the proposed requirements is to enhance the safe and effective use of prescription drug products by making it easier for health care practitioners to access, read, and use information in prescription drug product labeling.

As previously stated, FDA's legal authority to amend its regulations governing the content and format of labeling for human prescription drug and biologic products and to amend its regulations governing the requirements for prescription drug product labels derives from sections 201, 301, 501, 502, 503, 505, and 701 of the act (21 U.S.C. 321, 331, 351, 352, 353, 355, and 371) and section 351 of the PHS Act (42 U.S.C. 262).

2. Description and Estimate of the Number of Small Entities Affected

This proposed rule would affect all small entities required to design their prescription drug labeling to comply with this rule. The Small Business Administration (SBA) considers firms in Standardized Industrial Classification Code 2834, Pharmaceutical Preparations, with fewer than 750 employees to be small entities. Although U.S. Census size categories do not correspond to SBA size categories, of the approximately 600 firms identified, over 90 percent have fewer than 500 employees.[26] Thus, most of the firms in the pharmaceutical industry are considered small entities for Regulatory Flexibility Act purposes. In contrast, an agency review of NDA's received in FY 97, 98, and 99 found that about 19 small entities submit NDA's each year. In addition, an equal number of small firms that submit BLA's, ES's and/or reformatted professional labeling for approval would also be affected, for a total of about 38.

[25] $16,000 per product = $8,000/page × 2 pages.

[26] U.S. Department of Commerce, Bureau of the Census, *1992 Census of Manufacturers, Industry Series, Drugs, MC92–1–28C.*

Census of Manufactures data on revenues per firm apply to all establishments classified in 2834, Pharmaceutical Preparations. As noted above, only a subset of this industry is affected by this rule. The agency does not know the average revenues for the affected sectors.

3. Description of the Compliance Requirements

The compliance requirements for small entities under this proposed rule are the same as those described above for other affected entities. Compliance primarily involves: (1) Designing labeling that conforms to the format requirements as illustrated in the FDA-designed prototype; and (2) once the labeling is approved by FDA, ensuring that all future printed labeling (including labeling used for promotional purposes) is in the new format. Because sponsors already submit labeling with NDA's and supplements to FDA, no additional skills will be required to comply with the proposed rule.

The group of small entities likely to bear the highest total costs under this proposed rule are those firms that have: (1) Existing products with labeling that must be revised in the first year; or (2) more than one affected high-volume product per year, such as a small firm with two or three recently approved, high-volume products that must undergo labeling reformatting simultaneously in the same year. However, the high-cost small entities are also the small firms with the highest sales of affected product; thus, their incremental cost per unit sold is likely to be relatively low. In contrast, small firms with a single, low-volume product would have lower total costs of compliance, but the incremental cost per unit sold would be higher.

To illustrate the impact on small entities with different production volumes, the following examples estimate the professional labeling costs for a small firm with a single carton-enclosed product (marketed under an NDA) that must: (1) Have its labeling reformatted in year 3 of the rule, and (2) add patient information in year 1. Table 10 outlines the projected per-unit and total costs to the firm under three different levels of production: 1,000, 10,000, and 100,000 units produced per year.

TABLE 10.—ESTIMATED COSTS FOR HYPOTHETICAL SMALL FIRM WITH A SINGLE PRODUCT, UNDER THREE ALTERNATIVE LEVELS OF PRODUCTION

Cost category	Number of units produced and sold each year		
	100,000	10,000	1,000
Example 1—Change labeling approved less than 1 year before effective date:			
Professional labeling redesign/application	$7,500	$7,500	$7,500
Printing package inserts [1]	87	88	9
Printing professional labeling used for promotional purposes [2]	1,611	161	16
Total	9,987	7,749	7,525
Additional cost per unit sold	0.10	0.77	7.53
Example 2—Add patient information to labeling of an existing product:			
Professional labeling redesign	2,600	2,600	2,600
Printing package inserts [3]	710	71	7
Printing longer PDR [4]	16,000	16,000	16,000
Total	19,310	18,671	18,607
Additional cost per unit sold	0.87	1.87	18.61

[1] Number of package inserts printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $.00796 per label.
[2] Incremental costs associated with printing labeling used for promotional purposes are assumed to be 184% of the costs of printing package inserts, based on the ratio of the average number of pieces printed for mailings to the average number printed as package inserts.
[3] Number of package inserts printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $.00645 per package insert.
[4] Assume that professional labeling is already being printed in the PDR.

In addition to the costs identified in table 10, a very small number of small firms might incur equipment costs to include longer prescription drug labeling in carton-enclosed products. It is likely, however, that this one-time capital cost (estimated at $200,000) will affect a total of no more than two or three small firms in the 10 years following implementation of the rule. Based on this analysis, FDA finds that the impact of this proposed rule would not be significant for most small entities in this industry, but it is possible that more than a few small firms may incur significant costs. The agency solicits public comment on the potential impact of the proposed rule on small entities.

4. Alternatives Considered

a. *Formatting alternatives.* FDA has considered numerous alternative formats, including a longer highlights section. The highlights section was limited to about one-half page to respond to health professionals' concerns about length as well as to reduce the incremental printing costs to sponsors.

The agency also considered increasing the minimum required font size from 8 point to 10 point. The larger font size would increase labeling by approximately 196 square inches, whereas labeling printed in 8-point font size is estimated to increase by only 93 square inches. Furthermore, the incremental costs for labeling printed in 10 point font size would be approximately $16,850 per million inserts, more than double the incremental costs of labeling printed in 8-point font size. Over 10 years, the total present value of producing longer labeling would increase by $111.5 million with the larger font size, compared to $52.7 million for the 8-point font size. Although the agency has tentatively rejected the minimum 10-point font size requirement because of the additional burden on industry, FDA solicits comment on minimum font size requirements.

b. *Alternative categories of affected products.* Three alternative categories of products to be covered by the

rulemaking were considered: (1) All drugs, (2) a proposed set of innovator and generic drugs on a ''top 200 most prescribed'' list, and (3) the ''top 100'' or ''top 200'' drugs with the most adverse drug reactions. The agency has tentatively rejected these three alternatives because it was uncertain whether the benefits would exceed the costs, especially in the case of older drugs and generic drugs for which physicians infrequently consult labeling. In addition, the ''top 200'' lists were excluded because the agency believed that the most important subset of these products would be covered by the currently proposed rule. However, FDA solicits comment on these alternative criteria for selecting drugs to be affected by the rulemaking.

c. *Alternative implementation schedule.* FDA considered a shorter implementation schedule, requiring that the labeling for all applications and efficacy supplements approved 5 years prior to the implementation date be revised 3 years after the effective date. The more gradual implementation schedule has been proposed primarily to reduce the impact of the rule on small entities as well as the immediate impact of the rulemaking on the industry as a whole.

XI. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this proposal by March 22, 2001. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. LittleJohn, J.K., ''Package Insert: View of a Rural Town Practitioner,'' *Drug Information Journal*, vol. 21, pp. 63–65, 1987.

2. National BioSystems, Inc., ''Focus Group Report: Physician's Perceptions of Prescription Drug Labeling Information,'' Contract #223–91–3501, February 1992.

3. Wogalter, M.S., ''Factors Influencing the Effectiveness of Warnings,'' in *Visual Information for Everyday Use: Design and Research Perspectives*, edited by H.J.G. Zwaga, T. Boersema, and H.C.M. Hoonhout, Taylor & Francis, 1999.

4. Council for International Organization of Medical Sciences, ''Guidelines for Preparing Core Clinical-Safety Information on Drugs: Report of CIOMS Working Group III,'' 1995.

5. Wilkins, A.G., and M.I. Nimmo-Smith, ''The Clarity and Comfort of Printed Text,'' *Ergonomics*, vol. 30, pp. 1705–1720, 1987.

6. Silver, N.C., and C.C. Braun, ''Perceived Readability of Warning Labels with Varied Font Sizes and Styles,'' *Safety Science*, vol. 16, pp. 615–625, 1993.

7. Tinker, M.A., Legibility of Print, Ames, IA, Iowa State University Press, 1963.

8. Steering Committee for the Collaborative Development of a Long-Range Action Plan for the Provision of Useful Prescription Medicine Information, ''Action Plan for the Provision of Useful Prescription Medicine Information,'' Washington, DC, 1996.

9. Kripalani, S., ''The Write Stuff: Simple Guidelines Can Help You Write and Design Effective Patient Education Materials,'' *Texas Medicine*, vol. 91, pp. 40–45, 1995.

10. Backinger, C.L., and P.A. Kingsley, ''Write it Right: Recommendations for Developing User Instructions for Medical Devices Used in Home Health Care,'' Department of Health and Human Services, Publication No. FDA 93–4258, 1993.

11. Mettger, W., and J. Mara, ''Clear & Simple: Developing Effective Print Materials for Low-Literate Readers,'' Bethesda, MD, National Cancer Institute, Publication No. NIH 95–3594, 1994.

12. Leape, L., ''Systems Analysis of Adverse Drug Events,'' *Journal of the American Medical Association*, vol. 274, pp. 35–41, 1995.

13. *Pharmacopeial Forum*, vol. 20, No. 4, pp. 7885–7887, July and August 1994.

14. Randolph, L., Physician Characteristics and Distribution in the United States, 1997/1998 ed., Chicago, IL, American Medical Association, 1998.

15. Classen, D.C. *et al.*, ''Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality,'' *Journal of the American Medical Association*, vol. 277, pp. 301–306, 1997.

16. Bates, D.W. *et al.,* ''Incidence of Adverse Drug Events and Potential Adverse Drug Events,'' *Journal of the American Medical Association,* vol. 274, pp. 29–34, 1995.

17. Bates, D.W. *et al.,* ''The Costs of Adverse Drug Events in Hospitalized Patients,'' *Journal of the American Medical Association,* vol. 277, pp. 307–311, 1997.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 201 be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

§ 201.55 [Amended]

2. Section 201.55 *Statement of dosage* is amended by revising the third sentence to read as follows: ''When this occurs, a statement of the recommended or usual dosage is not required on the label or carton.''

3. Section 201.56 is revised to read as follows:

§ 201.56 Requirements on content and format of labeling for human prescription drugs and biologics.

(a) *General requirements.* Prescription drug labeling described in § 201.100(d) must meet the following general requirements:

(1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular.

(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans shall be identified as such and included with human data in the appropriate section of the labeling.

(b) *Categories of prescription drugs subject to the labeling content and format requirements in §§ 201.56(d) and 201.57.* (1) The following categories of prescription drug products are subject to the labeling requirements in paragraph (d) of this section and § 201.57 in accordance with the implementation schedule in paragraph (c) of this section:

(i) Prescription drug products for which a new drug application (NDA), biological license application (BLA), or efficacy supplement has been approved by the Food and Drug Administration (FDA) anytime from 0 up to and including 5 years before [effective date of final rule];

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on [effective date of final rule]; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after [insert effective date of final rule].

(2) Prescription drug products not described in paragraph (b)(1) of this section are subject to the labeling requirements in paragraph (e) of this section and § 201.80.

(c) *Schedule for implementing the labeling content and format*

requirements in §§ 201.56(d) and 201.57. For products described in paragraph (b)(1) of this section, labeling conforming to the requirements in paragraph (d) of this section and § 201.57 must be submitted according to the following schedule:

(1) For products for which an NDA, BLA, or efficacy supplement is submitted for approval on or after [effective date of the final rule], proposed conforming labeling must be submitted as part of the application.

(2) For products for which an NDA, BLA, or efficacy supplement is pending at [effective date of final rule], or that has been approved any time from [effective date of final rule] up to and including 1 year before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 3 years after [effective date of the final rule].

(3) For products for which an NDA, BLA, or efficacy supplement has been approved from 1 year up to and including 2 years before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 4 years after [effective date of the final rule].

(4) For products for which an NDA, BLA, or efficacy supplement has been approved from 2 years up to and including 3 years before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 5 years after [effective date of the final rule].

(5) For products for which an NDA, BLA, or efficacy supplement has been approved from 3 years up to and including 4 years before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 6 years after [effective date of the final rule].

(6) For products for which an NDA, BLA, or efficacy supplement has been approved from 4 years up to and including 5 years before [effective date of the final rule], a supplement with proposed conforming labeling must be submitted no later than 7 years after [effective date of the final rule].

(d) *Labeling requirements for newly and more recently approved prescription drug products.* This paragraph applies only to prescription drug products described in paragraph (b)(1) of this section and must be implemented according to the schedule specified in paragraph (c) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.57(a), (b), and (c) under the following section headings and subheadings and in the following order:

Highlights of Prescribing Information
- Product Names, Other Required and Optional Information
- Boxed Warning
- Recent Labeling Changes
- Indications and Usage
- Dosage and Administration
- How Supplied
- Contraindications
- Warnings/Precautions
- Drug Interactions
- Use in Specific Populations

Comprehensive Prescribing Information: Index

Comprehensive Prescribing Information
- !Boxed Warning
- 1 Indications and Usage
- 2 Dosage and Administration
- 3 How Supplied/Storage and Handling
- 4 Contraindications
- 5 Warnings/Precautions
- 6 Drug Interactions
- 7 Use in Specific Populations
  - 7.1 Pregnancy
  - 7.2 Labor and delivery
  - 7.3 Lactating women
  - 7.4 Pediatric use
  - 7.5 Geriatric use
- 8 Adverse Reactions
- 9 Drug Abuse and Dependence
- 10 Overdosage
- 11 Description
- 12 Clinical Pharmacology
  - 12.1 Mechanism of action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
  - 12.4 Other clinical pharmacology information
- 13 Nonclinical Toxicology
  - 13.1 Carcinogenesis, mutagenesis, impairment of fertility
  - 13.2 Animal toxicology and/or pharmacology
- 14 Clinical Studies
- P Patient Counseling Information

(2) The labeling may contain an additional section entitled ''R References'' if appropriate and if in compliance with § 201.57(c)(16).

(3) Sections or subsections of the labeling required under § 201.57(a), (b), or (c) may be omitted if clearly inapplicable.

(4) The labeling required under § 201.57(c) may contain a ''Product Title'' section preceding any boxed warning as required in § 201.57(c)(1) or, in the absence of such warning, preceding the ''Indications and Usage'' section, and containing only the information required by §§ 201.57(c)(12)(i)(A) through (c)(12)(i)(D) and 201.100(e). The information required by § 201.57(c)(12)(i)(A) through (c)(12)(i)(D) must appear in the ''Description'' section of the labeling, whether or not it also appears in a ''Product Title'' section.

(5) The labeling required under § 201.57(c) may include additional nonstandardized subheadings under the standardized subheadings listed in paragraphs (d)(1) and (d)(2) of this section to emphasize specific topics within the text of the required sections where the use of additional subheadings will enhance labeling organization, presentation, or ease of use (*e.g.,* subheadings may be used to set off individual warnings or precautions, or for each drug interaction). If additional subheadings are used, they must be assigned a decimal index number that corresponds to their placement in labeling and is consistent with the standardized index numbers and identifiers listed in paragraphs (d)(1) and (d)(2) of this section (*e.g.,* subheadings added to the ''Warnings/Precautions'' subsection could be numbered 5.1, 5.2, and so on; subheadings in the ''Patient Counseling Information'' subsection could be numbered P.1, P.2, and so on).

(e) *Labeling requirements for older prescription drug products.* This paragraph applies only to approved prescription drug products not described in paragraph (b)(1) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.80 under the following section headings and in the following order:

Description
Clinical Pharmacology
Indications and Usage
Contraindications
Warnings
Precautions
Adverse Reactions
Drug Abuse and Dependence
Overdosage
Dosage and Administration
How Supplied

(2) The labeling may contain the following additional section headings if appropriate and if in compliance with § 201.80(l) and (m):

Animal Pharmacology and/or Animal Toxicology
Clinical Studies
References

(3) The labeling may omit any section or subsection of the labeling format if clearly inapplicable.

(4) The labeling may contain a ''Product Title'' section preceding the ''Description'' section and containing only the information required by § 201.80(a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(1)(iv) and § 201.100(e). The information required by § 201.80(a)(1)(i) through (a)(1)(iv) shall appear in the

''Description'' section of the labeling, whether or not it also appears in a ''Product Title.''

(5) The labeling must contain the date of the most recent revision of the labeling, identified as such, placed prominently after the last section of the labeling.

4. Section 201.57 is redesignated as § 201.80 and new § 201.57 is added to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs and biologic products described in § 201.56(b)(1).

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirements in paragraphs (c)(2)(ii), (c)(2)(iii), (c)(3), (c)(13)(ii), (c)(15)(i), and (c)(17) of this section, which must be implemented no later than 1 year after [effective date of the final rule].

(a) *Highlights of prescribing information.* This section must appear in all prescription drug labeling. Statements made in promotional labeling and advertisements must be consistent with all information included in labeling under paragraph (c) of this section in order to comply with § 202.1(e) and § 201.100(d)(1) of this chapter. The section must include the following information under the identified subheading, if any, in the following order:

(1) *Drug names, dosage form, route of administration and controlled substance symbol.* The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed.

(2) *Inverted black triangle symbol.* The ''▼'' 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. This symbol must be placed on the same line as the proprietary name of the product, or the established or proper name if there is no proprietary name.

(3) *Prescription drug symbol.* The ℞ symbol to indicate that the drug is a prescription drug. This symbol must be placed on the same line as the proprietary name of the product, or the established or proper name if there is no proprietary name, immediately following any ''▼'' symbol.

(4) *Boxed warnings or contraindications.* The full text of any boxed warning or contraindication required by paragraph (c)(1) of this section, provided that the text does not exceed a length of 20 lines. Where the text exceeds 20 lines, a statement summarizing the contents of the boxed warning(s) or contraindication(s) must be included, also not to exceed a length of 20 lines. The boxed warning or summary statement of the boxed warning must be preceded by a heading, in upper-case letters, containing the word ''WARNING(S)'' and other words that are appropriate to identify the subject of the warning. Both the text of the boxed warning or summary statement of the boxed warning and heading must be contained within a box and bolded. For summary statements of a boxed warning, the following statement shall be placed immediately following the heading of the boxed warning: ''See ! for full boxed warning.''

(5) *Recent labeling changes.* A listing of the section(s) of the comprehensive prescribing information in paragraph (c) of this section that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(2) or (d)(2) of this chapter, or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's index number or identifier. This section must be retained in the labeling for at least 1 year after the date of the labeling change, and may be retained until such time that the labeling is reprinted for the first time following the change.

(6) *Indications and usage.* A concise statement of each of the product's indications as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., particular subsets of the population, second line therapy status, or antimicrobials limited to certain microorganisms) must be briefly noted.

(7) *Dosage and administration.* The most important aspects of the comprehensive prescribing information required under paragraph (c)(3) of this section, with any appropriate subheadings. This would include the most common dosage regimen(s) and critical differences among population subsets, monitoring requirements, and other therapeutically important clinical pharmacologic information. The use of tables is encouraged, where appropriate (*e.g.,* when there are different dosage regimens for different indications).

(8) *How supplied.* A concise summary of information concerning the product's dosage form(s) that is required under paragraph (c)(4) of this section. This would ordinarily include the metric strength or strengths of the dosage form and whether the product is scored. If appropriate, the information in this section of the labeling should include subheadings to specify different dosage forms (*e.g.*, tablets, capsules, injectables, suspension).

(9) *Contraindications.* A concise summary of the comprehensive prescribing information required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) *Warnings/precautions.* A concise summary of the most clinically significant aspects of the comprehensive prescribing information required under paragraph (c)(6) of this section, with any appropriate subheadings. Clinically significant warnings and precautions include those that affect prescribing because of their severity and consequent influence on the decision to use the drug, because it is critical to safe use of the drug to monitor patients for them, or because measures can be taken to prevent or mitigate harm. This section of the the labeling must also include the subheading ''Most Common Adverse Reactions (≥ n/100).'' Under this subheading, the most frequently occurring adverse reactions (*i.e.*, noxious and unintended responses for which there is a reasonable causal association with the use of the drug), as described in paragraph (c)(9) of this section, must be listed along with the incidence rate used to determine inclusion. Typically, the incidence rate for inclusion would be expected to be ≥ 1/100. When appropriate, adverse reactions important for other reasons (*e.g.*, because they lead to discontinuation or dosage adjustment) may be included.

(11) *ADR reporting contacts.* For drug products other than vaccines, the verbatim statement ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number)* or FDA's MedWatch at (insert current FDA MedWatch number).'' For vaccines, the verbatim statement ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or

VAERS at (*insert the current VAERS number*).''

(12) *Drug interactions.* A concise summary of other prescription and over-the-counter drugs or foods that interact in clinically significant ways with the product, from the comprehensive prescribing information required under paragraph (c)(7) of this section, with any appropriate subheadings.

(13) *Use in specific populations.* A concise summary of any clinically important differences in response or use of the drug in specific populations, from the comprehensive prescribing information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(14) *Patient counseling information statement.* When applicable, the verbatim statement ''See P for Patient Counseling Information.'' If the product has approved patient labeling or a Medication Guide, the verbatim statement ''See P for Patient Counseling Information, followed by (*insert name of drug*)'s (*insert either* approved patient labeling *or* Medication Guide).''

(15) *Highlights limitation statement.* The verbatim statement ''These highlights do not include all the information needed to prescribe (*insert name of drug product*) safely and effectively. See (*insert name of drug product*)'s comprehensive prescribing information provided below.''

(16) *Revision date.* The date of the most recent revision of the labeling, identified as such, placed at the end of the highlights section.

(17) *Index number placement.* Any subheadings required by paragraphs (a)(4) through (a)(10), (a)(12), and (a)(13) of this section, as well as additional subheadings included in the highlights section of the labeling under § 201.56(d)(5), must be followed by their index number in parentheses.

(b) *Comprehensive prescribing information: Index.* This section must appear in all prescription drug labeling immediately following the information required under paragraph (a) of this section and must contain a list of each subheading required under § 201.56(d)(1), if not omitted under § 201.56(d)(3), preceded by the index number or identifier required under § 201.56(d)(1) or (d)(2). The section must also contain additional subheading(s) included in the comprehensive prescribing information section of labeling under § 201.56(d)(5), preceded by the index number or identifier assigned under that section of the labeling.

(c) *Comprehensive prescribing information.* This section must appear in prescription drug labeling immediately following the information required under paragraph (b) of this section. The section of the labeling must contain the information in the order required under paragraphs (c)(1) through (c)(17) of this section, together with the subheadings and index numbers or identifiers required under § 201.56(d)(1), unless omitted under § 201.56(d)(3). If additional subheadings are used within a labeling subsection in accordance with § 201.56(d)(5), they must be preceded by the index number assigned under that section.

(1) *Boxed warnings and contraindications.* Special problems, particularly those that may lead to death or serious injury, may be required by FDA to be placed in a prominently displayed box. The boxed warning(s) or contraindication(s) ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of boxed information in the absence of clinical data. If a box containing warning(s) or contraindication(s) is required, it must be located preceding the ''Indications and Usage'' section of the labeling. The box must be preceded by an exclamation point (!) and must contain, in uppercase letters, a heading inside the box that includes the word ''WARNING(S)'' and is appropriate to communicate the general focus of the boxed information. If the information related to the boxed risk is extensive, the detailed information must be included under a bolded subheading in the appropriate section of the labeling (either ''Contraindications'' or ''Warnings/Precautions''). The brief explanation of the risk(s) in the box must be followed by a reference (*i.e.*, the appropriate index number) to this more detailed information.

(2) *1 Indications and usage.* (i) This section of the labeling must state that:

(A) The drug is indicated in the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition; and/or

(B) The drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of an important manifestation of a recognized disease or condition; and/or

(c) The drug is indicated for the relief of symptoms associated with a recognized disease or syndrome; and/or

(D) The drug, if used for a particular indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), is an adjunct to the mode of therapy.

(ii) For drug products other than biologics, all indications listed in this section of the labeling must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section.

(iii) For biologics, all indications listed in this section of the labeling must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section of the labeling.

(iv) This section of the labeling must also contain the following additional information:

(A) If evidence is available to support the safety and effectiveness of the drug or biologic only in selected subgroups of the larger population with a disease, syndrome, manifestation, or symptom under consideration (*e.g.*, patients with mild disease or patients in a special age group), or if evidence to support the indication is based on surrogate endpoints (*e.g.*, CD4 cell counts or viral load), this section of the labeling must succinctly describe the available evidence and state the limitations of usefulness of the drug. In such cases, reference should be made to the ''Clinical Studies'' section of the labeling for a detailed discussion of the methodology and results of clinical studies relevant to such limitation(s). The labeling must also identify specific tests needed for selection or monitoring of the patients who need the drug (*e.g.*, microbe susceptibility tests). Information on the approximate kind, degree, and duration of improvement to be anticipated must be stated if available and for all drugs except biological products must be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such information must be based upon substantial evidence. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it must be stated in the ''Dosage and Administration'' section of the labeling and referenced in this section of the labeling.

(B) If safety considerations are such that the drug should be reserved for certain situations (*e.g.*, cases refractory to other drugs), this information must be stated in this section of the labeling.

(C) If there are specific conditions that should be met before the drug is used on a long-term basis (*e.g.*, demonstration

of responsiveness to the drug in a short-term trial in a given patient), the labeling must identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling must identify the specific indications for each use.

(D) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that the labeling state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(E) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(3) *2 Dosage and administration.* This section of the labeling must state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established. Dosages must be stated for each indication and subpopulation when appropriate. Dosing regimens must not be implied or suggested in other sections of labeling if not included in this section of the labeling. When established and clinically important, efficacious and/or toxic drug and/or metabolite concentration ranges and therapeutic concentration windows for drug and/or metabolites must be stated in this section of the labeling. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section of the labeling when TDM is clinically necessary. This section of the labeling must also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations (*e.g.*, in children, in geriatric age groups, or in patients with renal or hepatic disease). Specific tables or monographs should be used when they would clarify dosage schedules. Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it. This section of the labeling must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (*e.g.*, the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: ''Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.'')

(4) *3 How supplied/storage and handling.* This section of the labeling must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must ordinarily include:

(i) The strength or potency of the dosage form in metric system (*e.g.,* 10-milligram tablets), and, if the apothecary system is used, a statement of the strength must be placed in parentheses after the metric designation;

(ii) The units in which the dosage form is ordinarily available for prescribing by practitioners (*e.g.,* bottles of 100);

(iii) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code number; and

(iv) Special handling and storage conditions.

(v) A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity. Where there are standards and test procedures for determining that the container meets the requirements for specified types of containers as defined in an official compendium, such terms may be used. For example, ''Dispense in tight, light-resistant container as defined in the National Formulary.'' Where standards and test procedures for determining the types of containers to be used in dispensing the drug product are not included in an official compendium, the specific container or types of containers known to be adequate to maintain the identity, strength, quality, and purity of the drug products must be described. For example, ''Dispense in containers that (*statement of specifications that clearly enable the dispensing pharmacist to select an adequate container*).''

(5) *4 Contraindications.* This section of the labeling must describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit. These situations include administration of the drug to patients known to have a severe hypersensitivity reaction to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities must be listed (*e.g.,* if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section of the labeling must state ''None known.''

(6) *5 Warnings/precautions.* (i) *General.* Under this section heading, the labeling must describe clinically significant adverse reactions and other potential safety hazards, including those resulting from drug/drug interactions; limitations in use imposed by them; and steps that should be taken if they occur. The labeling must be revised to include a warning as soon as there is reasonable evidence of an association of a clinically significant hazard with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the ''Indications and Usage'' section of the labeling may be required by FDA if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with clinically significant risk or hazard. The frequency of all clinically significant adverse reactions (including those that do not require a boxed warning) and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, must be expressed as provided under the ''Adverse Reactions'' section of the labeling.

(ii) *Other special care precautions.* This section of the labeling must also contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (*e.g.,* precautions not required

under any other specific section or subsection of the labeling).

(iii) *Monitoring: Laboratory tests.* This subsection of the labeling must identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) *Interference with laboratory tests.* If the product is known to interfere with laboratory tests, this subsection of the labeling must briefly note this interference and reference where the detailed information is discussed (typically this will be under the ''Drug Interactions'' section).

(v) *ADR reporting contacts.* This section of the labeling must include the statement: ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA's MedWatch at (*insert current FDA MedWatch number*).'' For vaccines, this section of the labeling must include the statement: ''To report SUSPECTED SERIOUS ADR's, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS number*).''

(7) 6 *Drug interactions.* (i) This section of the labeling must contain specific practical guidance for the practitioner on preventing clinically significant drug/drug interactions with other prescription or over-the-counter drugs, and drug/food interactions (for example, interactions with dietary supplements and such foods as grapefruit juice) that may occur in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo must be identified, and the mechanism(s) of the interaction must be briefly described. Information in this section of the labeling must be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments should not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Interactions that have particularly serious consequences may be described briefly in the ''Contraindications'' or ''Warnings/Precautions'' sections of labeling, as appropriate, with a more complete description under this section of the labeling. Drug incompatibilities, *i.e.,* drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, must be discussed under the ''Dosage and Administration'' section of the labeling rather than under this section of the labeling.

(ii) This section of the labeling must also contain practical guidance on known interference of the drug with laboratory tests.

(8) *7 Use in specific populations.* This section of the labeling must contain the following subsections:

(i) *7.1 Pregnancy.* This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling must contain the following information:

(A) *Teratogenic effects.* Under this subheading, the labeling must identify one of the following categories that applies to the drug, and the labeling must bear the statement required under the category:

(*1*) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state: ''Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling must also contain a description of the human studies. If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must also state: ''Reproduction studies have been performed in (*kinds of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*).'' The labeling must also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*2*) *Pregnancy category B.* If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling must state: ''Pregnancy Category B. Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.'' If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state: ''Pregnancy Category B. Reproduction studies in (*kind(s) of animal(s)*) have shown (*describe findings*) at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling must also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*3*) *Pregnancy category C.* If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state: ''Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'' The labeling must contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling must state: ''Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman

only if clearly needed.'' The labeling must contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*4*) *Pregnancy category D.* If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling must state: ''Pregnancy Category D. See 'Warnings/Precautions' section.'' Under the ''Warnings/Precautions'' section, the labeling must state: (*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.''

(*5*) *Pregnancy category X.* If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling must state: ''Pregnancy Category X. See 'Contraindications' section.'' Under ''Contraindications,'' the labeling must state: ''(Name of drug) may (*can*) cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) (*Name of drug*) is contraindicated in women who are or may become pregnant. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.''

(B) *Nonteratogenic effects.* Under this subheading, the labeling must contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading must include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(ii) *7.2 Labor and delivery.* If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling must describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection of the labeling is unknown, it must state that the information is unknown.

(iii) *7.3 Lactating women.* (A) If a drug is absorbed systemically, this subsection of the labeling must contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring must be described.

(B) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling must contain one of the following statements, as appropriate. If the drug is associated with clinically significant adverse reactions or if the drug has a known tumorigenic potential, the labeling must state: ''Because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue producing milk for consumption or to discontinue the drug, taking into account the importance of the drug to the lactating woman.'' If the drug is not associated with clinically significant adverse reactions and does not have a known tumorigenic potential, the labeling must state: ''Caution should be exercised when (*name of drug*) is administered to a lactating woman.''

(C) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling must contain one of the following statements, as appropriate. If the drug is associated with clinically significant adverse reactions or has a known tumorigenic potential, the labeling must state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue producing milk for consumption or to discontinue the drug, taking into account the importance of the drug to the lactating woman.'' If the drug is not associated with clinically significant adverse reactions and does not have a known tumorigenic potential, the labeling must state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (*name of drug*) is administered to a lactating woman.''

(iv) *7.4 Pediatric use.* (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(8)(iv)(B) through (c)(8)(iv)(H) of this section, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the ''Indications and Usage'' section of the labeling, and appropriate pediatric dosage information must be given under the ''Dosage and Administration'' section of the labeling. The ''Pediatric use'' subsection of the labeling must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug.

Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or ''Clinical Studies'' section. As appropriate, this information must also be contained in the ''Contraindications,'' and/or ''Warnings/Precautions'' section(s) of the labeling.

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the ''Pediatric use'' subsection of the labeling and discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' and ''Clinical Studies'' sections. Appropriate pediatric dosage must be given under the ''Dosage and Administration'' section of the labeling. The ''Pediatric use'' subsection of the

labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (*e.g.,* neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the ''Contraindications,'' and/or ''Warnings/Precautions'' section(s) of the labeling.

(D) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the ''Pediatric use'' subsection of the labeling must contain either the following statement, or a reasonable alternative:

The safety and effectiveness of (drug name) have been established in the age groups____to—(note any limitations, *e.g.,* no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).

Data summarized in the preceding prescribed statement in this subsection of the labeling must be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or the ''Clinical Studies'' section of the labeling. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the ''Clinical Pharmacology'' section of the labeling. Pediatric dosing instructions must be included in the ''Dosage and Administration'' section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the ''Pediatric use'' subsection of the labeling and, as appropriate, in the ''Contraindications,'' ''Warnings/Precautions,'' and ''Dosage and Administration'' sections.

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the ''Pediatric use'' subsection of the labeling must contain an appropriate statement such as ''Safety and effectiveness in pediatric patients below the age of (____) have not been established.'' If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection of the labeling, or, if appropriate, the hazard must be stated in the ''Contraindications'' or ''Warnings/Precautions'' section of the labeling and this subsection must refer to it.

(F) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling must contain the following statement: ''Safety and effectiveness in pediatric patients have not been established.'' If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard must be described in this subsection of the labeling, or, if appropriate, the hazard must be stated in the ''Contraindications'' or ''Warnings/Precautions'' section of the labeling and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(8)(iv)(B) through (c)(8)(iv)(F) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(H) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the ''Contraindications'' or ''Warnings/Precautions'' section of the labeling.

(v) *7.5 Geriatric use.* (A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the ''Indications and Usage'' section of the labeling, and appropriate geriatric dosage must be stated under the ''Dosage and Administration'' section of the labeling. The ''Geriatric use'' subsection of the labeling must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the ''Geriatric use'' subsection of the labeling must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling must be discussed in more detail, if appropriate, under ''Clinical Pharmacology'' or the ''Clinical Studies'' section of the labeling. As appropriate, this information must also be contained in the ''Warnings/Precautions'' or ''Contraindications'' section of the labeling.

(B) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the ''Geriatric use'' subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (*e.g.,* postmarketing studies or adverse drug reaction reports). The ''Geriatric use'' subsection of the labeling must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(*1*) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly

subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the ''Geriatric use'' subsection of the labeling must include the following statement:

Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(*2*) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the ''Geriatric use'' subsection of the labeling must contain the following statement:

Of the total number of subjects in clinical studies of (name of drug),____percent were 65 and over, while____percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(*3*) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the ''Geriatric use'' subsection of the labeling must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, must refer to more detailed discussions in the ''Contraindications,'' ''Warnings/Precautions,'' ''Dosage and Administration,'' or other sections of the labeling.

(C)(*1*) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the ''Geriatric use'' subsection of the labeling and in detail under the ''Clinical Pharmacology'' section of the labeling. The ''Clinical Pharmacology'' and ''Drug interactions'' section of the labelings ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

(*2*) If a drug is known to be substantially excreted by the kidney, the ''Geriatric use'' subsection of the labeling must include the statement:

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

(D) If use of the drug in the elderly appears to cause a specific hazard, the hazard must be described in the ''Geriatric use'' subsection of the labeling, or, if appropriate, the hazard must be stated in the ''Contraindications'' or ''Warnings/Precautions'' section of the labeling, and the ''Geriatric use'' subsection must refer to those sections of the labeling.

(E) Labeling under paragraphs (c)(8)(v)(A) through (c)(8)(v)(C) of this may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, *e.g.,* for a sedating drug, it could be stated that: ''Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely.''

(F) If the sponsor believes that none of the requirements described in paragraphs (c)(8)(v)(A) through (c)(8)(v)(E) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(vi) *Additional subsections of the labeling.* Additional subsections of the labeling may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (*e.g.,* renal or hepatic impairment).

(9) *8 Adverse reactions.* An adverse reaction is a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response (*i.e.,* the relationship cannot be ruled out).

(i) *Listing of adverse reactions.* This section of the labeling must list the adverse reactions (not all the adverse events) that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(ii) *Categorization of adverse reactions.* In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category must be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, must be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category must be listed in decreasing order of severity. The approximate frequency of each adverse reaction must be expressed in rough estimates or orders of magnitude essentially as follows:

The most frequent adverse reaction(s) to (*name of drug*) is (are) (*list reactions*). This (these) occur(s) in about (*e.g.,* one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (*list reactions*), which occur in approximately (*e.g.,* one in 100 patients). Other adverse reactions, which occur rarely, in approximately (*e.g.,* one in 1,000 patients), are (*list reactions*).

Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter (except for biological products), they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(iii) *Potentially fatal adverse reactions.* The ''Warnings/Precautions'' section of the labeling or, if appropriate, the ''Contraindications'' section of the labeling must identify any potentially fatal adverse reaction.

(iv) *Comparisons of adverse reactions between drugs.* For drug products other than biologics, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined

in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

(10) *9 Drug abuse and dependence.* This section of the labeling must contain the following subsections, as appropriate for the specific drug.

(i) *Controlled substance.* If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

(ii) *Abuse.* This subsection of the labeling must be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection of the labeling must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations must be identified.

(iii) *Dependence.* This subsection of the labeling must describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and must identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details must be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state must be provided, and the principles of treating the effects of abrupt withdrawal must be described.

(11) *10 Overdosage.* This section of the labeling must describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section of the labeling must be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information must be provided about the following:

(i) Signs, symptoms, and laboratory findings associated with an overdosage of the drug;

(ii) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis);

(iii) Concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the ''Clinical Pharmacology'' section of the labeling also may be referenced here, if applicable to overdoses;

(iv) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening;

(v) Whether the drug is dialyzable; and

(vi) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(12) *11 Description.* (i) This section of the labeling must contain:

(A) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug or, for biologics, the proper name (as defined in § 600.3 of this chapter) and any appropriate descriptors;

(B) The type of dosage form(s) and the route(s) of administration to which the labeling applies;

(C) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for drug labels or §§ 610.60 and 610.61 of this chapter for biologic labels;

(D) If the drug is for other than oral use, the names of all inactive ingredients, except that:

(*1*) Flavorings and perfumes may be designated as such without naming their components.

(*2*) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in subchapter A of this chapter.

(*3*) Trace amounts of harmless substances added solely for individual product identification need not be named. If the drug is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients must be listed, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection, it need not be named.

(E) If the product is sterile, a statement of that fact;

(F) The pharmacological or therapeutic class of the drug;

(G) For drug products other than biologics, the chemical name and structural formula of the drug; and

(H) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(ii) If appropriate, other important chemical or physical information, such as physical constants, or pH, must be stated.

(13) *12 Clinical pharmacology.* (i) Under this section, the labeling must contain information relating to the human clinical pharmacology and actions of the drug in humans. Information based on in vitro data using human biomaterials (*e.g.,* human liver slices) and/or pharmacologic animal models or preparations may be included if it is essential to a description of the biochemical and/or physiological mode of action of the drug or drug/drug interactions or is otherwise pertinent to human therapeutics. The section of the labeling must include the following subheadings and information:

(A) *12.1 Mechanism of action.* This section of the labeling must summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (*e.g.,* receptor, membrane, tissue, organ, whole body). A brief description of disease pathophysiology may be included to help facilitate an understanding of the drug's action and impact on this process. If the mechanism of action is not known, the labeling must contain a statement about the lack of information.

(B) *12.2 Pharmacodynamics.* This section of the labeling must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites thought to be related to preventing, diagnosing, mitigating, curing, or treating disease, and/or those related to adverse effects or toxicity. Dose and/or concentration response relationship(s) and the time course of action must be included if known. Information on activity of metabolites, if available, must also be included in this section of the labeling. Recommendations based on pharmacodynamic information regarding dosage titration, monitoring of therapeutic effects, or drug concentration monitoring and dosage adjustment should appear in other sections of the labeling such as the ''Warnings/Precautions'' and/or ''Dosage and Administration''sections. If pharmacokinetic/pharmacodynamic relationships are not demonstrated or are unknown, the labeling must contain a statement about the lack of information.

(C) *12.3 Pharmacokinetics.* This section of the labeling must include clinically relevant pharmacokinetic information. In general, the focus should be on factors that lead to and/or explain altered critical measures (*e.g.,*

C_{max}, AUC, half-life). Information about the pharmacokinetics of a drug or active metabolites must include pertinent absorption, distribution, metabolism (including metabolic pathways and identification of the enzyme systems involved), and excretion parameters. Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), pertinent half-lives (t½), time to reach steady state, accumulation route(s) of elimination, routes of clearance (*e.g.,* CL-total, renal, hepatic), and volume of distribution (V_d) for clinical doses must be presented as appropriate. Information regarding nonlinearity in pharmacokinetic parameters, metabolic induction or inhibition, and clinically relevant binding (plasma protein, erythrocyte) parameters must also be presented as appropriate. Qualitative and quantitative assessment of metabolism must be presented in this section of the labeling. The impact of age, gender, ethnicity, disease states, and other factors on pharmacokinetic parameters must be noted and referenced to other sections of the labeling as necessary (*e.g.,* ''Use in Specific Populations,'' ''Warnings/Precautions,'' ''Dosage and Administration''). The clinical significance of any factors that change the product's pharmacokinetics must be noted, and recommendations based on this pharmacokinetic information must appear in other sections of the labeling, such as the ''Warnings/Precautions'' and/or ''Dosage and Administration'' sections, as necessary. If important pharmacokinetic information is unavailable, the labeling must contain a statement about the lack of information.

(D) *12.4 Other clinical pharmacology information.* Under this heading, information may be presented that is not required under other sections of the labeling where such information is helpful to an understanding of the clinical pharmacology of the product. Information within this section of the labeling may include in vitro data related to the clinical pharmacology of drug/drug interactions or use in specific populations. If specific data on alternative dosing regimens (*e.g.,* for hepatically or renally impaired patients) is included in this section of the labeling, it must also be included under § 201.57(c)(3) (*i.e.,* the ''Dosage and Administration'' section of the comprehensive prescribing information).

(ii) In vitro or animal data related to the activity or efficacy of a drug that have not been shown by adequate and well-controlled studies to be pertinent to clinical use may only be included in this section of the labeling if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

(14) *13 Nonclinical toxicology.* Under this section heading, the labeling must contain the following subsections as appropriate for the drug:

(i) *13.1 Carcinogenesis, mutagenesis, impairment of fertility.* This subsection of the labeling must state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information must be included under the ''Warnings/Precautions'' section of the labeling.

(ii) *13.2 Animal toxicology and/or pharmacology.* In many cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans must ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data must be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(15) *14 Clinical studies.* This section of the labeling generally must contain a discussion of clinical study design and results that are important to a prescriber's understanding of the basis for approval of the drug. However, this section of the labeling must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. The section generally will provide more specific information than contained elsewhere in labeling on the effects of the drug in relevant clinical studies, and especially on the extent of the product's demonstrated benefits (*e.g.,* how the drug was used in clinical trials, who was studied, and critical parameters that were monitored). Although typically not needed, a brief reference to a specific important clinical study may be made in any section of the labeling required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the information in that section of the labeling. Following a succinct description of the available evidence, reference must be made to ''Clinical Studies'' for presentation of more detailed discussion of the methodology and results of relevant studies. A clinical study (including Phase I, pharmacokinetic, etc.) may be discussed in prescription drug labeling only under the following conditions:

(i) For drug products other than biologics, any clinical study that is discussed that relates to an indication for or use of the drug must be adequate and well-controlled as described in § 314.126(b) of this chapter and must not imply or suggest indications or uses or dosing regimens not stated in the ''Indications and Usage'' or ''Dosage and Administration'' section of the labeling. For biological products, any clinical study that is discussed that relates to an indication for or use of the biologic must contitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the ''Indications and Usage'' or ''Dosage and Administration'' section of the labeling.

(ii) Any discussion of a clinical study that relates to a risk or risks from the use of the drug must also reference the other sections of the labeling for the drug where the risk or risks are identified or discussed.

(16) *R References.* This section may appear in labeling in the place of a detailed discussion of a subject that is of limited interest, but nonetheless important. References may appear in sections of the labeling format, other than the ''References'' section, in rare circumstances only. A reference may be cited in prescription drug labeling only under the following conditions:

(i) If the reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for or use of a drug or biological product, the reference must be based upon an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter or for a biological product, upon substantial evidence of effectiveness.

(ii) If the reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks must also be identified or discussed in the appropriate section of the labeling for the drug.

(17) *P Patient counseling information.* This section of the labeling must contain information useful for patients to know for safe and effective use of the drug (*e.g.,* precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). This section of the labeling must appear as the last section of the comprehensive prescribing information. Any approved printed patient information or Medication Guide must be referenced in this section of the labeling and the full text of such patient information or Medication Guide must be reprinted immediately following this section of the labeling.

(d) *Format requirements.* All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(4) through (a)(10), (a)(12), (a)(13), and (a)(14) of this section must be highlighted in bold type and must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(10), (a)(12), or (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11), and (a)(15) must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points.

(7) The index numbers and identifiers (*i.e.,* ''P'' and ''R'') required by § 201.56(d) and paragraphs (c)(1) through (c)(17) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (*i.e.,* two squares of the size of the letter ''m'' in 8-point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4), must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8½ by x 11 inches), single spaced, in 8-point type with ½-inch margins on all sides and between columns, would fit on one-half of the page.

(9) The comprehensive labeling sections or subsections identified in paragraph (a)(5) of this section (*i.e.,* those containing recent labeling changes) must be highlighted by the inclusion of a vertical line on the left edge of the new or modified text.

5. Section 201.58 is amended by revising the first sentence to read as follows:

§ 201.58 Requests for waiver of requirement for adequate and well-controlled studies to substantiate certain labeling statements.

A request under § 201.57(c)(2)(ii), (c)(2)(iv)(A), and (c)(9)(iv), or a request under § 201.80(b)(2), (c)(2), (c)(3)(i), (c)(3)(v), and (g)(4) for a waiver of the requirements of § 314.126(b) of this chapter must be submitted in writing as provided in § 314.126(c) of this chapter to the Director, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or, if applicable, the Director, Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892.

* * *

§ 201.59 [Removed]

6. Section 201.59 *Effective date of §§ 201.56, 201.57, 201.100(d)(3), and 201.100(e)* is removed.

7. Newly redesignated § 201.80 is amended by revising paragraphs (b)(2), (c)(2), (f)(2), and (m)(1) and by adding a new sentence after the first sentence of paragraph (j) to read as follows:

§ 201.80 Specific requirements on content and format of labeling for human prescription drugs and biologics; older drugs not described in § 201.56(b)(1).

* * * * *

(b) * * *

(2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled studies to be pertinent to clinical use may be included under this section of the labeling only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

(c) * * *

(2)(i) For drug products other than biologics, all indications listed in this section of the labeling must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section of the labeling.

(ii) For biologics, all indications listed in this section of the labeling must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section of the labeling.

* * * * *

(f) * * *

(2) *Information for patients.* This section of the labeling must contain information useful for patients to know for safe and effective use of the drug (*e.g.,* precautions concerning driving or the concomitant use of other sustances that may have harmful additive effects). Any approved printed patient information or Medication Guide must be referenced in this section of the labeling and the full text of such patient information or Medication Guide must be reprinted immediately following the last section of labeling.

* * * * *

(j) *Dosage and administration.* * * * Dosing regimens must not be implied or suggested in other sections of labeling if not included in this section of the labeling. * * *

* * * * *

(m) * * *

(1) If the clinical study or reference is cited in the labeling in place of a detailed discussion of data and information concerning an indication for use of the drug, the reference must be based upon, or the clinical study must constitute, an adequate and well-controlled study as described in § 314.126(b) of this chapter, except for biological products, and must not imply or suggest indications or uses or dosing regimens not stated in the ''Indications and Usage'' or ''Dosage and Administration'' section of the labeling.

* * * * *

8. Section 201.100 is amended by removing paragraphs (b)(5) and (b)(7), by redesignating paragraph (b)(6) as paragraph (b)(5), by adding a new paragraph (b)(6), and by revising paragraphs (b)(2) and (d)(3) and newly redesignated paragraph (b)(5) to read as follows:

§ 201.100 Prescription drugs for human use.

* * * * *

(b) * * *

(2) The recommended or usual dosage, unless not required under § 201.55; and

* * * * *

(5) An identifying lot or control number from which it is possible to

determine the complete manufacturing history of the package of the drug.

(6) In the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraphs (b)(2) and (b)(3) of this section may be contained in other labeling on or within the package from which it is to be dispensed; the information referred to in paragraph (b)(1) of this section may be placed on such outer container only; and the information required by this paragraph (b)(6) may be on the crimp of the dispensing tube.

* * * * *

(d) * * *

(3) The information required, and in the format specified, by §§ 201.56, 201.57, and 201.80.

* * * * *

Dated: August 4, 2000.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

Note: The following appendix will not appear in the Code of Federal Regulations.

BILLING CODE 4160–01–P

HIGHLIGHTS OF PRESCRIBING INFORMATION

CAPOTEN® TABLETS ▼℞
(captopril tablets)

WARNING: USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality (5.5).

RECENT LABELING CHANGES

Indications (1.x)
Warnings/Precautions (5.x, 5.y, 5.z)
Adverse Reactions (8.x)

INDICATIONS AND USAGE

- **Hypertension** (caution in renally-impaired patients), alone or in combination with other anti-hypertensives (1.1)
- **Congestive Heart Failure,** usually in combination with diuretics and digitalis (1.2)
- **Left Ventricular (LV) Dysfunction after Myocardial Infarction** to improve survival and reduce morbidity in clinically stable patients with LV ejection fraction ≤ 40% (1.3)
- **Diabetic Nephropathy** (Type I IDD with proteinuria > 500 mg/day and retinopathy) (1.4)

DOSAGE AND ADMINISTRATION

General: Take 1 hour before meals. Individualize dosage.

Indication	Initiation of Therapy	Usual Daily Dose	Do Not Exceed
Hypertension	25 mg bid or tid	25-150 mg bid or tid*	450 mg/day
Heart Failure	25 mg tid	50-100 mg tid	450 mg/day
LV Dysfunction after MI	12.5 mg tid†	50 mg tid	
Diabetic Nephropathy		25 mg tid	

* Usual daily dosing does not exceed 50 mg BID or TID. Consider adding a thiazide-type diuretic. (2.2)
† A single dose of 6.25 mg should precede initiation of 12.5 mg therapy. (2.4)
Adjust dose in renal impairment (2.6, 5.7)

HOW SUPPLIED

Tablets: 12.5, 25, 50, 100 mg; scored (3)

CONTRAINDICATIONS

Known hypersensitivity (e.g., angioedema) to any ACE inhibitor.

WARNINGS/PRECAUTIONS

- Angioedema with possibility of airway obstruction (5.1)
- Neutropenia (<1000/mm³) with myeloid hypoplasia (5.2)
- Excessive hypotension (5.4)
- Fetal/Neonatal Morbidity and Mortality (5.5)
- Hepatic failure (5.6)
- Use with caution in renal impairment. (2.6, 5.7)
- Hyperkalemia (5.8)
- Cough (5.9)

Most Common Adverse Reactions (≥ n/100) (8)

- rash (sometimes with arthralgia and eosinophilia), taste impairment (diminution or loss), cough, pruritus, chest pain, palpitations, tachycardia, proteinuria

To report SUSPECTED SERIOUS ADRs, call (manufacturer) at (phone #) or FDA's MedWatch at 1-800-FDA-1088

DRUG INTERACTIONS

- Diuretics (6.1)
- Other vasodilators (6.2)
- Agents Causing Renin Release (6.3)
- Beta-Blockers (6.4)
- Agents Increasing Serum Potassium (6.5)
- Lithium (6.7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Fetal/Neonatal Morbidity and Mortality (5.5)
- Lactating Women: Potential for serious adverse reactions in nursing infants. (7.3)
- Pediatric Use: Safety and effectiveness not established. Use only if other measures ineffective. (7.4)
- Renal-impairment: Use with caution. (2.6, 5.7)

See P for PATIENT COUNSELING INFORMATION

These highlights do not include all the information needed to prescribe Capoten safely and effectively. See Capoten's comprehensive prescribing information provided below.

m/yy

COMPREHENSIVE PRESCRIBING INFORMATION: INDEX

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! WARNING: USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality (5.5).

1 INDICATIONS AND USAGE

1.1 **Hypertension:** CAPOTEN is indicated for the treatment of hypertension.

In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS/PRECAUTIONS).

CAPOTEN (captopril) may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive.

1.2 **Heart Failure:** CAPOTEN is indicated in the treatment of congestive heart failure usually in combination with diuretics and digitalis. The beneficial effect of captopril in heart failure does not require the presence of digitalis, however, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment.

1.3 **Left Ventricular Dysfunction After Myocardial Infarction:** CAPOTEN is indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤ 40% and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients.

1.4 **Diabetic Nephropathy:** CAPOTEN is indicated for the treatment of diabetic nephropathy (proteinuria >500 mg/day) in patients with type I insulin-dependent diabetes mellitus and retinopathy. CAPOTEN decreases the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis).

2 DOSAGE AND ADMINISTRATION

2.1 CAPOTEN (captopril) should be taken one hour before meals. Dosage must be individualized.

2.2 **Hypertension:** Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting CAPOTEN.

The initial dose of CAPOTEN is 25 mg bid or tid. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg bid or tid. Concomitant sodium restriction may be beneficial when CAPOTEN (captopril) is used alone.

The dose of CAPOTEN in hypertension usually does not exceed 50 mg tid. Therefore, if the blood pressure has not been satisfactorily controlled after one to two weeks at this dose, (and the patient is not already receiving a diuretic), a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily), should be added. The diuretic dose may be increased at one- to two-week intervals until its highest usual antihypertensive dose is reached.

If CAPOTEN is being started in a patient already receiving a diuretic, CAPOTEN therapy should be initiated under close medical supervision (see DRUG INTERACTIONS regarding hypotension (6.1)), with dosage and titration of CAPOTEN as noted above.

If further blood pressure reduction is required, the dose of CAPOTEN may be increased to 100 mg bid or tid and then, if necessary, to 150 mg bid or tid (while continuing the diuretic).

The usual dose range is 25 to 150 mg bid or tid. A maximum daily dose of 450 mg CAPOTEN should not be exceeded.

For patients with severe hypertension (e.g., accelerated or malignant hypertension), when temporary discontinuation of current antihypertensive therapy is not practical or desirable, or when prompt titration to more normotensive blood pressure levels is indicated, diuretic should be continued but other current antihypertensive medication stopped and CAPOTEN dosage promptly initiated at 25 mg bid or tid, under close medical supervision.

When necessitated by the patient's clinical condition, the daily dose of CAPOTEN may be increased every 24 hours or less under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose of CAPOTEN is reached. In this regimen, addition of a more potent diuretic, e.g., furosemide, may also be indicated.

Beta-blockers may also be used in conjunction with CAPOTEN therapy (see DRUG INTERACTIONS (6.4)), but the effects of the two drugs are less than additive.

2.3 **Heart Failure:** Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg tid may minimize the magnitude or duration of the hypotensive effect (see WARNINGS/PRECAUTIONS: Hypotension (5.4)); for these patients, titration to the usual daily dosage can then occur within the next several days.

For most patients the usual initial daily dosage is 25 mg tid. After a dose of 50 mg tid is reached, further increases in dosage should be delayed, where possible, for at least two weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg tid. A maximum daily dose of 450 mg of CAPOTEN should not be exceeded.

CAPOTEN should generally be used in conjunction with a diuretic and digitalis. CAPOTEN therapy must be initiated under very close medical supervision.

2.4 **Left Ventricular Dysfunction After Myocardial Infarction:** The recommended dose for long-term use in patients following a myocardial infarction is a target maintenance dose of 50 mg tid.

Therapy may be initiated as early as three days following a myocardial infarction. After a single dose of 6.25 mg, CAPOTEN therapy should be initiated at 12.5 mg tid. CAPOTEN should then be increased to 25 mg tid during the next several days and to a target dose of 50 mg tid over the next several weeks as tolerated (see CLINICAL PHARMACOLOGY (12.2)) .

CAPOTEN may be used in patients treated with other post-myocardial infarction therapies, e.g., thrombolytics, aspirin, beta blockers.

2.5 **Diabetic Nephropathy:** The recommended dose of CAPOTEN for long term use to treat diabetic nephropathy is 25 mg tid.

Other antihypertensives such as diuretics, beta blockers, centrally acting agents or vasodilators may be used in conjunction with CAPOTEN if additional therapy is required to further lower blood pressure.

2.6 **Dosage Adjustment in Renal Impairment:** Because CAPOTEN is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses.

Accordingly, for patients with significant renal impairment, initial daily dosage of CAPOTEN should be reduced, and smaller increments utilized for titration, which should be quite slow (one- to two-week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment. (See also WARNINGS/PRECAUTIONS: Hemodialysis (5.12))

3 HOW SUPPLIED

12.5 mg tablets in bottles of 100 and 1000, 25 mg tablets in bottles of 100 and 1000, 50 mg tablets in bottles of 100 and 1000, and 100 mg tablets in bottles of 100. Bottles contain a desiccant-charcoal canister.

Unimatic unit-dose packs containing 100 tablets are also available for each potency: 12.5 mg, 25 mg, 50 mg, and 100 mg.

The 12.5 mg tablet is a biconvex oval with a partial bisect bar; the 25 mg tablet is a biconvex rounded square with a quadrisect bar; the 50 and 100 mg tablets are biconvex ovals with a bisect bar. All captopril tablets are white and may exhibit a slight sulfurous odor.

Storage: Do not store above 86° F. Keep bottles tightly closed (protect from moisture).

4 CONTRAINDICATIONS

CAPOTEN (captopril) is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

5 WARNINGS/PRECAUTIONS

To report SUSPECTED SERIOUS ADRs, call (manufacturer) at (phone #) or FDA's MedWatch at 1-800-FDA-1088

5.1 Angioedema

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of captopril; some cases required medical therapy. (See PATIENT COUNSELING INFORMATION (P) and ADVERSE REACTIONS (8).)

5.2 Neutropenia/Agranulocytosis

Neutropenia (<1000/mm^3) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in U.S. reports.

In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine ≥ 1.6 mg/dL and more than 75 percent were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within three months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm^3) the physician should withdraw captopril and closely follow the patient's course.

5.3 Proteinuria

Total urinary proteins greater than 1 g per day were seen in about 0.7 percent of patients receiving captopril. About 90 percent of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

5.4 Hypotension

Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See DRUG INTERACTIONS (6.1).)

In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure greater than 20 percent were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, producing either no symptoms or brief mild lightheadedness, although in rare instances it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6 percent of patients with heart failure.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first two weeks of treatment and whenever the dose of captopril and/or diuretic is increased. In patients with heart failure, reducing the dose of diuretic, if feasible, may minimize the fall in blood pressure.

Hypotension is not *per se* a reason to discontinue captopril. Some decrease of systemic blood pressure is a common and desirable observation upon initiation of CAPOTEN (captopril) treatment in heart failure. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilizes within a week or two, and generally returns to pretreatment levels, without a decrease in therapeutic efficacy, within two months.

5.5 Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury,

including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

5.6 Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

5.7 Impaired Renal Function

Hypertension--Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion.

Heart Failure--About 20 percent of patients develop stable elevations of BUN and serum creatinine greater than 20 percent above normal or baseline upon long-term treatment with captopril. Less than 5 percent of patients, generally those with severe preexisting renal disease, required discontinuation of treatment due to progressively increasing creatinine; subsequent improvement probably depends upon the severity of the underlying renal disease.

See CLINICAL PHARMACOLOGY (12), DOSAGE AND ADMINISTRATION (2.6), ADVERSE REACTIONS: Altered Laboratory Findings (8.1).

5.8 Hyperkalemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. In a trial of type I diabetic patients with proteinuria, the incidence of withdrawal of treatment with captopril for hyperkalemia was 2% (4/207). In two trials of normotensive type I diabetic patients with microalbuminuria, no captopril group subjects had hyperkalemia (0/116). (See PATIENT COUNSELING INFORMATION (P); DRUG INTERACTIONS (6.5); ADVERSE REACTIONS: Altered Laboratory Findings (8.1).)

5.9 Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

5.10 Valvular Stenosis

There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction as others.

5.11 Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

5.12 Hemodialysis

Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (e.g., AN69) in patients receiving ACE inhibitors. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

6 DRUG INTERACTIONS

6.1 Hypotension--Patients on Diuretic Therapy

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with CAPOTEN or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

6.2 Agents Having Vasodilator Activity

Data on the effect of concomitant use of other vasodilators in patients receiving CAPOTEN for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting CAPOTEN. If resumed during CAPOTEN therapy, such agents should be administered cautiously, and perhaps at lower dosage.

6.3 Agents Causing Renin Release

Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

6.4 Agents Affecting Sympathetic Activity

The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking

agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

6.5 Agents Increasing Serum Potassium

Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

6.6 Inhibitors Of Endogenous Prostaglandin Synthesis

It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g., aspirin) may also have this effect.

6.7 Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

6.8 Drug/Laboratory Test Interaction

Captopril may cause a false-positive urine test for acetone.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy Categories C (first trimester) and D (second and third trimesters) See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality (5.5).

7.3 Lactating Women

Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN (captopril) to the mother. (See USE IN SPECIFIC POPULATIONS: Pediatric Use (7.4).)

7.4 Pediatric Use

Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

8 ADVERSE REACTIONS

Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About one of 100 patients developed proteinuria (see WARNINGS/PRECAUTIONS (5.3)).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS/PRECAUTIONS (5.2)). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4 to 7 (depending on renal status and dose) of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photo sensitivity, have also been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see DRUG INTERACTIONS (6.1) for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See PATIENT COUNSELING INFORMATION (P).)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials. (See WARNINGS/PRECAUTIONS: Cough (5.9).)

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Body as a whole: Anaphylactoid reactions (see WARNINGS/PRECAUTIONS: Hemodialysis (5.12)).

General: Asthenia, gynecomastia.

Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.

Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.

Gastrointestinal: Pancreatitis, glossitis, dyspepsia.

Hematologic: Anemia, including aplastic and hemolytic.

Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.

Metabolic: Symptomatic hyponatremia.

Musculoskeletal: Myalgia, myasthenia.

Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.

Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.

Special Senses: Blurred vision.

Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality

See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality.

8.1 Altered Laboratory Findings

Serum Electrolytes: Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see WARNINGS/PRECAUTIONS (5.8)).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

10 OVERDOSAGE

Correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

11 DESCRIPTION

CAPOTEN (captopril) is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II.

CAPOTEN is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline [MW 217.29].

Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor; it is soluble in water (approx. 160 mg/mL), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate.

CAPOTEN is available in potencies of 12.5 mg, 25 mg, 50 mg, and 100 mg as scored tablets for oral administration. Inactive ingredients: microcrystalline cellulose, corn starch, lactose, and stearic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of CAPOTEN has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

CAPOTEN prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase," and CAPOTEN may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E^2 may also have a role in the therapeutic effect of CAPOTEN .

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

12.2 Pharmacodynamics

Administration of CAPOTEN results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of CAPOTEN and glomerular filtration rate is usually unchanged.

Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of CAPOTEN. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume depleted patients. Abrupt withdrawal of CAPOTEN has not been associated with a rapid increase in blood pressure.

12.3 Pharmacokinetics

After oral administration of therapeutic doses of CAPOTEN, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than 2 hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION (2.6)).

Studies in rats and cats indicate that CAPOTEN does not cross the blood-brain barrier to any significant extent.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. The high dose in these studies is 150 times the maximum recommended human dose of 450 mg, assuming a 50-kg subject. On a body-surface-area basis, the high doses for mice and rats are 13 and 26 times the maximum recommended human dose, respectively.

Studies in rats have revealed no impairment of fertility.

13.2 Animal Toxicology

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD) of 450 mg, assuming a 50-mg subject. On a body-surface-area, these doses are 5 to 25 times maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD on a body-weight basis (4 to 15 times MRHD on a surface-area basis). The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys in mice and rats at doses 7 to 200 times MRHD on a body-weight basis (0.6 to 35 times MRHD on a surface-area basis); in monkeys at 20 to 60 times MRHD on a body-weight basis (7 to 20 times MRHD on a surface-area

basis); and in dogs at 30 times MRHD on a body-weight basis (15 times MRHD on a surface-area basis).

Gastric erosions/ulcerations were increased in incidence in male rats at 20 to 200 times MRHD on a body-weight basis (3.5 and 35 times MRHD on a surface-area basis); in dogs at 30 times MRHD on a body-weight basis (15 times on MRHD on a surface-area basis); and in monkeys at 65 times MRHD on a body-weight basis (20 times MRHD on a surface-area basis). Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD on a body-weight basis (10 times MRHD on a surface-area basis) for only 5 to 7 days.

In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7 to 200 times MRHD) on a body-weight basis; 1 to 35 times MRHD on a surface-area basis in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

14 CLINICAL STUDIES

Congestive Heart Failure: In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated. These hemodynamic and clinical effects occur after the first dose and appear to persist for the duration of therapy. Placebo controlled studies of 12 weeks duration in patients who did not respond adequately to diuretics and digitalis show no tolerance to beneficial effects on ETT; open studies, with exposure up to 18 months in some cases, also indicate that ETT benefit is maintained. Clinical improvement has been observed in some patients where acute hemodynamic effects were minimal.

Left Ventricular Dysfunction After Myocardial Infarction: The Survival and Ventricular Enlargement (SAVE) study was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 2,231 patients (age 21-79 years) who survived the acute phase of a myocardial infarction and did not have active ischemia. Patients had left ventricular dysfunction (LVD), defined as a resting left ventricular ejection fraction ≤ 40%, but at the time of randomization were not sufficiently symptomatic to require ACE inhibitor therapy for heart failure. About half of the patients had had symptoms of heart failure in the past. Patients were given a test dose of 6.25 mg oral CAPOTEN (captopril) and were randomized within 3-16 days post-infarction to receive either CAPOTEN or placebo in addition to conventional therapy. CAPOTEN was initiated at 6.25 mg or 12.5 mg tid and after two weeks titrated to a target maintenance dose of 50 mg tid. About 80% of patients were receiving the target dose at the end of the study. Patients were followed for a minimum of two years and for up to five years, with an average follow-up of 3.5 years.

Baseline blood pressure was 113/70 mm Hg and 112/70 mm Hg for the placebo and CAPOTEN groups, respectively. Blood pressure increased slightly in both treatment groups during the study and was somewhat lower in the CAPOTEN group (119/74 vs. 125/77 mm Hg at 1 yr).

Therapy with CAPOTEN improved long-term survival and clinical outcomes compared to placebo. The risk reduction for all cause mortality was 19% ($P = 0.02$) and for cardiovascular death was 21% ($P = 0.014$). Captopril treated subjects had 22% ($P = 0.034$) fewer first hospitalizations for heart failure. Compared to placebo, 22% fewer patients receiving captopril developed symptoms of overt heart failure. There was no significant difference between groups in total hospitalizations for all cause (2056 placebo; 2036 captopril).

CAPOTEN was well tolerated in the presence of other therapies such as aspirin, beta blockers, nitrates, vasodilators, calcium antagonists and diuretics.

Diabetic Nephropathy: In a multicenter, double-blind, placebo controlled trial, 409 patients, age 18-49 of either gender, with or without hypertension, with type I (juvenile type, onset before age 30) insulin-dependent diabetes mellitus, retinopathy, proteinuria ≥ 500 mg per day and serum creatinine ≤ 2.5 mg/dL, were randomized to placebo or CAPOTEN (25 mg tid) and followed for up to 4.8 years (median 3 years). To achieve blood pressure control, additional antihypertensive agents (diuretics. beta blockers, centrally acting agents or vasodilators) were added as needed for patients in both groups.

The CAPOTEN group had a 51% reduction in risk of doubling of serum creatinine ($P < 0.01$) and a 51% reduction in risk for the combined endpoint of end-stage renal disease (dialysis or transplantation) or death ($P < 0.01$). CAPOTEN treatment resulted in a 30% reduction in urine protein excretion within the first 3 months ($P < 0.05$), which was maintained throughout the trial. The CAPOTEN group had somewhat better blood pressure control than the placebo group, but the effects of CAPOTEN on renal function were greater than would be expected from the group differences in blood pressure reduction alone. CAPOTEN was well-tolerated in this patient population.

In two multicenter, double-blind, placebo controlled studies, a total of 235 normotensive patients with insulin-dependent diabetes mellitus, retinopathy and microalbuminuria (20-200 μg/min) were randomized to placebo or CAPOTEN (50 mg bid) and followed for up to 2 years. CAPOTEN delayed the progression to overt nephropathy (proteinuria ≥ 500 mg/day) in both studies (risk reduction 67% to 76%; $P < 0.05$). CAPOTEN also reduced the albumin excretion rate. However, the long term clinical benefit of reducing the progression from microalbuminuria to proteinuria has not been established

P PATIENT COUNSELING INFORMATION

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (e.g., swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See WARNINGS/PRECAUTIONS (5.1).)

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician. (See WARNINGS/PRECAUTIONS (5.8); DRUG INTERACTIONS (6.5); ADVERSE REACTIONS (8).)

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that CAPOTEN (captopril) should be taken one hour before meals (see DOSAGE AND ADMINISTRATION (2.1)).

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

[FR Doc. 00–32375 Filed 12–21–00; 8:45 am]

BILLING CODE 4160–01–C