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Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 314, and 601

[Docket No. 2000N–1269] (formerly Docket No. 00N–1269)

RIN 0910–AA94

Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format of labeling for human prescription drug products (including biological products that are regulated as drugs). The final rule revises current regulations to require that the labeling of new and recently approved products include highlights of prescribing information and a table of contents. The final rule also reorders certain sections, requires minor content changes, and sets minimum graphical requirements. These revisions will make it easier for health care practitioners to access, read, and use information in prescription drug labeling. The revisions will enhance the safe and effective use of prescription drug products and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information. For both new and recently approved products and older products, the final rule requires that all FDA-approved patient labeling be reprinted with or accompany the labeling. The final rule also revises current regulations for prescription drug labeling of older products by clarifying certain requirements. These changes will make the labeling for older products more informative for health care practitioners.

DATES: This rule is effective June 30, 2006. See section III of this document for the implementation dates of this final rule.

FOR FURTHER INFORMATION CONTACT:

For information on drug product labeling: Janet Norden, Center for Drug Evaluation and Research (HFD–40), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4202, Silver Spring, MD 20993–0002, 301–796–2270, *nordenj@CDER.FDA.GOV*, or Elizabeth Sadove, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041, *sadovee@CDER.FDA.GOV*.

For information on labeling of biological products that are regulated as prescription drugs: Toni M. Stifano, Center for Biologics Evaluation and Research (HFM–600), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20856, 301–827–6190, *stifano@CBER.FDA.GOV*, or Kathleen Swisher, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–6210.

SUPPLEMENTARY INFORMATION:

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I. Background

In the **Federal Register** of December 22, 2000 (65 FR 81082), FDA issued a proposed rule to revise its regulations governing the content and format of labeling for human prescription drug products, which appear in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57).[1]

A. FDA-Approved Prescription Drug Labeling

A prescription drug product's FDA-approved labeling (also known as ''professional labeling,'' ''package insert,'' ''direction circular,'' or ''package circular'') is a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. This labeling contains information necessary for safe and effective use. It is written for the health care practitioner audience, because prescription drugs require ''professional supervision of a practitioner licensed by law to administer such drug'' (section 503(b) of the act (21 U.S.C. 353(b))). FDA-approved labeling is defined in section 201(m) of the act (21 U.S.C. 321(m)) and is subject to all applicable provisions of section 502 of the act (21 U.S.C. 352). It satisfies the requirement of § 201.100(d) (21 CFR 201.100(d)) that ''[a]ny labeling, as defined in section 201(m) of the act * * * that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug * * * contains * * * [a]dequate information for such use,'' as further described in that provision. FDA-approved labeling also accompanies ''promotional'' materials, as described in § 202.1(l)(2) (21 CFR 202.1(l)(2)). FDA-approved labeling also ''bears adequate information'' within the meaning of § 201.100(c)(1), which applies to ''labeling on or within the package from which a prescription drug is to be dispensed'', referred to in this document as ''trade labeling.'' In this document, FDA-approved labeling for prescription drugs is referred to as ''labeling'' or ''prescription drug labeling.''

B. Developing the Proposed Rule

In recent years, there has been an increase in the length, detail, and complexity of prescription drug labeling, making it harder for health care practitioners to find specific information and to discern the most critical information. Before issuing the proposal, the agency evaluated the usefulness of prescription drug labeling for its principal audience to determine whether, and how, its content and format could be improved. The agency used focus groups, a national physician survey, a public meeting, and written comments to develop multiple prototypes and to ascertain how prescription drug labeling is used by health care practitioners, what labeling information practitioners consider most important, and how practitioners believed labeling could be improved. The agency developed a prototype based on this accumulated information as the model for the proposed rule.

[1] Although §§ 201.56 and 201.57 do not specifically mention the term ''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. (See section VII of this document for legal authority.) For the purposes of this document, unless otherwise specified, all references to ''drugs'' or ''drug products'' include human prescription drug products and biological products that are also drugs.

C. The Proposed Rule

The agency's proposed changes were designed to enhance the ability of health care practitioners to access, read, and use prescription drug labeling.

1. Proposed Provisions for New and Recently Approved Drugs

FDA proposed the following changes for the labeling for prescription drugs that were approved on or after the effective date of the final rule, drugs that had been approved in the 5 years before the effective date of the final rule, and older approved drugs for which an efficacy supplement is submitted. FDA believed that applying the revised content and format requirements only to more recently approved products was appropriate because, among other reasons, health care practitioners are more likely to refer to the labeling of recently approved products (see comment 113).

- The addition of introductory prescribing information, entitled ''Highlights of Prescribing Information'' (Highlights).
- The addition of a table of contents.
- Reordering and reorganizing to make the labeling easier to use and read.
- Minimum graphical requirements for format.
- Certain revisions to the content requirements, such as modifying the definition of ''adverse reaction'' to make the ''Adverse Reactions'' section of labeling more meaningful and useful to health care practitioners.

2. Proposed Provisions for Older Approved Drugs

The agency proposed that older approved drug products would not be subject to these proposed changes. These older products would, instead, be subject to the labeling requirements at proposed § 201.80. The agency proposed to redesignate then-current § 201.57 as § 201.80 to describe labeling requirements for older drugs and add new § 201.57 to describe labeling requirements for new and recently approved drugs.

3. Proposed Provisions for All Drugs

FDA also proposed certain revisions to the requirements governing the content of labeling to help ensure that statements appearing in labeling related to effectiveness or dosage and administration are sufficiently supported. These provisions would have applied to all drugs.

- The labeling for all drugs would contain all FDA-approved patient labeling (i.e., approved printed patient information and Medication Guides) for the drug, not just the information required by regulation to be distributed to patients (see table 2).
- Minor revisions would be made to the requirements for labels affixed to prescription drug containers and packaging.

The proposal called for the submission of comments by March 22, 2001. At the request of the Pharmaceutical Research and Manufacturers of America, and to provide all interested persons additional time to comment, the comment period was reopened until June 22, 2001 (66 FR 17375, March 30, 2001). After careful consideration of the comments, FDA has revised the proposal and is issuing this final rule.

The following sections of this document provide:

- An overview of the final rule including changes to the proposed rule (section II of this document),
- A discussion of the implementation requirements for the final rule (section III of this document),
- An overview of the agency's prescription drug labeling initiatives (section IV of this document),
- The implications of this rule for the electronic labeling initiative (section V of this document),
- A discussion of the comments received on the proposal and the agency's responses to the comments (section VI of this document),
- A statement of legal authority (section VII of this document),
- A description of the information collection provisions of the rule (section VIII of this document),
- An statement on the environmental impact of the rule (section IX of this document),
- A statement on federalism (section X of this document),
- An analysis of the economic impacts of the rule (section XI of this document),
- A statement on the impact of the rule on the civil justice system (section XII of this document), and
- A list of references (section XIII of this document).

II. Overview of the Final Rule Including Changes to the Proposed Rule

This final rule amends part 201 (21 CFR part 201) of FDA regulations by revising the requirements for the content and format of labeling for prescription drug products (see tables 1 and 2 of this document). Table 1 lists the sections required for prescription drug labeling before the effective date of this final rule (and which will remain in effect for older products), and, for new and recently approved products, the sections FDA proposed in 2000 and those required by this final rule.

BILLING CODE 4160–01–S

Table 1.--Prescription Drug Labeling Sections

Sections Required for All Products Before the Effective Date of the Final Rule and for Older Products On and After the Effective Date of the Final Rule	Sections That Were Proposed for New and Recently Approved Products	Sections Required for New and Recently Approved Products On or After the Effective Date of the Final Rule
Description Clinical Pharmacology Indications and Usage Contraindications Warnings Precautions Adverse Reactions Drug Abuse and Dependence Overdosage Dosage and Administration How Supplied Optional: Animal Pharmacology and/or Animal Toxicology Clinical Studies References	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 8 Adverse Reactions 9 Drug Abuse and Dependence 10 Overdosage 11 Description 12 Clinical Pharmacology 13 Nonclinical Toxicology 14 Clinical Studies R References P Patient Counseling Information	Highlights of Prescribing Information Product Names, Other Required Information Boxed Warning Recent Major Changes Indications and Usage Dosage and Administration Dosage Forms and Strengths Contraindications Warnings and Precautions Adverse Reactions Drug Interactions Use in Specific Populations Full Prescribing Information: Contents Full Prescribing Information Boxed Warning 1 Indications and Usage 2 Dosage and Administration 3 Dosage Forms and Strengths 4 Contraindications 5 Warnings and Precautions 6 Adverse Reactions 7 Drug Interactions 8 Use in Specific Populations 9 Drug Abuse and Dependence 10 Overdosage 11 Description 12 Clinical Pharmacology 13 Nonclinical Toxicology 14 Clinical Studies 15 References 16 How Supplied/Storage and Handling 17 Patient Counseling Information

The final rule requires that any FDA-approved patient labeling either: (1) Accompany the prescription drug labeling or (2) be reprinted at the end of such labeling (§§ 201.57(c)(18) and 201.80(f)(2)). Table 2 lists the requirement in effect before the effective date of this final rule, the 2000 proposed requirement, and the final requirement (see comment 92 for discussion of FDA-approved patient labeling). For the purposes of this document, the term ''FDA-approved patient labeling'' will be used to refer to any approved printed patient information or Medication Guide, unless a comment is addressing one or the other specifically.

TABLE 2.—FDA-APPROVED PATIENT LABELING WITH PRESCRIPTION DRUG LABELING

Requirement for All Products Before the Effective Date of the Final Rule	Proposed Requirement for All Products	Final Requirement for All Products
To be reprinted at the end of labeling: • Full text of FDA-approved patient labeling that is required to be distributed to patients	To be reprinted at the end of labeling: • Full text of any FDA-approved patient labeling	To be reprinted at the end of labeling or to accompany the labeling: • Full text of any FDA-approved patient labeling

In this rulemaking, the agency finalizes many of the provisions in the December 2000 proposal. In addition, the final rule reflects revisions the agency made in response to comments on the December 2000 proposal and revisions made by the agency on its own initiative. FDA also has made editorial changes to clarify provisions, correct cross-references, and support the agency's plain language initiative. Table 3 lists the substantive changes made to the general provisions and Highlights and table 4 lists the substantive changes made to the Full Prescribing Information (FPI).

A. Content and Format of Labeling for New and More Recently Approved Prescription Drug Products

The final rule, like the proposed rule, requires that the labeling for new and more recently approved drug products comply with revised content and format requirements (§ 201.56(d)) (see table 1). Like the proposed rule, the final rule provides that new and more recently approved products include drug products with an NDA, BLA, or efficacy supplement that: (1) Was approved between June 30, 2001, and June 30, 2006; (2) is pending on June 30, 2006; or (3) is submitted anytime on or after June 30, 2006 (§ 201.56(b)(1)).

On its own initiative, the agency added a provision on pediatric risk information to the general labeling requirements of the final rule. Section 11 of the Best Pharmaceuticals for Children Act (Public Law 107–109) (BPCA), which was signed into law on January 4, 2001, addresses labeling requirements for generic versions of drugs with pediatric patent protection or exclusivity. The agency added a provision in § 201.56(d)(5) of the final rule to make clear that any risk information from the ''Contraindications,'' ''Warnings and Precautions,'' or ''Use in Specific Populations'' section is ''pediatric contraindications, warnings, or precautions'' within the meaning of section 11 of the BPCA (21 U.S.C. 355A(l)(2)). By adding § 201.56(d)(5), the agency intends to avoid any possible confusion as to what information the agency may require in generic labeling that otherwise omits a pediatric indication or other aspect of labeling pertaining to pediatric use protected by patent or exclusivity.

In addition, the agency declined to adopt the use of symbols that were proposed to emphasize or identify information in prescription drug labeling. Based on comments, FDA declined to use the inverted black triangle (see comment 15) and the exclamation point (!) to emphasize the boxed warning (see comment 43). On its own initiative, for the same reasons that FDA rejected use of the two symbols commented upon, FDA declined to use the following three proposed symbols:

• The Rx symbol (proposed § 201.57(a)(3)) in Highlights. The agency proposed the symbol to identify a product that is available only by prescription under section 503(b) of the act. The agency decided that the Rx symbol in Highlights is unnecessary because the new prescription drug labeling format is so distinct from the over-the-counter (OTC) drug labeling format that it will be clear to prescribers that labeling in the new format is for a prescription drug product.

• The ''R'' symbol in the FPI (proposed § 201.56(d)(2)), which would have identified the ''References'' section.

• The ''P'' symbol in the FPI (proposed § 201.57(c)(18)), which would have identified the ''Patient Counseling Information'' section.

1. Highlights of Prescribing Information

Like the proposed rule, the final rule requires that the labeling for new and more recently approved products include introductory information entitled ''Highlights of Prescribing Information'' (Highlights) (§§ 201.56(d)(1) and 201.57(a)) (see table 1).

The final rule requires the same headings for Highlights as proposed, except that, in response to comments, FDA moved ''Most Common Adverse Reactions'' from ''Warnings and Precautions'' (proposed § 201.57(a)(10)) to a new heading entitled ''Adverse Reactions'' (§§ 201.56(d)(1) and 201.57(a)(11)) (see table 1 and comment 28). Like the proposed rule, the final rule requires that Highlights, except for the boxed warning, be limited in length to one-half of the page (§ 201.57(d)(8)) (see comment 104).

The agency is also revising its regulations on supplements and other changes to an approved application in §§ 314.70 and 601.12 (21 CFR 314.70 and 601.12) to require applicants to obtain prior approval of any labeling changes to Highlights, except for identified minor changes (see comment 5).

TABLE 3.—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE: GENERAL PROVISIONS AND TO HIGHLIGHTS

21 CFR Section in Final Rule	Description of Change from Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
201.55, 201.57(c)(4)(v), 201.57(c)(12)(i)(D), and 201.100(b)	Container Labels • Withdrew proposed amendments regarding content of container labels and associated proposed amendments to the labeling (106 and 107)

TABLE 3.—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE: GENERAL PROVISIONS AND TO HIGHLIGHTS—Continued

21 CFR Section in Final Rule	Description of Change from Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
201.56(a)(2)	General Requirement • Revised to clarify that the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading (114)
201.56(d)	Product Title • Deleted proposed § 201.56(d)(4), which permitted a ''Product Title'' section to be included at the beginning of the FPI (39)
201.56(d)(4)	Format of Contents • Revised to require that the Contents identify if sections have been omitted (37)
201.56(d)(5)	Pediatric Risk Information • Added, on its own initiative, a provision to make clear that pediatric risk information within the meaning of the BPCA may be located in the ''Use in Specific Populations'' section (II.A)
201.57 and 201.80	Unsubstantiated Claims • Removed the 1-year implementation requirement for provisions in §§ 201.57 and 201.80 that prohibit inclusion of unsubstantiated claims in labeling (114)
201.57	Promotional Labeling • Removed, on its own initiative, the reference to statements made in promotional labeling and advertising in proposed 201.57(a) (111)
201.57(a)(1)	Highlights Limitation Statement • Moved the Highlights limitation statement to the beginning of Highlights (35)
201.57(a)(3)	Inverted Black Triangle Symbol • Instead of an inverted black triangle symbol, labeling will state the ''Initial U.S. Approval'' date (15)
201.57(a)(4)	Boxed Warning • Revised to require that Highlights contain a concise summary of any boxed warning in the FPI (16)
201.57(a)(5)	Recent Labeling Changes • Changed the heading to ''Recent Major Changes'' and revised to identify only substantive changes to the ''Boxed Warning,'' ''Indications and Usage,'' ''Dosage and Administration,'' ''Contraindications,'' and ''Warnings and Precautions'' sections and the date of the change(s) (18–22)
201.57(a)(6)	Indications and Usage • Revised to require identification of the pharmacologic class of the drug if it is a member of an established pharmacologic class (6)
201.57(a)(8)	How Supplied • Changed the heading to ''Dosage Forms and Strengths'' (41)
201.57(a)(11)	Adverse Reactions • Moved ''Most Common Adverse Reactions'' from ''Warnings and Precautions'' to a new heading: ''Adverse Reactions'' (28) • Revised the criteria used for determining which adverse reactions to include in Highlights and that the criteria used be specified (28) • Revised to require that the adverse reactions reporting contact statement be included under the ''Adverse Reactions'' heading of Highlights; deleted proposed § 201.57(c)(6)(v) that would have required that this statement also be included in the FPI (28 and 30) • Revised the requirements associated with the adverse reactions reporting contact statement (31 and 32)
201.58	Waiver Provision • Revised to make clear applicants can request waivers from any requirement under §§ 201.56, 201.57, and 201.80 (104)

2. Full Prescribing Information: Contents

Like the proposed rule, the final rule requires that the labeling for new and recently approved products include, after Highlights, a list of headings and subheadings contained in the FPI preceded by the numerical identifier for the heading or subheading (§ 201.57(b)). FDA has revised, on its own initiative, the heading for this portion of the labeling to read ''Full Prescribing Information: Contents'' (Contents) instead of proposed ''Comprehensive Prescribing Information: Index.'' FDA made this change for editorial reasons to correctly reflect the function of the section. In response to comments, FDA added certain format requirements for the Contents (see table 3 and comments 37 and 101).

3. Full Prescribing Information

FDA has revised, on its own initiative, the heading for this portion of the labeling to read ''Full Prescribing Information'' instead of proposed ''Comprehensive Prescribing Information.'' FDA made this change to more accurately reflect that this portion of prescription drug labeling contains the information that FDA determined is necessary for the safe and effective use of the drug, but may not contain all known information about the drug (e.g., details of all clinical trials).

The final rule revises the requirements for the content and format of the FPI in former §§ 201.56(d) and 201.57 for new and recently approved products (see tables 1 and 2). The final rule establishes minimum requirements for key graphic elements, including bold type, bullet points, type size, spacing and use of vertical and horizontal lines. The final rule requires the same sections for the labeling of these products as proposed except the major, substantive changes listed in table 4, which the agency made in response to comments and, in a few cases as noted, on its own initiative. In addition, FDA made revisions, none of which changed substantive requirements, to the ''Dosage and Administration,'' ''Indications and Usage,'' ''Overdosage,'' ''Clinical Pharmacology,'' and ''Drug Interactions'' sections. FDA made these changes in response to comments that requested FDA to clarify these proposed requirements.

In addition, FDA has revised, on its own initiative, ''Contraindications'' to emphasize that the section must only describe situations in which the potential risks associated with drug use outweigh any possible benefit. FDA believes that including relative or hypothetical hazards diminishes the usefulness of the section. For clarity and emphasis, FDA is requiring that ''none'' be stated when no contraindications are known. Similarly, FDA deleted, on its own initiative, proposed § 201.57(c)(9)(iii) because it was redundant with requirements in ''Warnings and Precautions'' and ''Contraindications.''

TABLE 4.—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE: FULL PRESCRIBING INFORMATION

21 CFR Section in Final Rule	Description of Change From Proposed Rule
	See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
201.57(c)(3)	Dosage and Administration • Revised to make clear that this section must include dosing recommendations based on clinical pharmacologic data, certain dosage modifications, and specified compliance information (51–54)
201.57(c)(4) and 201.57(c)(17)	How Supplied/Storage and Handling • Reorganized information in proposed ''How Supplied/Storage and Handling'' (§ 201.57(c)(4)) such that the information is now contained in two sections: § 201.57(c)(4) retitled ''Dosage Forms and Strengths'' and ''How Supplied/Storage and Handling'' at § 201.57(c)(17) (41)
201.57(c)(7)	Adverse Reactions • Moved the ''Adverse Reactions'' section (proposed § 201.57(c)(9)) to follow ''Warnings and Precautions'' (38) • Withdrew the proposed definition of adverse reaction and retained the definition at former § 201.57(g) (designated in this final rule at § 201.80(g)), with a minor modification (68) • Revised the requirements on how to classify and categorize adverse reactions and how to describe adverse reaction rates (71-75) • Revised to require a description of the overall adverse reaction profile based on entire safety database (70 and 77)
201.57(c)(9)	Use in Specific Populations • Withdrew the proposed warning statements at §§ 201.57(c)(8)(i)(A)(4) and (c)(8)(i)(A)(5) for pregnancy categories D and X and will continue to require the warning statements at former §§ 201.57(f)(6)(i)(d) and (f)(6)(i)(e) be used (66) • Withdrew the proposed revisions for the ''Nursing Mothers'' subsection at § 201.57(c)(8)(iii) and will continue to use the language at former § 201.57(f)(8) (66)
201.57(c)(13)(ii) and 201.80(b)(2)	In Vitro Data for Anti-infectives • Deferred action on proposed §§ 201.57(c)(13)(ii) and 201.80(b)(2) that would have only permitted in vitro data for anti-infective drugs not shown by adequate and well-controlled studies to be pertinent to clinical use be included in labeling if a waiver was granted (81)
201.57(c)(18) and 201.80(f)(2)	Patient Counseling Information • Revised to require that the full text of FDA-approved patient labeling either accompany labeling or be reprinted at the end of the labeling and clarified the type size requirements that apply (93 and 94)(see table 7)
201.57(d)(6)	Font size • Revised to require that font for trade labeling be a minimum of 6-point type instead of 8-point type (102)
201.57(c)(16) and 201.80(l)	References • Clarified requirements for including a reference (89)

B. Content and Format for Older Prescription Drug Products

Like the proposed rule, the final rule redesignates former § 201.57 as § 201.80. New § 201.80 provides content and format requirements for labeling of older prescription drug products (older products) that are not subject to the labeling requirements at new § 201.57 (see tables 1 and 2).

Section 201.80 is the same as former § 201.57 with the following exceptions that are the same as the changes for new and more recently approved products:

- Modifications that help ensure that statements currently appearing in labeling for older products relating to effectiveness or dosage and administration are sufficiently supported (§ 201.80(c)(2)(i), (c)(2)(ii), (j), and (m)(1)).
- Deletion of proposed § 201.80(b)(2) regarding in vitro data for anti-infectives (see table 4 and comment 81).
- Deletion of ''induced emesis'' as an example of treatment procedures in the ''Overdosage'' section of labeling.
- Revisions that allow manufacturers the option of either reprinting the FDA-approved patient labeling immediately following the last section of the prescription drug labeling or having it accompany such labeling (§ 201.80(f)(2))(see table 4 and comment 93).
- Addition of the font size provision to redesignated § 201.80(f)(2) (on the agency's own initiative with modifications made in response to comments) (see table 4 and comments 93 and 94).

C. Content of Prescription Drug Product Labels

FDA has reconsidered its proposal to revise the requirements for the content of prescription drug product labels (proposed §§ 201.55 and 201.100(b)). In response to comments, FDA has decided to withdraw these proposed revisions at this time (see comments 106 and 107). The agency had proposed to move certain information about inactive ingredients and storage conditions from the product label to the prescription drug labeling and to remove the requirement to include the statement ''See package insert for dosage information'' on the product label in cases when it is currently required to be used. These proposed requirements (proposed § 201.57(c)(4)(v) and (c)(12)(i)(D)) were also withdrawn.

The agency intends to conduct a comprehensive evaluation of information required to be contained on product labels. If necessary, FDA will propose changes to these requirements after that evaluation has been completed.

III. Implementation

The final rule is effective June 30, 2006. The final rule has the same implementation plan as proposed for the revised labeling content and format requirements at §§ 201.56(d) and 201.57 for new and more recently approved products (see table 5). Manufacturers of older products that voluntarily elect to revise the format and content of their labeling to be consistent with §§ 201.56(d) and 201.57 may submit a supplement with proposed labeling at any time (see table 5).

TABLE 5.—IMPLEMENTATION PLAN

Applications (NDAs, BLAs, 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 June 30, 2006	Time of submission
Applications pending on June 30, 2006 and applications approved 0 to 1 year before June 30, 2006	June 30, 2009
Applications approved 1 to 2 years before June 30, 2006	June 30, 2010
Applications approved 2 to 3 years before June 30, 2006	June 30, 2011
Applications approved 3 to 4 years before June 30, 2006	June 30, 2012
Applications approved 4 to 5 years before June 30, 2006	June 30, 2013
Applications approved more than 5 years before June 30, 2006	Voluntarily at any time

As indicated in the proposed rule, the implementation plan for revised labeling for products approved or submitted for approval under an ANDA depends on the labeling of the listed drug referenced in the ANDA. In accordance with § 314.94(a)(8) (21 CFR 314.94(a)(8)), 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 (§ 314.93 (21 CFR 314.93)) or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

As the agency proposed (65 FR at 81099), the provisions requiring FDA-approved patient labeling to accompany labeling (§§ 201.57(c)(18) and 201.80(f)(2) of the final rule) will be implemented by June 30, 2007. The agency clarified this provision at §§ 201.57 and 201.56(e)(6).

IV. Overview of Agency Initiatives to Improve the Content and Format of Prescription Drug Labeling

The agency is engaged in a broad effort to improve the communication to health care practitioners of information necessary for the safe and effective use of prescription drugs. A major component of this effort is improvement of the content and format of prescription drug labeling to make the information in labeling easier for health care practitioners to access, read, and use.

Elsewhere in this issue of the **Federal Register**, the agency is announcing the availability of four guidance documents on content and format of labeling.[2] These guidances are intended to assist manufacturers and FDA reviewers in developing clear, concise, and

[2] The agency announces the availability of guidances in the **Federal Register**. Draft and final guidances for the Center for Drug Evaluation and Research (CDER)-related information are posted on the Internet at *http://www.fda.gov/cder/guidance/index.htm*. The Center for Biologics Evaluation and Research (CBER)-related information is posted at *http://www.fda.gov/cber/guidelines.htm* (21 U.S.C. 371(h), 21 CFR 10.115).

accessible prescription drug labeling. The four guidances are as follows:

1. A draft guidance entitled ''Labeling for Human Prescription Drug and Biological Products—Implementing the New Content and Format Requirements'' (the new labeling format guidance). This guidance, which is intended to assist manufacturers in complying with the provisions of this final rule, includes, among other things, how to determine what information from the FPI should be included in Highlights.

2. A draft guidance entitled ''Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format'' (the ''Warnings and Precautions'' section guidance).

3. A guidance entitled ''Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format '' (the ''Adverse Reactions'' section guidance). The agency issued a draft of this guidance on June 21, 2000 (65 FR 38563).

4. A guidance entitled ''Clinical Studies Section of Labeling for Prescription Drug and Biological Products—Content and Format'' (the ''Clinical Studies'' section guidance). The agency issued a draft of this guidance on July 9, 2001 (66 FR 35797).

The agency is also developing two additional guidances on the content and format of specific sections of labeling—the ''Clinical Pharmacology'' and ''Dosage and Administration'' sections. In the future, the agency may develop guidance for additional sections of prescription drug labeling, if necessary.

FDA has undertaken additional rulemaking related to prescription drug labeling. The agency published a final rule in the **Federal Register** entitled ''Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use'' that became effective on February 4, 2004 (68 FR 6062, February 6, 2003). This rule requires that the labeling for all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use include certain statements about using antibiotics in a way that will reduce the development of drug-resistant bacterial strains. The rule encourages health care practitioners: (1) To prescribe systemic antibacterial drugs only when clinically indicated and (2) to counsel their patients about the proper use of such drugs and the importance of taking them exactly as directed.

The agency is also engaged in an effort to revise the regulations concerning the content and format of the ''Pregnancy'' subsection of prescription drug labeling (see the notice of a 21 CFR part 15 hearing to discuss the pregnancy category requirements (62 FR 41061, July 31, 1997) and the notice of a public advisory committee meeting to discuss possible changes to pregnancy labeling (64 FR 23340, April 30, 1999)).

V. Implications of This Final Rule for the Electronic Labeling Initiative

Developing standards for the conversion of paper labeling to an electronic format is a high priority for the agency. On December 11, 2003, FDA published its final rule in the **Federal Register** entitled ''Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format'' (68 FR 69009). The final rule requires the content of prescription drug labeling, including text, tables, and figures, to be submitted to FDA in an electronic format that the agency can process, review, and archive.

The agency views this final rule on the content and format of labeling as an essential step towards the success of its electronic labeling initiative. The labeling format required by this rule for new and more recently approved products should facilitate transition to an electronic format. The agency believes that an electronic version of labeling in the new format, particularly Highlights and Contents, will significantly expand health care practitioners' ability to access information in prescription drug labeling, enable them to rapidly obtain answers to questions for a range of drug products, and ultimately facilitate the development of a comprehensive repository for drug labeling. For example, FDA envisions that an electronic version of the new format will eventually enable health care practitioners to quickly access labeling information for all drugs in a pharmacologic or therapeutic class with a single electronic query.

FDA realizes that this final rule will affect the agency's existing electronic labeling requirements and guidances and will work to ensure consistency with the electronic labeling initiative.[3] The agency believes the electronic labeling initiative, in conjunction with this new format for labeling described in this final rule, could dramatically improve the way practitioners obtain information about prescription drugs and, as a consequence, significantly improve patient care.

VI. Comments on the Proposed Rule

The agency received 97 comments on the December 22, 2000, proposal. Comments were received from prescription drug manufacturers and related companies; trade organizations representing prescription drug manufacturers and other interested parties; professional associations and organizations representing health care practitioners; health care and consumer advocacy organizations; individual physicians, pharmacists, and consumers; and others.

A. General Comments on the Proposed Rule

Most comments expressed broad agreement that prescription drug labeling could be more effective in communicating drug information to health care practitioners and overwhelming support for the agency's goal of improving the content and format of prescription drug labeling to make information easier for health care practitioners to access, read, and use.

Many comments expressed approval of all the major features of the proposal, indicating that the proposed changes represent an important improvement in the organization, clarity, and overall usefulness of prescription drug labeling. For example, there was near universal support for the proposal to place at the front of labeling those sections that practitioners refer to most frequently and consider most important, although some comments recommended sequences slightly different from those proposed by FDA (see section VI.G of this document). There was also broad support for restructuring the old ''Precautions'' section into new sections devoted to use in specific populations, drug interactions, and patient counseling information and for combining the remainder of the ''Precautions'' section with the ''Warnings'' section.

Comments from manufacturers, while strongly supportive of the agency's efforts to improve the content and format of labeling, generally expressed concerns about some of the major elements of the proposal. In particular, as discussed in greater detail in sections VI.C and VI.D of this document, many manufacturers were concerned about the inclusion of Highlights. Manufacturers also expressed concern about the proposed requirements to re-evaluate, within 1 year of the effective

[3] See *http://www.fda.gov/cder/guidance/index.htm* under ''Electronic Submissions'' and *http://www.fda.gov/cber/guidelines.htm* for the most recent guidances on submission of labeling in an electronic format for drug and biological products, respectively.

date of the final rule, all prescription drug labeling to identify and remove any claims for indications and dosing regimens that are not supported by substantial evidence and to remove in vitro data that are not supported by clinical data.

Specific issues raised by the comments and the agency's responses follow.

B. Comments on the Process for Development of the Proposed Rule

As discussed in detail in the preamble to the proposed rule, FDA relied on focus group testing of physicians, a national physician survey, and a public meeting held in 1995 to develop the labeling prototype that was used as the basis for the proposal (65 FR 81082 at 81083 through 81085).

(Comment 1) Several comments questioned the process that FDA used to develop the proposed rule. A number of comments expressed concern that health care practitioners other than physicians were not surveyed or otherwise consulted. Two comments indicated that a majority of pharmacists refer to prescription drug labeling at least once a day. The comments cited a survey finding that the sections most frequently referred to by pharmacists are, in descending order, ''Dosage and Administration,'' ''Adverse Reactions,'' ''Contraindications,'' ''Indications and Usage,'' ''Warnings and Precautions,'' and ''How Supplied/Storage and Handling.'' The comments urged FDA to consult with all relevant audiences to revise prescription drug labeling and labels.

FDA recognizes the important roles that health care practitioners other than physicians play in the health care delivery system and recognizes that prescription drug information is relied upon by health care practitioners other than physicians. The agency focused its research efforts on how physicians use labeling, because they are the principal intended audience (i.e., they use labeling for prescribing decisions). The agency also sought input from all interested parties in the development of the proposed rule, especially those whose use of labeling could be expected to impact patient safety. Panelists and participants in the 1995 public meeting included nurse practitioners, pharmacists, and physician assistants. Their comments and observations directly contributed to refining the third version of FDA's prototype into the version that was the basis for the proposed rule. Moreover, the agency has carefully reviewed and considered all comments received on the proposed rule, which included comments from a broad range of health care practitioners that rely on prescription drug labeling, and has determined the optimal ordering for labeling sections, as reflected in this final rule.

FDA notes that the sections most commonly referred to by pharmacists in the cited survey are the same as those most commonly referred to by physicians, although in a somewhat different rank order. FDA believes that, although the rank order of the sections is not identical for the two groups, the formatting improvements required by this final rule make the information in these sections readily accessible to all health care practitioners who use prescription drug labeling.

C. Highlights of Prescribing Information—General Comments

FDA proposed to require that prescription drug labeling for products described in proposed § 201.56(b)(1) (i.e., new and more recently approved prescription drug products) contain introductory prescribing information entitled ''Highlights of Prescribing Information'' (proposed §§ 201.56(d) and 201.57(a)).

(Comment 2) Comments expressed different opinions about the utility and patient care implications of Highlights. Physicians, pharmacists, other health care practitioners, health care advocacy groups, and professional societies and organizations representing health care practitioners expressed unequivocal enthusiasm about and uniform support for Highlights. Manufacturers, with some exceptions, were opposed, or strongly opposed, to the inclusion of Highlights.

Comments supporting Highlights stated that it would be an excellent vehicle for drawing attention to the most important information about a product, a useful and convenient source for quick reminder information in routine prescribing situations, and a useful vehicle to efficiently direct practitioners to the more detailed information in the FPI. Several comments stated that Highlights is probably the most important innovation in the proposed rule. One comment stated that Highlights is the element of the proposal that will most enhance the clinical utility of prescription drug labeling. Several comments stated that by making prescription drug labeling easier to navigate, Highlights would help to make labeling easier for patients and health care practitioners to understand.

Several comments endorsed the Highlights format as a means of making labeling information more accessible. Some comments stated that the proposed format for Highlights is a good design because it makes use of multiple formats (e.g., text, tables, bulleted lists) and bolded headings, which make the labeling information more accessible. One comment noted that, because Highlights contains pointers to the location of more detailed information in the FPI, the pointers will increase the likelihood that health care practitioners will refer to the FPI. The comment also stated that the user-friendly Highlights format would be likely to increase the frequency with which health care practitioners consult the labeling for drug information and would enhance their ability to use the information.

Comments opposing inclusion of Highlights stated that manufacturers would be forced to pick certain important warnings listed in the FPI for inclusion in Highlights and, because of space limitations, exclude other important information. These comments maintained that, by extracting from the FPI only selected portions of the information needed for safe and effective use, Highlights would omit important information and lack detail and context, and might, therefore, be misleading. They contended that these shortcomings might outweigh any convenience derived from condensing information into Highlights. One comment maintained that the FPI is itself a condensation of a complex body of information and that it is problematic and illogical to try to further condense the information from the FPI into Highlights.

Several comments from manufacturers stated that the limited content of Highlights is of concern because practitioners would have a tendency to rely only on the information in Highlights when making prescribing decisions, even though that information alone would not be an adequate basis for making such decisions. Some of these comments maintained that there is a lack of evidence to support the premise that Highlights will facilitate practitioners' access to more detailed information in the FPI. They asserted that there is a high likelihood that Highlights would be the only part of the labeling read by practitioners.

Another comment stated that, rather than requiring inclusion of Highlights in labeling, the agency and manufacturers should work together to make the FPI better.

FDA has determined that the Highlights provisions of the final rule are an essential element of the agency's efforts to improve the accessibility, readability, and usefulness of information in prescription drug labeling and reduce the number of

adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information. By means of focus group testing, a nationwide physician survey, and a public meeting, the agency carefully evaluated the drug information needs of physicians and ways to best address those needs in prescription drug labeling. Some of the principal findings were that: (1) The relative importance of information in labeling varies, (2) physicians typically refer to labeling to answer a specific question, (3) physicians have considerable difficulty locating the information they need to make prescribing decisions, and (4) physicians strongly prefer to have a separate introductory summary of the most important information contained in the full prescribing information, located at the beginning of labeling, to make it easier to find the information necessary to prescribe the drug safely and effectively (65 FR 81082 at 81083 through 81085; see also Ref. 11). Many of the comments submitted in response to the proposed rule concur with these findings, particularly those from health care practitioners and their organizations.

This preference for highlighting the most important information that is part of a larger body of information is consistent with good risk communication practices and with well-established cognitive principles. The agency employed these principles in designing Highlights.

For example, cognitive research has shown that, because there is a limit to the amount of information that an individual can hold in memory at one time, individuals tend to organize similar information into ''chunks'' to: (1) Increase the amount of available space in memory and (2) facilitate retrieval of information (Refs. 1 through 3). ''Chunking'' complex information into smaller, more manageable units makes it easier to remember and process information efficiently and effectively (decreases ''cognitive load'').

FDA research conducted during development of new rules for OTC drug labeling demonstrated that ''chunking'' information in a standardized format with graphic emphasis on the most important information helped individuals make correct product use decisions, decreased reading time, and increased the individuals' confidence in their ability to use that information (Ref. 4). This research supports the approach adopted in this final rule for prescription drug labeling.

In designing Highlights, the agency employed established techniques to enhance effective communication of large amounts of complex information. Highlights summarizes the information from the FPI that is most important for prescribing the drug safely and effectively and organizes it into logical groups, or ''chunks,'' to enhance accessibility, retention, and access to the more detailed information. This design, combined with the use of multiple formats (e.g., tables, bulleted lists) and graphic emphasis (e.g., bolded text), improves visual and cognitive access to the information so that practitioners can more easily find information, and improves recall of the information.

Importantly, Highlights must include identifying numbers indicating where in the FPI to find details of the information that is cited or concisely summarized in Highlights. In the final rule, FDA has revised proposed § 201.57(a)(17) (§ 201.56(d)(3) in the final rule) to require that any information referenced in Highlights, not just subheadings, be accompanied by the identifying number corresponding to the location of the information in the FPI. The agency believes that these identifying numbers will facilitate access to the detailed information in the FPI.

The Highlights design—a broad array of important information in a discrete, visually accessible location—also increases the variety of information that a practitioner is exposed to in a typical labeling referral. That is, the Highlights design increases the likelihood that practitioners will be exposed to and retain critical information about a drug in addition to the information that the practitioner sought in referring to the labeling, such as the recommended dose. The practitioner therefore is likely to know more about a drug after exposure to labeling with Highlights than after exposure to labeling without Highlights. In addition, by making labeling easier to use and an overall better source of drug information, the Highlights design is likely to increase the frequency with which practitioners rely on labeling for prescription drug information. In a survey regarding labeling for vaccines, 71 percent of physicians surveyed indicated that they would increase their use of labeling if a summary of prescribing information were included in labeling (65 FR 81082 at 81084). Highlights should result in health care practitioners being better informed about prescription drugs. Therefore, the agency concludes that prescription drug labeling with Highlights more effectively communicates drug information to prescribers than labeling without Highlights.

(Comment 3) Some comments stated that FDA should do additional testing to determine whether Highlights is necessary to accomplish FDA's goal of making information in prescription drug labeling more useful and accessible or whether the other proposed format changes, without Highlights (i.e., an index, reordering of the sections of the FPI, and enhanced formatting) would be adequate to accomplish the agency's goal. One comment requested that FDA evaluate whether simply reordering the sections of the prescribing information would be adequate to accomplish the agency's goal. Some comments stated that the agency should test whether the proposed format would change prescriber behavior as intended and lead to a reduction in medication errors.

The agency believes it is unnecessary to compare the prototype labeling with Highlights to the prototype labeling without Highlights (i.e., a version with a table of contents, reordered sections in the FPI, and enhanced graphics, or a version with only reordered sections and enhanced graphics). The requirements of this final rule are built on extensive testing conducted by FDA, established principles of cognitive processing, previous research conducted by FDA for OTC drug labeling, and evaluation of comments submitted in response to this proposal. FDA has determined that Highlights, because it will efficiently and effectively convey information about a drug product and will help to facilitate the transition to electronic labeling, is a vital component of the efforts to reduce the numbers of adverse reactions from medication errors due to misunderstood or incorrectly applied drug information.

(Comment 4) In the proposed rule, FDA specifically sought comment on whether, and under what circumstances, it might be inappropriate to include the proposed Highlights in the labeling of a particular drug or drug class.

The vast majority of comments supported Highlights for all products or no products. One comment stated that if the agency retains the requirement to include Highlights, all products required to have the new format should be required to have Highlights. One comment stated it would not be useful to include Highlights if the entire labeling is very short (e.g., one page).

The agency concludes that there should be no exceptions to the Highlights requirement for drugs subject to the new content and format requirements at §§ 201.56(d) and 201.57. The agency acknowledges that prescription drug labeling for some drugs may be very short and that this

may result in short Highlights. However, as discussed previously, the agency has determined that Highlights improves the usefulness, readability, and accessibility of information in prescription drug labeling and is consistent with good risk communication practices.

(Comment 5) Several comments stated that there should be more specific criteria for selecting information for inclusion in Highlights to ensure consistency for all drug products. These comments stated that, without specific criteria, the information in Highlights for different drugs within the same drug class may be different, and these differences could be used to the competitive advantage or disadvantage of some products. Some comments stated that the agency should designate the precise information that must be included in Highlights. One comment said that, for products with class labeling, FDA must designate which class labeling statements must be included in Highlights to ensure consistency among drugs in the class. Another comment stated that the relative importance of drug information, and, as a result, the basis for selecting information for inclusion in the section, can vary depending on a drug's indication. The comment maintained that Highlights would have to provide for differences in safety profiles for drugs with multiple indications and those that are used in different populations.

The agency believes that these concerns are not unique to Highlights. The agency agrees that, for a given drug, if there are significant differences in safety profiles or dosing considerations for different indications or populations, Highlights must reflect these differences. The agency also agrees that it is critical to ensure accuracy and consistency in the information included in Highlights because it contains a summary of the most important information for prescribing the drug safely and effectively.

In general, however, the agency believes that it would not be appropriate, or possible, to specify in the final rule the precise content of Highlights. Judgment will continue to be necessary to determine what information from the broad range of information necessary for the safe and effective use of the prescription drug appearing in the FPI must also appear in Highlights (e.g., differences in safety profiles or dosing considerations for differing indications or populations). However, because Highlights is a summary of the most important information for prescribing decisions and some comments expressed concerns about the difficulty involved in summarizing the complex and often lengthy information in the FPI (see e.g., comments 16, 23 and 27), the agency believes that it is essential for FDA to review and approve most proposed changes to the information in Highlights. Accordingly, the agency is revising its regulations on supplements and other changes to an approved application. Under §§ 314.70(b)(2)(v)(C) and (c)(6)(iii), and 601.12(f)(1) and (f)(2)(i), applicants are required to obtain prior approval of any labeling changes to Highlights, except for editorial or similar minor changes, including removal of a listed section(s) from ''Recent Major Changes'' or a change to the most recent revision date of the labeling. Sections 314.70(d)(2)(x) and 601.12(f)(3)(i)(D) allow these editorial and similar minor changes in the labeling to be reported in an annual report.

In addition, as noted, the agency is making available guidance to assist manufacturers and FDA reviewers in developing prescription drug labeling. This guidance addresses, among other things, how to select information for inclusion in Highlights (section IV of this document).

In some instances, a statement for a drug or class of drugs is currently required by regulation to be included in a specific section of prescription drug labeling (e.g., § 201.21). In these cases, when converting labeling to the new format, the statements must be included in the corresponding section in the new format (e.g., a statement required to be included in the ''Boxed Warning'' section in the old format must be included in the ''Boxed Warning'' section in the new format). However, some statements are currently required to be included in labeling sections that have been altered or eliminated by this final rule. In these instances, the statements must be located in the FPI as outlined in table 6.

TABLE 6.—LOCATION OF STATEMENTS REQUIRED TO BE INCLUDED IN LABELING

Location—Old Format	Location—New Format
Warnings	Warnings and Precautions
Precautions (General)	Warnings and Precautions
Precautions (Drug interactions)	Drug Interactions
Precautions (Specific Populations)	Use in Specific Populations
Precautions (Information for patients)	Patient Counseling Information
How Supplied (or after How Supplied)	How Supplied/Storage and Handling

Where statements are required in labeling but not in a specific labeling section, the agency may specify the location in the FPI for the statements for the drug or class of drugs to ensure consistency within drug classes. Whether a specific statement required by regulation must appear in Highlights will be determined by the agency.

(Comment 6) Several comments stated that Highlights should mention the drug's therapeutic or pharmacologic class. They maintained that this information is informative to practitioners when the drug is a member of an established class because it puts the drug in a context with other therapies and helps prevent duplicative therapy.

The agency agrees that information about a drug's therapeutic or pharmacologic class is important and appropriate for inclusion in Highlights. If a drug is a member of an established therapeutic or pharmacologic class, the identity of that class can provide a practitioner with important information about what to expect from that product and how it relates to other therapeutic options. The agency also agrees with the comment that making the identity of a drug's class more prominent could reduce the likelihood of prescribers placing a patient on more than one therapy within the same class when such use would not be appropriate.

The agency believes that information about drug class is an important supplement to the information contained in a drug's ''Indications and Usage'' section and should be placed under that heading in Highlights. Accordingly, the agency has revised proposed § 201.57(a)(6) to require that when a drug is a member of an established pharmacologic class, the class must be identified in the ''Indications and Usage'' section in Highlights.

(Comment 7) One comment stated that Highlights should also include information about managing drug

overdose (recommended a new section entitled ''Toxicity and Overdose'') and characteristics by which a tablet can be identified (color, markings, shape, etc.).

The agency acknowledges the importance of information about managing drug overdose and characteristics by which a tablet can be identified and took care to make this information prominent in the FPI. However, space for Highlights is limited and the agency has made judgments about which information is most important for safe and effective use and thus must appear in Highlights. The agency has concluded that information about managing overdose or product identification characteristics (except scoring) will not be required in Highlights. The agency has retained scoring in Highlights because this information is needed to appropriately tailor a dose for some patients (e.g., a patient is unable to take two tablets of a drug because of a particular side effect, but is able to take one-and-one-half tablets).

(Comment 8) One comment stated that the information presented in Highlights should be in bulleted format to the extent possible to avoid redundancy with the information in the FPI.

FDA agrees that information presented in Highlights, not otherwise required to be bulleted under § 201.57(d)(4), should be succinctly summarized and in a format (e.g., bulleted) that calls attention, and provides easy access, to the more detailed information in the FPI. Highlights is not a verbatim repetition of selected information contained in the FPI.

(Comment 9) One comment requested that the sections in Highlights be reordered to lend more prominence to risk information. The comment stated that all risk information, including contraindications and drug interactions, should be placed before the ''Dosage and Administration'' and ''How Supplied'' sections.

The order of the sections in Highlights tracks the order of the corresponding sections in the FPI. The agency believes the order of information in Highlights must be consistent with the FPI so that practitioners can efficiently navigate from Highlights to the corresponding section of the FPI. As discussed in more detail in the preamble to the proposed rule (65 FR 81082 at 81084), the revised order of the sections in the FPI was based on extensive focus group testing and surveys of physicians to determine which sections they believe are most important to prescribing decisions and which sections they reference most frequently.

The agency believes that the order of information in Highlights required by the final rule gives sufficient prominence to risk information. The agency also believes that the formatting requirements, the one-half page length restriction for Highlights (excluding space for a boxed warning, if one is required) (§ 201.57(d)(8)), and the limitations on the amount of information that can be included in Highlights will ensure that all the information in Highlights has adequate prominence and is visually accessible.

(Comment 10) One comment expressed concern about the implications of Highlights for FDA's initiative to improve pregnancy labeling. The comment stated that the preliminary format FDA has discussed in public meetings (which would replace the pregnancy category designations) could not be readily condensed into an informative single sentence in Highlights. The comment suggested that electronic labeling could potentially solve this problem by linking to additional information about prescribing in specific patient populations and by linking to pregnancy registry databases and tertiary specialty texts as well.

The agency anticipates that the planned revisions to the requirements for the ''Pregnancy'' subsection of labeling are unlikely to affect the information in Highlights about use of drugs during pregnancy. The agency agrees that the electronic labeling initiative holds great promise for providing rapid access to related information of varying levels of complexity and detail, including information about drug exposure during pregnancy.

(Comment 11) Several comments recommended that there be an educational campaign in conjunction with the publication of the final rule to ensure that practitioners understand that Highlights contains only limited information and should not be relied on without reference to the FPI.

The agency agrees that there should be, and it plans to initiate, an educational campaign to familiarize health care practitioners with the new labeling format. The agency also agrees that an important component of the educational message should be that Highlights alone does not contain all the information FDA has determined is needed to use a drug safely and effectively.

D. Comments on Product Liability Implications of the Proposed Rule

In the proposal, FDA requested comments on the product liability implications of revising the labeling for prescription drugs.

(Comment 12) In comments, some manufacturers expressed concerns that, by highlighting selected information from the FPI to the exclusion of information not highlighted, they make themselves more vulnerable to product liability claims. Some of these comments also stated that the Highlights limitation statement, which states that Highlights does not contain all the information needed to prescribe a drug safely and effectively and that practitioners should also refer to the FPI, would not constitute an adequate legal defense in a case alleging failure to provide adequate warning of a drug's risks.

Based on the agency's research and analysis in developing the prototype labeling that was the basis for the proposed rule (see comment 2), the agency has concluded that a labeling format that includes Highlights is more effective than a format that omits Highlights. In response to the comments and as discussed in the response to comment 35, FDA has taken steps to enhance the prominence of the Highlights limitation statement. FDA believes the statement will be effective in reminding prescribers that the information in the Highlights should not be relied on exclusively in making prescribing decisions and that it is important to consult the more detailed information in the FPI. We also believe that this limitation statement will help to ensure that the labeling will be considered in its entirety in any product liability action. FDA acknowledges the comment's concerns and, as discussed more fully in response to comment 13, believes that under existing preemption principles such product liability claims would be preempted.

(Comment 13) Some comments stated that the new format requirements might have product liability implications for drugs that are not subject to the new requirements. These comments expressed concern that labeling in the old format might be characterized by plaintiffs as inferior to labeling in the new format and, as a result, could be used as evidence that a manufacturer did not provide adequate warnings. They requested that the agency state in the final rule that FDA approval of labeling, whether it be in the old or new format, preempts conflicting or contrary State law, regulations, or decisions of a

court of law for purposes of product liability litigation.

FDA believes that under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law. Indeed, the Department of Justice (DOJ), on behalf of FDA, has filed a number of amicus briefs making this very point. In order to more fully address the comments expressing concern about the product liability implications of revising the labeling for prescription drugs, we believe it would be useful to set forth in some detail the arguments made in those amicus briefs. The discussion that follows, therefore, represents the government's long standing views on preemption, with a particular emphasis on how that doctrine applies to State laws that would require labeling that conflicts with or is contrary to FDA-approved labeling.

Under the act, FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading. Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (21 U.S.C. 355(d)). FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to the use of the product in day-to-day clinical practice, such as the nature of the disease or condition for which the product will be indicated, and the need for risk management measures to help assure in clinical practice that the product maintains its favorable benefit-risk balance. The centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate.

Changes to labeling typically are initiated by the sponsor, subject to FDA review, but are sometimes initiated by FDA. Under FDA regulations, to change labeling (except for editorial and other minor revisions), the sponsor must submit a supplemental application fully explaining the basis for the change (§§ 314.70 and 601.12(f) (21 CFR 314.70 and 601.12(f))). FDA permits two kinds of labeling supplements: (1) Prior approval supplements, which require FDA approval before a change is made (§§ 314.70(b) and 601.12(f)(1)); and (2) ''changes being effected'' (CBE) supplements, which may be implemented before FDA approval, but after FDA notification (§§ 314.70(c) and 601.12(f)(2)). While a sponsor is permitted to add risk information to the FPI without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading under section 502(a) of the act (21 U.S.C. 352). Thus, in practice, manufacturers typically consult with FDA prior to adding risk information to labeling. As noted in response to comment 5, however, a sponsor may not use a CBE supplement to make most changes to Highlights.

Since the proposed rule was published, FDA has learned of several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act. In one case, for example, an individual plaintiff claimed that a drug manufacturer had a duty under California State law to label its products with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated.[4] In some of these cases, the court determined that the State law claim could not proceed, on the ground that the claim was preempted by Federal law,[5] or was not properly before the court by operation of the doctrine of primary jurisdiction.[6] In some cases, however, the court has permitted the claim to proceed.[7]

State law actions can rely on and propagate interpretations of the act and FDA regulations that conflict with the agency's own interpretations and frustrate the agency's implementation of its statutory mandate. For example, courts have rejected preemption in State law failure-to-warn cases on the ground that a manufacturer has latitude under FDA regulations to revise labeling by adding or strengthening warning statements without first obtaining permission from FDA. (*See, e.g., Eve* v. *Sandoz Pharm. Corp.*, 2002 U.S. Dist. LEXIS 23965 (S.D. In. Jan. 28, 2002); *Ohler* v. *Purdue Pharma, L.P.*, 2002 U.S. Dist. LEXIS 2368 (E.D. La. Jan. 22, 2002); *Motus* v. *Pfizer Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000); *Bansemer* v. *Smith Labs., Inc.*, 1988 U.S. Dist. LEXIS 16208 (E.D. Wis. Sept. 12, 1988); *McEwen* v. *Ortho Pharm Corp.*, 528 P.2d 522 (Ore. 1974).) In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act. A manufacturer may, under FDA regulations, strengthen a labeling warning, but in practice manufacturers typically consult with FDA before doing so to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to enforcement action).

Another misunderstanding of the act encouraged by State law actions is that FDA labeling requirements represent a minimum safety standard. According to many courts, State law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act. (*See, e.g., Brochu* v. *Ortho Pharm. Corp.*, 642 F.2d 652 (1st Cir. 1981); *Salmon* v. *Parke-Davis and Co.*, 520 F.2d 1359 (4th Cir. 1975); *Caraker* v. *Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill.

[4] *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).

[5] *E.g., Ehlis* v. *Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002), *aff'd on other grounds*, 367 F.3d 1013 (8th Cir. 2004).

[6] *E.g., Bernhardt* v. *Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963 (S.D.N.Y. Nov. 16, 2000). This doctrine allows a court to refer a matter to an administrative agency for an initial determination where the matter involves technical questions of fact and policy within the agency's jurisdiction. If a court finds that the agency has primary jurisdiction, the court stays the matter and instructs the plaintiff to initiate an action with the agency. *See, e.g., Israel* v. *Baxter Labs., Inc.*, 466 F.2d 272, 283 (D.C. Cir. 1972); see also 21 CFR 10.60.

[7] *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), *reversed*, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004); *Bernhardt* v. *Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963 (S.D.N.Y. November 16, 2000); *Motus* v. *Pfizer, Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000), summary judgment granted, 196 F. Supp. 2d 984, 986 (C.D. Cal. 2001), aff'd, 2004 U.S. App. LEXIS 1944 (9th Cir. February 9, 2004); *In re Paxil Litigation*, 2002 U.S. Dist. LEXIS 16221 (C.D. Cal. August 16, 2002), transferred, 296 F. Supp. 2d 1374 (J.P.M.L. 2003).

2001); *Mazur* v. *Merck & Co., Inc.*, 742 F. Supp. 239 (E.D. Pa. 1990); *In re Tetracycline Cases*, 747 F. Supp. 543 (W.D. Mo. 1989).) In fact, FDA interprets the act to establish both a ''floor'' and a ''ceiling,'' such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading. Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.

State law requirements can undermine safe and effective use in other ways. In the preamble accompanying the proposal, FDA noted that liability concerns were creating pressure on manufacturers to expand labeling warnings to include speculative risks and, thus, to limit physician appreciation of potentially far more significant contraindications and side effects (65 FR 81082 at 81083). FDA has previously found that labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to ''lose its significance'' (44 FR 37434 at 37447, June 26, 1979). Overwarning, just like underwarning, can similarly have a negative effect on patient safety and public health. (See section X of this document.) Similarly, State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the act. (*See, e.g., Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002) (allowing to proceed a lawsuit involving a California State law requiring warnings in the labeling of nicotine replacement therapy products that FDA had specifically found would misbrand the products under the act), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).)

State law actions also threaten FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs. State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA—sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief—including the threat of significant damage awards or penalties—that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose ''defensive labeling'' to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

FDA has previously preempted State law requirements relating to drugs in rulemaking proceedings. For example:

- In 1982, FDA issued regulations requiring tamper-resistant packaging for OTC drugs. In the preamble accompanying the regulations, FDA stated its intention that the regulations preempt any State or local requirements that were ''not identical to * * * [the rule] in all respects'' (47 FR 50442 at 50447, November 5, 1982).
- In 1986, FDA issued regulations requiring aspirin manufacturers to include in labeling a warning against use in treating chicken pox or flu symptoms in children due to the risk of Reye's Syndrome. In the accompanying preamble, FDA said the regulations preempted ''State and local packaging requirements that are not identical to it with respect to OTC aspirin-containing products for human use'' (51 FR 8180 at 8181, March 7, 1986).
- In 1994, FDA amended 21 CFR 20.63 to preempt State requirements for the disclosure of adverse event-related information treated as confidential under FDA regulations (59 FR 3944, January 27, 1994). (See also 47 FR 54750, December 3, 1982) (''FDA believes that differing State OTC drug pregnancy-nursing warning requirements would prevent accomplishment of the full purpose and objectives of the agency in issuing the regulation and that, under the doctrine of implied preemption, these State requirements are preempted by the regulation as a matter of law.'')

As noted previously, DOJ has made submissions to courts in a number of cases in which private litigants asserted a State law basis for challenging the adequacy of risk information provided by manufacturers for drugs in accordance with FDA requirements under the act. In each case, DOJ argued that the doctrine of preemption precluded the plaintiff's claim from proceeding.[8] The practice of addressing conflicting State requirements through participation in litigation (including product liability cases) in which the Government is not a party is not new. For example, DOJ participated on FDA's behalf in favor of pre-emption in *Jones* v. *Rath Packing Company*, 430 U.S. 519 (1977), *Grocery Manufacturers of America, Inc.* v. *Gerace*, 755 F.2d 993 (2d Cir. 1985), *Eli Lilly & Co., Inc.* v. *Marshall*, 850 S.W.2d 155 (Tex. 1993), and *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 352–53 (2001). FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated. In such cases, including the statement in labeling or advertising would render the drug misbranded under the act (21 U.S.C. 352(a) and (f)). The agency believes that State law conflicts with and stands as an obstacle to achievement of the full objectives and purposes of Federal law if it purports to preclude a firm from including in labeling or advertising a statement that is included in prescription drug labeling. By complying with the State law in such a case and removing the statement from labeling, the firm would be omitting a statement required under § 201.100(c)(1) as a condition on the exemption from the requirement of adequate directions for use, and the omission would misbrand the drug under 21 U.S.C. 352(f)(1). The drug might also be misbranded on the ground that the omission is material within the meaning of 21 U.S.C. 321(n) and makes the labeling or advertising misleading under 21 U.S.C. 352(a) or (n).

Consistent with its court submissions and existing preemption principles, FDA believes that at least the following

[8] The DOJ submissions in these cases relied on the doctrine of implied preemption or primary jurisdiction. Although the act itself contains no general express pre-emption provision for drugs, a provision of legislation amending the drug provisions addresses the relationship of the legislation to State law. Section 202 of the Drug Amendments of 1962 (Public Law 87-781, Title II, section 202, 76 Stat. 793 (October 10, 1962)) provides: ''Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.'' The existence of a legislative provision addressing pre-emption does not bar the operation of ordinary principles of implied preemption (*Geier* v. *American Honda Motor Co., Inc.*, 529 U.S. 861, 869 (2000)).

claims would be preempted by its regulation of prescription drug labeling: (1) Claims that a drug sponsor breached an obligation to warn by failing to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling; (2) claims that a drug sponsor breached an obligation to warn by failing to include in an advertisement any information the substance of which appears anywhere in the labeling, in those cases where a drug's sponsor has used Highlights consistently with FDA draft guidance regarding the ''brief summary'' in direct-to-consumer advertising (''Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements,'' 69 FR 6308 (February 2004)) (see comment 112); (3) claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that meets the standards set forth in this rule, including § 201.57(c)(5) (requiring that contraindications reflect ''[k]nown hazards and not theoretical possibilities'') and (c)(7); (4) claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn (unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning before plaintiff claims the sponsor had the obligation to warn); (5) claims that a drug sponsor breached an obligation to warn by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising; and (6) claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label (unless FDA has made a finding that the sponsor withheld material information relating to the statement). Preemption would include not only claims against manufacturers as described above, but also against health care practitioners for claims related to dissemination of risk information to patients beyond what is included in the labeling. (See, e.g., *Bowman* v. *Songer*, 820 P.2d 1110 (Col. 1991).)

FDA recognizes that FDA's regulation of drug labeling will not preempt all State law actions. The Supreme Court has held that certain State law requirements that parallel FDA requirements may not be preempted (*Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 495 (1996) (holding that the presence of a State law damages remedy for violations of FDA requirements does not impose an additional requirement upon medical device manufacturers but ''merely provides another reason for manufacturers to comply with * * * federal law''); id. at 513 (O'Connor, J., concurring in part and dissenting in part); id)). *But see Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 352–53 (2001) (holding that ''fraud on the FDA'' claims are preempted by Federal law); 21 U.S.C. 337(a) (restricting the act enforcement to suits by the United States); *In re Orthopedic Bone Screw Prods. Liability Litig.*, 159 F.3d 817, 824 (3d Cir. 1998) (''Congress has not created an express or implied private cause of action for violations of the FDCA or the MDA [Medical Device Amendments]'').

E. Highlights—Comments on Specific Provisions

The agency received comments on the following provisions of the proposed rule relating to the content of Highlights:

- *Drug names, dosage form, route of administration, and controlled substance symbol (proposed § 201.57(a)(1))*

In proposed § 201.57(a)(1), FDA specified the information concerning the identity of the product that would be included at the beginning of Highlights.

(Comment 14) One comment recommended that this information be moved above the title ''Highlights of Prescribing Information'' in Highlights.

The agency does not agree that the information required by § 201.57(a)(1) should be placed above the title ''Highlights of Prescribing Information.'' The agency believes that the title of each of the three major portions of prescription drug labeling (''Highlights of Prescribing Information,'' ''Full Prescribing Information: Contents,'' and ''Full Prescribing Information'') should be placed at the beginning of the corresponding information so that the title is readily apparent to users.

- *Inverted black triangle (proposed § 201.57(a)(2))*

FDA proposed to require that products that contain a new molecular entity, new biological product, or new combination of active ingredients have in their labeling an inverted black triangle to indicate that the drug or drug combination had been approved in the United States for less than 3 years (proposed § 201.57(a)(2)). This proposal also applied to marketed products approved for a new indication, for use by a new route of administration, or with a novel drug delivery system.

(Comment 15) Several comments opposed, or expressed reservations about, the use of an inverted black triangle to identify a product, indication, or dosage form that has been approved for less than 3 years. There were concerns that the symbol is not universally understood and could therefore be confusing to practitioners. One comment stated that use of icons to convey public health information has historically been unsuccessful. Some of the comments stated that if the inverted black triangle were retained, the agency would need to conduct an extensive educational campaign to educate practitioners about its meaning and purpose. Some comments also expressed the concern that labeling containing the symbol could be in circulation much longer than 3 years after approval, which would undermine the significance of the symbol. One comment stated that the symbol implies, without basis, that newer drugs are inherently less safe than older drugs. Some comments stated that the criteria for when a new indication would extend the time for which a product must have the inverted black triangle are not clear.

Two comments stated that a bold approval date might be more informative than the inverted black triangle. Another comment recommended using the designation ''New-Rx'' to identify a product that has been approved for less than 3 years.

Other comments expressed strong support for the inverted black triangle as a mechanism to prompt practitioners to more carefully scrutinize the labeling of newer products and more diligently report adverse events. The comments maintained that use of the inverted black triangle could lead to earlier detection of rare, serious adverse reactions and, thus, could potentially save lives. One comment suggested extending the time that the inverted black triangle would be required to 5 years.

The agency has reconsidered its proposal to require use of the inverted black triangle to identify products that have been marketed for less than 3 years. The agency continues to believe strongly in the goals of the inverted black triangle—to help ensure that prescribers use a product with particular care during its initial years of marketing and to make prescribers more diligent in reporting suspected adverse reactions for newer products. However, the agency agrees with comments that, in prescription drug labeling, the inverted black triangle is not universally

understood, could be confusing to the prescriber (even with a concerted educational effort) and therefore may not serve its intended purpose. The agency acknowledges that the recommended ''New-Rx'' designation may be more informative than the inverted black triangle, but is concerned that the ''New-Rx'' designation might also be confusing because practitioners are not familiar with it.

The agency agrees with comments that use of the initial date of approval in the United States would be a better mechanism than the inverted black triangle to call attention to the relative newness of a product. Therefore, the final rule requires that Highlights include the year in which a drug was initially approved in the United States. Highlights must contain the phrase ''Initial U.S. Approval'' followed by the four-digit year of initial approval in bold face type (§ 201.57(a)(3) and (d)(5)). Because this statement takes up more space than the proposed inverted black triangle, the final rule requires that the statement be placed on its own line directly below the established name of the product (proper name of the product for biological products) rather than on the same line as the proprietary name (§ 201.57(a)(3)).

In contrast to the proposed rule, the final rule does not require identification of the initial date of U.S. approval of a new indication for a new population, new route of administration, or novel delivery system. The agency agrees with comments that expressed concerns that also requiring the inverted black triangle for new indications, routes of administration, and novel delivery systems could diminish the significance of the inverted black triangle and could be confusing to practitioners. Similarly, the agency believes that referring to multiple dates, including the date of initial approval of a new indication, new route of administration, or a novel delivery system for a drug would be confusing and would diminish the significance of these references. The agency is, therefore, limiting identification of the initial date of U.S. approval to new molecular entities, new biological products, or new combinations of active ingredients because this is sufficient to accomplish the goals of increasing prescriber vigilance and reporting of suspected adverse reactions when using newer products.

The agency believes the date of initial U.S. approval will continue to be informative throughout a product's life cycle. Although the agency does not subscribe to the view that newer drugs are inherently less safe, it does believe that alerting a practitioner to the fact that a drug has been marketed for an extended period could provide some added assurance about the drug's safety margin based on cumulative, safe experience with the product. Therefore, the requirement to include the initial date of U.S. approval in Highlights will not lapse 3 years after approval of the product for marketing.

• *Boxed warnings or contraindications (proposed § 201.57(a)(4))*

FDA proposed to require that the full text of boxed warning(s) or contraindication(s) required by proposed § 201.57(c)(1) be included in Highlights unless the boxed warning was longer than 20 lines, in which case a summary of the contents of the boxed warning would be required (proposed § 201.57(a)(4)). The agency specifically sought comment on whether the full text of a boxed warning should be included in Highlights, regardless of length.

(Comment 16) Some comments supported the proposed 20-line limitation on the length of a boxed warning in Highlights. Other comments recommended that the boxed warning in Highlights always be a summarized version of the boxed warning in the FPI. Others expressed concern that summarizing boxed warnings might result in the omission of key information or lead to misinterpretations of the warning. They stated that the boxed warning is already succinct and the language is carefully negotiated with FDA and, therefore, that the boxed warning should always be included in its entirety in Highlights.

The agency has retained the 20-line length limitation on boxed warnings in Highlights. The agency believes that 20 lines is sufficient space to alert practitioners to the critical risk information contained in a boxed warning and to refer them to more detailed information in the FPI (complete boxed warning and other sections in the FPI).

The agency agrees with the comments that stated that manufacturers should always be required to present summarized boxed warning information in Highlights. The agency has determined that information from boxed warnings can readily be condensed without omitting critical risk information. The agency believes a summarized boxed warning in Highlights, with references to more detailed information in the FPI, is the most effective way to communicate critical risk information to practitioners. The agency has revised proposed § 201.57(a)(4) to require that boxed warnings be summarized concisely in Highlights.

(Comment 17) Several comments stated that inclusion of the full boxed warning in Highlights and in the FPI was needlessly duplicative and recommended that the boxed warning be included in only one location. One comment maintained the boxed warning should appear only in the ''Warnings and Precautions'' section in the FPI.

As discussed in the response to the previous comment, the boxed warning in Highlights is required to be a summary of the complete boxed warning in the FPI. Thus, the boxed warning in Highlights will not duplicate the boxed warning in the FPI. The agency believes that a summarized boxed warning must be included in Highlights to ensure that practitioners are exposed to critical information at the beginning of prescription drug labeling and that the complete boxed warning is needed to expand on the summary in Highlights.

The agency does not agree that the complete boxed warning in the FPI should be placed in the ''Warnings and Precautions'' section rather than at the beginning of the FPI. Placement of the complete boxed warning at the beginning of the FPI, where it can be easily located, is consistent with good risk communication practices, as well as health care practitioner preferences articulated in public comments and FDA's physician surveys and focus group research.

• *Recent labeling changes (proposed § 201.57(a)(5))*

FDA proposed to require in Highlights a heading entitled ''Recent Labeling Changes'' that identifies the sections in the FPI that contain recent FDA-approved or authorized substantive labeling changes (proposed § 201.57(a)(5)).

(Comment 18) In general, comments supported the addition of a ''Recent Labeling Changes'' heading to labeling and many comments thought the information would be very useful to practitioners. However, one comment recommended that the proposed heading ''Recent Labeling Changes'' be changed to ''Sections Revised'' to accommodate changes that, although no longer truly recent, would be important to call to the attention of practitioners for an extended period of time (e.g., through multiple labeling revisions). Another comment recommended that the heading be changed to ''Last Labeling Revisions'' to accommodate changes that could no longer reasonably be considered recent (e.g., a situation in which years elapse between labeling changes).

The agency agrees that the proposed heading should be changed to better reflect the function of including the information. Thus, the final rule requires the heading ''Recent Major Changes'' (§ 201.57(a)(5)). FDA believes that it is important to characterize the changes listed under the heading as both ''recent'' and ''major'' to draw attention to the relative newness of the changes and to let practitioners know that identified changes are significant to clinical use of the drug (i.e., substantive), and not merely editorial.

(Comment 19) In the proposal, the agency specifically sought comment on whether there should be a time limit by which information under the proposed heading (now ''Recent Major Changes'') must be removed. Some comments supported a 1-year time limit for inclusion of information under the proposed heading. Other comments stated that there should be no fixed time limit for removal of information identified as a recent labeling change. These comments expressed concern that requiring labeling to be revised for the sole purpose of removing information from under the heading would lead to unnecessary expense, and that such information be removed at the next substantive labeling revision. Other comments stated that no time limit should be imposed for removal, but that removal should occur at the first convenient opportunity after 1 year from the date of the labeling change. Another comment stated that information should remain under the ''Recent Major Changes'' heading for 1 to 3 years after the change to keep practitioners up-to-date on labeling changes.

The agency agrees that, although there should not be a rigid time limit for removal of information from ''Recent Major Changes,'' the information should not remain in Highlights indefinitely. The purpose of the heading is to alert practitioners to recent substantive labeling changes. The agency is concerned that the information might be ignored by practitioners if it often identifies changes that are no longer recent. The agency will, therefore, require that labeling changes identified under this heading be deleted at the first reprinting of the labeling after the change has been in labeling for 1 year. This requirement should ensure that labeling changes identified under the ''Recent Major Changes'' heading are current without imposing unnecessary costs on industry by requiring labeling revisions solely for the purpose of removing the information.

(Comment 20) Because there could be multiple changes to labeling in a calendar year, some comments recommended that each change appearing under ''Recent Major Changes'' be dated in a month/year format so that practitioners can readily identify the most recent changes.

The agency agrees that it would be useful to date the labeling changes identified under this heading. The agency has, therefore, revised proposed § 201.57(a)(5) to require that sections of prescription drug labeling listed under ''Recent Major Changes'' be followed by the month and year in which the change was incorporated in the labeling.

(Comment 21) One comment recommended that the rule specify that changes should be listed chronologically beginning with most recent.

The agency does not agree. Where there are multiple recent changes and those changes appear in more than one section, to avoid confusion, the order in which the sections are listed under ''Recent Major Changes'' should be consistent with the order of the sections in the FPI. FDA has revised proposed § 201.57(a)(5) accordingly.

(Comment 22) Some comments requested that the agency clarify how it will determine whether a labeling change is substantive and thus required to be included under ''Recent Major Changes.''

The agency recognizes that a product may have a large number of labeling changes ranging from inclusion of very important new risk information to typographical or editorial changes. Identifying all these changes under ''Recent Major Changes'' would obscure the most significant changes and would not be informative for practitioners. Therefore, the agency has revised proposed § 201.57(a)(5) to require that only substantive labeling changes in the ''Boxed Warning,'' ''Indications and Usage,'' ''Dosage and Administration,'' ''Contraindications,'' and ''Warnings and Precautions'' sections be included under ''Recent Major Changes.'' These would include only those changes that are significant to the clinical use of the drug and, therefore, have significant clinical implications for practitioners (i.e., substantive changes). Thus, ''Recent Major Changes'' would not include any changes in the sections subject to this requirement that are typographical or editorial.

• *Indications and usage (proposed § 201.57(a)(6))*

FDA proposed to require that Highlights include an ''Indications and Usage'' heading that contains a concise statement of each of the product's indications, as specified in proposed § 201.57(c)(2), with any appropriate subheadings (proposed § 201.57(a)(6)). This information would include major limitations of use (e.g., particular subsets of the populations, second line therapy status). The agency specifically sought comment on whether the information required under the ''Indications and Usage'' heading of Highlights should be presented verbatim from the FPI or summarized in a bulleted format.

(Comment 23) Several comments stated that it was important to reproduce the ''Indications and Usage'' section verbatim to prevent confusion or misinterpretations. Other comments maintained that there should be flexibility to reproduce the information in the ''Indications and Usage'' section verbatim or summarize it in a bulleted format, depending on factors such as the amount of information in the ''Indications and Usage'' section and whether the information can be summarized and still effectively communicate what a practitioner should know about a drug's indications. Other comments recommended that there be bulleted summaries of the indications in all cases. One of these comments suggested that each bullet be preceded by an index number that corresponds with the index number of the full description of the indication in the FPI.

The agency has determined that the amount of information that must be included in Highlights from the ''Indications and Usage'' section of the FPI will vary. In most cases, the ''Indications and Usage'' section can be readily condensed (e.g., bulleted format) to provide prescribers with an accurate and informative summary, even if there is space available in Highlights to reproduce the ''Indications and Usage'' section from the FPI in its entirety (i.e., the one-half page limit requirement would not be exceeded).

The agency recognizes that for some products with many indications, it may not be possible to limit Highlights to one-half page in length (§ 201.57(d)(8)), even using a summarized version of the ''Indications and Usage'' section. In such cases, FDA may waive the one-half page requirement and approve the labeling with slightly longer Highlights (see comment 104).

• *Dosage and administration (proposed § 201.57(a)(7))*

FDA proposed that Highlights include, under a ''Dosage and Administration'' heading, the most important information in the ''Dosage and Administration'' section of the FPI (proposed § 201.57(a)(7)).

(Comment 24) One comment recommended that ''Dosage and Administration'' in Highlights include,

in addition to the usual recommended doses, a range of doses known to be effective, and in particular, doses lower than the usual recommended doses. The comment stated that 76.2 percent of all adverse reactions are dose-related and many patients respond to lower doses than those recommended in labeling. Therefore, the comment suggested, lower doses may prevent adverse reactions.

FDA agrees that it is important to include in labeling the full range of doses that FDA has concluded are effective. The agency has revised proposed § 201.57(a)(7) to clarify the range of doses to be included under the ''Dosage and Administration'' heading in Highlights.

(Comment 25) Several comments supported tabular presentation of dosage and administration information in Highlights. One comment proposed the use of a titration dose column (a visual tool to depict a drug's titration regimen) in Highlights for drugs for which titration is relevant. One comment maintained that the dosage adjustment statement in the prototype that accompanied the proposed rule should be highlighted and enlarged.

FDA agrees with the comment that supported use of a tabular format for ''Dosage and Administration'' in Highlights. However, because a tabular format or a titration dose column may not be appropriate for all drug products, FDA is not requiring use of these formats under the ''Dosage and Administration'' heading.

With respect to highlighting and enlarging the dosage adjustment statement in the prototype, FDA believes that bolded type is sufficient to draw attention to particularly important dosage adjustment statements and that enlarging the statement is not necessary. Enlarging only dosage adjustment information in Highlights would make this information appear more significant than other information in Highlights, which would not be appropriate. Therefore, FDA is not requiring that dosage adjustment statements in Highlights be in larger font than other information in Highlights.

(Comment 26) One comment requested that when the labeling states that there may be a need for dosage adjustments in patients with renal or hepatic impairment, it also specify how to adjust the dose or dosing interval.

Highlights identifies important information about the need for dosage adjustments in specific populations and refers to the section of the FPI where more detailed information about how to adjust doses can be obtained. FDA believes that complete information about how to adjust dosages for various specific populations would in many cases require a great deal of space. Therefore, FDA is not requiring that such information be included in Highlights.

- *Warnings and precautions (proposed § 201.57(a)(10))*

FDA proposed to require that Highlights include, under a ''Warnings and Precautions'' heading, a concise summary of the most clinically significant aspects of the ''Warnings and Precautions'' section of the FPI (proposed § 201.57(a)(7)). The information chosen from the FPI would include those warnings and precautions that affect prescribing because of their severity and consequent influence on the decision to use the drug, because monitoring of them is critical to safe use of the drug, or because measures can be taken to prevent or mitigate harm.

(Comment 27) Some comments requested clarification of the scope of information to be included in Highlights under the ''Warnings and Precautions'' heading. Comments expressed concern that summarizing selected safety information from the ''Warnings and Precautions'' section of the FPI might cause some important safety information to be omitted from Highlights.

''Warnings and Precautions'' in Highlights serves to: (1) Identify the most clinically significant risks discussed in the ''Warnings and Precautions'' section in the FPI, (2) concisely summarize the salient features of those risks, and (3) direct the practitioner to the more detailed discussion of risks in the FPI. Information under the ''Warnings and Precautions'' heading in Highlights will typically include those risks that: (1) Affect decisions about whether to prescribe a drug, (2) require monitoring of patients to ensure safe use of the drug, or (3) require that measures be taken to prevent or mitigate harm. The agency has revised § 201.57(a)(10) to make clear the scope of information to include under this heading.

Because the risks identified under the ''Warnings and Precautions'' heading in Highlights will refer the prescriber to the full discussion in the ''Warnings and Precautions'' section of the FPI, the agency believes that important risk information will not be overlooked by practitioners.

(Comment 28) One comment stated that it would be misleading to include the most common adverse reactions under ''Warnings and Precautions'' in Highlights because the most common adverse reactions are not likely to be discussed in the ''Warnings and Precautions'' section of the FPI. Rather, they are more likely to be discussed in the ''Adverse Reactions'' section of the FPI. The comment recommended that the most common adverse reactions be listed under a separate section in Highlights immediately following the contact information for reporting suspected serious adverse reactions.

The agency agrees that it may be confusing to include under the ''Warnings and Precautions'' heading in Highlights information that is derived from both the ''Warnings and Precautions'' and ''Adverse Reactions'' sections of the FPI. The agency is, therefore, revising proposed § 201.57(a) by adding to Highlights a heading entitled ''Adverse Reactions'' (§ 201.57(a)(11)) that is required to follow the ''Warnings and Precautions'' section. Information under the ''Adverse Reactions'' heading must include: (1) A listing of the most frequently occurring adverse reactions identified in the ''Adverse Reactions'' section in the FPI and (2) contact information for reporting suspected adverse reactions. The sequence in which the information is presented in Highlights—the most frequently occurring adverse reactions followed by contact information for reporting suspected adverse reactions—is unchanged from the proposed rule.

(Comment 29) One comment requested clarification about whether only information that is supported by clinical data would be appropriate for inclusion in Highlights.

In most cases, the risk information in Highlights would be based on clinical data. However, risk information derived from animal data could be appropriate for inclusion in Highlights. For example, warnings about a drug's risks in pregnancy could be based entirely on animal data and might be appropriate for inclusion in Highlights. In such cases, Highlights must present only the clinically significant conclusions about risk in pregnancy (e.g., significant teratogen) and not include a discussion of the animal data that are the basis for the risk information presented.

- *ADR reporting contacts (proposed § 201.57(a)(11))*

FDA proposed (proposed § 201.57(a)(11)) to require that Highlights include, for drug products other than vaccines, a statement following the information under the ''Warnings and Precautions'' heading: ''To report SUSPECTED SERIOUS ADRs, 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 ADRs, call (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS number*).'' The agency specifically requested comment on whether it is necessary to include a contact number for reporting suspected adverse reactions in both Highlights and the ''Warnings and Precautions'' section of the FPI.

(Comment 30) Some comments stated that the contact information should be in both Highlights and FPI to make it more convenient to access and increase the likelihood that practitioners will be prompted to report suspected adverse reactions. Other comments stated that it would not be necessary to include contact information in both places because prominent placement of the information in Highlights alone would be sufficient to encourage practitioners to report adverse reactions. Some comments agreed that one location would be sufficient, but because those comments also opposed inclusion of Highlights in labeling, they recommended including the contact information in the FPI. Other comments suggested locating the contact information at the beginning of the labeling or in a ''box'' to increase its prominence. One comment recommended that the information be included only once and in close proximity to the name and address of the manufacturer in the FPI. The comment maintained that it is not intuitive to look for adverse reaction reporting contact information under ''Warnings and Precautions.'' One comment objected to inclusion of any adverse reaction reporting contact information in labeling. That comment maintained that contact information is not prescribing information and thus not appropriate for inclusion in labeling and, moreover, that there is no evidence that inclusion of such information in labeling will facilitate reporting of adverse reactions.

The agency agrees with the comments that support inclusion of contact information for reporting adverse reactions only in Highlights. Because the contact information is featured prominently in Highlights—bolded and set apart from other information—the agency believes that this is sufficient to make practitioners aware of the appropriate contacts to report adverse reactions and to encourage them to report suspected adverse reactions. The agency also believes that as prescribers become familiar with the content of Highlights, they will become increasingly aware of and familiar with the location of the adverse reaction reporting contact information. The agency does not believe that also including contact information in the FPI, even if moved to the beginning of the FPI, would result in meaningfully expanding the number of practitioners who become aware of the contact information. Therefore repeating the contact information in the FPI would not have a meaningful effect on the extent to which practitioners report adverse events. The agency also does not believe that placing the contact information for reporting suspected adverse reactions only in the FPI would afford the information adequate prominence. Accordingly, the final rule was revised to delete the proposed requirement at § 201.57(c)(6)(v) that contact information for adverse reaction reporting be included in the ''Warnings and Precautions'' section in the FPI. The agency believes it is unnecessary to further increase the prominence of the adverse reaction reporting contact information. Its current location—immediately following the listing of the most common adverse reactions—is the appropriate location, and the bolding and use of capitalization are sufficient to call attention to the information and distinguish it from adjacent information.

The agency does not agree that the adverse reaction reporting contact information should be omitted from labeling because it is not considered prescribing information. Including adverse reaction reporting contact information in labeling enables practitioners to report adverse reactions to FDA promptly. The agency monitors these reports and analyzes the adverse reactions data to determine whether labeling revisions are necessary for safe and effective use.

(Comment 31) Some comments recommended that only the manufacturer's phone number be included in prescription drug labeling, while others agreed that including the MedWatch phone number is important because manufacturers' phone numbers are subject to change. One comment requested that a telephone number for the relevant FDA review division also be included. Two comments recommended including the manufacturer's Web site in the reporting contact information.

The agency agrees that it is important to include both the manufacturer's phone number and FDA's phone number for voluntary reporting of adverse reactions. The agency believes that providing practitioners two options for reporting adverse reactions will help ensure that they always have someone to contact about an adverse reaction. The agency believes it is not appropriate to also include the phone number of the FDA review division that approved the drug. FDA review divisions are not the initial point of contact for postmarketing adverse reaction reports; therefore, manufacturers and practitioners should not send these reports to the review divisions for processing. It is critical that these reports be directed to the location(s) in FDA that are responsible for receiving and processing these reports so that they are evaluated and analyzed in an appropriate manner.

The agency agrees with comments recommending that, in addition to their phone number, manufacturers include the direct link to the section of their Web site for voluntary reporting of adverse reactions. The agency has revised proposed § 201.57(a)(11) to require the address of the Web site, if one is available. The agency will not require that manufacturers create a Web site to meet this requirement.

The agency has also decided to require that the adverse reaction reporting contact information include the FDA Web site address for voluntary reporting of adverse reactions (currently, *http://www.fda.gov/medwatch* for drug products except vaccines and *http://www.fda.gov/vaers* for vaccines). This Web site has become an increasingly important source of adverse reaction reports. The agency has concluded that providing practitioners with the convenience of being able to submit an adverse reaction report electronically may encourage reporting of adverse reactions that might not otherwise be reported. Thus, the agency believes it is very important to require identification of this Web site address in labeling, in addition to the FDA telephone number.

(Comment 32) Two comments stated that all adverse reactions should be reported, and not just serious adverse reactions.

The agency agrees that practitioners should not be discouraged from reporting adverse reactions that might not be considered serious. Certain adverse reactions that are not considered serious can be clinically significant. Moreover, practitioners may not always be able to determine whether an adverse reaction meets the regulatory definition of serious (21 CFR 310.305(b), 21 CFR 312.32(a), 21 CFR 314.80(a), and 21 CFR 600.80(a)). Also, there are limitations on the extent to which a drug's risks (serious and nonserious adverse reactions) can be delineated before marketing. The agency, therefore, believes that practitioners should be encouraged to submit all suspected adverse reactions to the manufacturer or FDA, without regard to the seriousness

of the reaction, to facilitate faster and more accurate characterization of a drug's risk profile. Accordingly, FDA has revised proposed § 201.57(a)(11) to require that the statement for adverse reaction reporting contact information refer to all suspected adverse reactions, not just serious ones.

• *Drug interactions (proposed § 201.57(a)(12))*

FDA proposed to require that Highlights contain a ''Drug Interactions'' heading that would include, with any appropriate subheadings, a concise summary of the drug interaction information in the FPI (i.e., prescription or over-the-counter drugs or foods that interact in clinically significant ways with the product)(proposed § 201.57(a)(12)).

(Comment 33) Several comments strongly supported inclusion of ''Drug Interactions'' as a separate heading in Highlights. One comment recommended requiring separate subheadings for drug-drug, drug-food, drug-laboratory, and possibly drug-herbal interactions.

FDA will not require that ''Drug Interactions'' in Highlights include specific subheadings depending on whether the interaction is a drug-drug, drug-food, drug-herbal, or drug-laboratory interaction. Use of these subheadings is typically most appropriate when a drug has a large number of interactions in each of these categories. In other cases, it is unlikely to provide additional clarification sufficient to justify use of space for the subheadings.

• *Use in specific populations (proposed § 201.57(a)(13))*

FDA proposed to require that Highlights contain a ''Use in Specific Populations'' heading (proposed § 201.57(a)(13)). The agency proposed that this heading include, with any appropriate subheadings, a concise summary of information from this section of the FPI on any clinically important differences in response or use of the drug in specific populations.

(Comment 34) One comment requested that the agency specify that the pregnancy category designation be included under the ''Use in Specific Populations'' heading in Highlights because the pregnancy category quickly communicates whether use of a drug is appropriate during pregnancy.

The agency does not agree that pregnancy category designations are appropriate for inclusion in Highlights or that they are effective in quickly communicating whether use of a drug is appropriate during pregnancy. The agency believes the pregnancy category, in isolation, tends to oversimplify the risks of drugs in pregnancy and, as a result, may be confusing. Decisions about use of a drug in pregnancy should be based on careful consideration of available data, not simply on a reference to the pregnancy category.

• *Highlights limitation statement (proposed § 201.57(a)(15))*

FDA proposed (proposed § 201.57(a)(15)) to require that Highlights 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.''

(Comment 35) Several comments recommended that the Highlights limitation statement be made more prominent by moving the statement to the beginning of Highlights. In addition, several comments recommended revisions to the language of the statement, such as including that practitioners ''must'' consult the comprehensive prescribing information, in addition to Highlights, to use a drug safely and effectively.

The agency agrees that it is important to emphasize to prescribers that Highlights does not include all the information needed to use a drug safely and effectively and that placement of the statement at the beginning of Highlights increases the prominence of this message. Therefore, FDA has revised proposed § 201.57(a)(15) to require that the statement appear at the beginning of Highlights (§ 201.57(a)(1)).

The agency does not agree, however, that it is necessary to revise the language of the Highlights limitations statement. Recognizing that FDA cannot require practitioners to consult the FPI, the agency believes that the language in this statement, with two minor editorial changes, very clearly states the limitations of Highlights.

F. Comments on the Index (Proposed § 201.57(b))

FDA proposed to require that prescription drug labeling for products described in proposed § 201.56(b)(1) (i.e., new and more recently approved prescription drug products) contain an index entitled ''Comprehensive Prescribing Information: Index'' (proposed § 201.57(b)). The index would list the subheadings required under proposed § 201.56(d)(1), if not omitted under proposed § 201.56(d)(3), and each optional subheading included in the FPI under proposed § 201.56(d)(5). Each subheading would be required to be preceded by its corresponding index number or identifier.

In the proposal, the agency specifically sought comment on whether it is necessary to require both an index and Highlights. As discussed in section II of this document, the agency has decided, on its own initiative, to change the title (now ''Full Prescribing Information: Contents'') to better reflect the function of this portion of the labeling.

(Comment 36) Most comments supported inclusion of an index (hereafter Contents). They maintained that Highlights alone cannot be relied upon to help locate all drug information in the FPI because Highlights is not comprehensive (Highlights includes information from only certain sections of the FPI). They stated that a table of contents is necessary to quickly and easily direct the reader to sections of the FPI that are not referred to in Highlights. Other comments stated that, despite the distinct purposes served by Highlights and Contents, the agency should consider consolidating them to save space. Some comments stated that there need not be both because they have similar functions and recommended that Contents be deleted if Highlights is retained. One comment recommended that prescription drug labeling include neither Contents nor Highlights. The comment stated that the reordered and reformatted FPI itself is adequate to facilitate practitioners' access to information in labeling.

FDA continues to believe that Highlights and Contents serve different purposes and has determined that both should be retained. Highlights presents a succinct summary of the information in the FPI that is most crucial for safe and effective use, with cross-references to direct prescribers to more details in the FPI. In contrast, Contents serves as a navigational tool that references all the sections and subsections in the FPI, some of which will not be referenced in Highlights. Therefore, the agency believes Contents has a unique and meaningful function in making information in the FPI accessible to practitioners.

In addition, Highlights and Contents both figure prominently in FDA's plans to convert prescription drug labeling to an electronic format (see section V of this document). The Contents will provide hyperlinks to all sections and subsections of the FPI, enabling practitioners to navigate the labeling more easily. Highlights will provide hyperlinks to the most frequently referenced and, typically, most important prescribing information, allowing rapid access to more detailed information on these critical topics.

(Comment 37) One comment recommended that, for sections of labeling that are omitted from the FPI

because they are not applicable, the agency consider including the section number and heading in Contents followed by the statement ''not applicable,'' rather than omitting the section number and heading. The comment noted that the prototype labeling in the proposed rule omitted a section and also omitted the listing of the section heading in Contents, and that this omission might confuse practitioners.

The purpose of Contents is to set forth the sections and subsections included in the FPI. For many drug products, some sections and subsections are not applicable (e.g., ''Drug Abuse and Dependence,'' ''References''). Currently, these sections are, in most cases, simply omitted from the labeling without discussion in accordance with former § 201.56(d)(3). The agency believes that this practice should continue, but recognizes that because identifying numbers are now required to be used for labeling of new and recently approved products, this practice may initially be confusing for some. The agency considered the comment's suggestion that the section identifying number and heading be included in Contents followed by the statement ''not applicable'' for labeling that omits a required section or subsection, but believes that this is not the best approach because of space considerations. Instead, to minimize any potential confusion regarding omitted sections, the agency has revised proposed § 201.56(d)(3) (designated in this final rule as § 201.56(d)(4)) to require in these cases that the Contents heading be followed by an asterisk and that the following statement be included at the end of Contents: ''* Sections or subsections omitted from the full prescribing information are not listed.''

In addition, for legal clarity, FDA revised proposed § 201.56(d)(3) and (e)(3) (§ 201.56(d)(4) and (e)(3) in this final rule) to make clear that clearly inapplicable sections, subsections, or specific information are omitted from labeling.

G. Full Prescribing Information—Comments on the Reorganization

FDA proposed to revise, for products described in proposed § 201.56(b)(1) (new and more recently approved prescription drug products), the content and format requirements of prescription drug labeling at then-current §§ 201.56(d) and 201.57. These revisions included, in proposed §§ 201.56(d) and 201.57(c), reordering the information in the FPI to make more prominent those sections that the agency identified (based on the physician surveys, focus groups, public comments, and its own experience) to be most important to, and most commonly referenced by, health care practitioners. For example, proposed § 201.57(c)(1) would require that any boxed warning(s) be the first substantive information to appear in the FPI, proposed § 201.57(c)(2) would require that the ''Indications and Usage'' section follow any boxed warnings in the FPI, and proposed § 201.57(c)(3) would require that the ''Dosage and Administration'' section follow the ''Indications and Usage'' section in the FPI.

(Comment 38) Virtually all the comments supported the proposed reordering of the FPI to give greater prominence to the sections that practitioners consider most important and refer to most often. Many comments agreed that the reordering, by better reflecting the way the information in the FPI is used, would make the FPI more useful and accessible to practitioners. Some comments, while supportive of the reordering generally, recommended certain changes to the sequence of the sections. One comment requested that the ''Adverse Reactions'' section be moved from its present location following the ''Use in Specific Populations'' section and be placed immediately after the ''Warnings and Precautions'' section. The comment also recommended that the ''Use in Specific Populations'' section be moved from its location following the ''Drug Interactions'' section and be placed immediately after the ''Dosage and Administration'' section. The comment maintained that use in specific populations frequently involves modifications to dose or dosage regimen, so it would be logical to place the section in close proximity to the ''Dosage and Administration'' section.

The agency agrees that it would be advantageous to group together the two major risk information sections—the ''Warnings and Precautions'' and ''Adverse Reactions'' sections. Placing the two sections sequentially consolidates risk information in one location and helps put in context the relative seriousness of the adverse reactions discussed in labeling. Thus, FDA has revised proposed § 201.57(c) to require that the ''Adverse Reactions'' section follow the ''Warnings and Precautions'' section.

The agency does not agree with the recommendation to place the ''Use in Specific Populations'' section immediately after the ''Dosage and Administration'' section. Although some of the information in the ''Use in Specific Populations'' section will have implications for dosing, most of the information in the section will be related to risk. The section is, therefore, more appropriately placed among the other labeling sections related to risk. In addition, the agency believes that all dosing information should be consolidated in a single section. If there are specific recommendations for dosage regimen modifications for use in specific populations, those modifications must be described in the ''Dosage and Administration'' section (see § 201.57(c)(3)).

(Comment 39) One comment requested that the agency require a ''Product Title'' section at the beginning of the FPI. The comment maintained that the title is short and repeating it would be useful to practitioners to avoid confusion.

The option to include a ''Product Title'' section is a vestige of the prescription drug labeling rule finalized in 1979 (44 FR 37434, June 26, 1979). The optional ''Product Title'' section was incorporated in the labeling regulations at that time in response to a comment to the proposed rule that was the basis for the 1979 final rule (44 FR 37440). The comment stated that the proposed labeling requirements did not require identification of the product at the beginning of labeling. Instead, the first required element in the proposed labeling regulations was the ''Description'' section. The comment recommended, and the agency agreed, that certain sections of the ''Description'' section could be pulled out of that section and used as a ''Product Title'' section at the beginning of labeling.

Under this final rule, a ''Product Title'' section is not needed for labeling subject to the requirements of new § 201.57, because under final § 201.57(a)(2), Highlights includes the name of the drug, dosage form, and route of administration and, for controlled substances, the controlled substance symbol. Because this information will appear at the beginning of labeling and is similar to the information required under the ''Product Title'' section, the agency believes it is not necessary or useful to provide the option to include a ''Product Title'' section at the beginning of the FPI. Accordingly, the agency has deleted proposed § 201.56(d)(4) from the requirements for products described in § 201.57(b)(1) (new and more recently approved drug products). This revision does not have any effect on the ''Product Title'' provision in current regulations (§ 201.56(e)(4)), which this final rule retains for products subject to § 201.80.

(Comment 40) One comment stated that, if the agency retains the

requirement for the boxed warning in both Highlights and the FPI, the boxed warning in the FPI should be placed in the ''Warnings and Precautions'' section rather than at the beginning of the FPI.

The agency disagrees. The agency believes that the summary sections in Highlights should appear in the same order as the corresponding sections in the FPI to facilitate access to the more detailed information contained in the corresponding sections in the FPI. The risk information presented in a boxed warning is of such importance that it warrants placement in the most prominent locations.

(Comment 41) Some comments recommended that the ''How Supplied/Storage and Handling'' section be kept at the end of the FPI, rather than moved toward the front of the FPI, as proposed. The comments expressed concern that, because of the variable length of the three labeling sections that precede the ''How Supplied/Storage and Handling'' section, it would not be in a consistent location; therefore, practitioners would have more difficulty locating the section than if it were always at the end of the FPI. One comment stated that pharmacists frequently access this section for information about storage conditions and that it would be more appropriate to place the section just before the ''Patient Counseling Information'' near the end of the labeling, where pharmacists are accustomed to finding it.

The proposed placement of the ''How Supplied/Storage and Handling'' section following the ''Dosage and Administration'' section was based on input from physicians who were surveyed about which information in labeling is most important and frequently referenced. Physicians indicated that their use of the ''Dosage and Administration'' section and the ''How Supplied/Storage and Handling'' section is linked. Physicians commonly refer to the ''Dosage and Administration'' section for dosing information and then to the ''How Supplied/Storage and Handling'' section for available dosage strengths and dosage forms. For this reason, the agency believes that keeping dosing and dosage forms and strengths information together in the labeling is important.

However, the agency recognizes that, under proposed § 201.57(c)(4), the ''How Supplied/Storage and Handling'' section would often have contained lengthy lists of available packaging and product identification information that may distract prescribers from other important information. For this reason, and in view of the comments received, the agency has decided to move this section toward the end of the labeling (§ 201.57(c)(17)). (See comments 55 and 107 for discussion of revisions (i.e., addition of imprinting as an example of an identifying characteristic and deletion of proposed § 201.57(c)(4)(v)).) FDA also has decided to require that information identified by prescribers as frequently referenced (i.e., dosage forms and strengths and some product identification information) be included in a section entitled ''Dosage Forms and Strengths'' (§ 201.57(c)(4)) following the ''Dosage and Administration'' section.

The agency believes that moving the ''How Supplied/Storage and Handling'' section toward the end of labeling will make it easier for pharmacists to locate product identification, packaging, and storage information. Retaining critical prescribing information in the ''Dosage Forms and Strengths'' section will continue to meet the needs of prescribers by keeping available dosage forms and strengths information together with information about dosage and administration. Under this final rule, some product identification information (e.g., shape, color, coating, scoring, and imprinting) may be required to appear in both the ''Dosage Forms and Strengths'' and ''How Supplied/Storage and Handling'' sections. FDA believes that the product identification information should be included in both sections to preserve the integrity and comprehensibility of each section.

(Comment 42) One comment requested that the agency clarify the conditions under which it would be appropriate, when amending existing labeling to the new labeling format, to move certain information from a section in old labeling to a different section in new labeling. For example, the comment asked what criteria would be used to determine whether information on use in specific populations, currently contained in the ''Clinical Pharmacology'' section, should be moved to the new ''Use in Specific Populations'' section.

The agency expects that, in many cases, amending labeling to meet new § 201.57(c) will involve rearranging large segments (sections and subsections) of information in existing labeling without substantially changing the content. In some cases, however, it will be necessary to parse information from several parts of the existing labeling into a new section. When information is to be consolidated into a new section, or when information is required in several places, there may be uncertainty about how the information should be divided into portions for clarity and to avoid redundancy. The agency recognizes the complexity of these issues and, therefore, is making available the new labeling format guidance to assist in determining how to reorganize existing labeling information into the new format (see section IV of this document).

H. Full Prescribing Information—Comments on Specific Provisions

As noted previously, for products described in proposed § 201.56(b)(1) (new and more recently approved prescription drug products), FDA proposed to revise the content and format requirements at then-current § 201.57 (proposed § 201.57(c)). A discussion of the comments pertaining to these provisions and the agency's responses follow.

- *Boxed warning (proposed § 201.57(c)(1))*

FDA proposed to require that a boxed warning in the FPI be preceded by an exclamation point (!) for indexing purposes (proposed § 201.57(c)(1)). The agency specifically requested comment on the different types of icons that could be used to signal the boxed warning and on the costs and benefits of different icon types.

(Comment 43) Several comments stated that an icon is unnecessary because practitioners are familiar with the meaning of a boxed warning and the box itself is sufficient to call attention to the warning. Some comments observed that the exclamation point was not a sufficiently distinct symbol because it could be confused with the numeral 1 and might be particularly difficult to recognize in small font. Some comments expressed concern about using any icon that is not universally understood. One comment recommended that a stop sign be used as it has a universally recognized meaning. Other comments expressed concern about added printing and software costs associated with any icon requirement.

FDA has reconsidered requiring an exclamation point, or any other icon, to identify a boxed warning. FDA agrees that the single black line box around the warning information is understood by practitioners in the United States and is sufficient to draw attention to the warning information. Therefore, the agency is not requiring an exclamation point or any other icon preceding the boxed warning in the FPI. Sections 201.56(d)(1), 201.57(a)(4), and (c)(1) of the final rule have been revised to remove the requirement.

- *Indications and usage (proposed § 201.57(c)(2)(i))*

FDA proposed to require that the ''Indications and Usage'' section of the

FPI (proposed § 201.57(c)(2)(i)) contain the same information as required at then-current § 201.57(c)(1) except that outdated examples of indications were removed.

(Comment 44) One comment recommended that the ''Indications and Usage'' section be retitled ''Food and Drug Administration—Approved Uses.'' The comment stated that the phrase ''indications and usage'' is regulatory jargon that is not meaningful to practitioners or patients.

The agency does not believe it would be worthwhile to change the title of the section in the manner recommended by the comment. The agency does not agree that ''indications and usage'' is jargon and not meaningful to practitioners. FDA believes practitioners are familiar with the section heading and understand that the uses described in this section are those for which FDA has found to be safe and effective.

(Comment 45) One comment stated that the ''Indications and Usage'' section should include approved uses in pregnancy.

The agency agrees, in part. Uses that have been specifically studied for conditions unique to pregnancy and for which a drug has been demonstrated to be safe and effective (e.g., to induce labor) would be appropriate for inclusion in the ''Indications and Usage'' section. Ordinarily, however, special considerations about the use of a drug in pregnancy for indications that do not differ from the general population would be placed in the ''Use in Specific Populations'' section.

• *Indications and usage—scope of information (proposed § 201.57(c)(2)(iv)(A))*

FDA proposed to revise the requirement at then-current § 201.57(c)(3)(i) to state that if evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with the disease or condition (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, then the available evidence and the limitations on the usefulness of the drug (or in the case of surrogate endpoints, the limitations of the supporting efficacy data) must be described succinctly in the ''Indications and Usage'' section (proposed § 201.57(c)(2)(iv)(A)). FDA proposed, further, to require reference to the ''Clinical Studies'' section of the FPI (proposed § 201.57(c)(15)) for a detailed discussion of the methodology and results of clinical studies relevant to such limitation(s). FDA also proposed to require that this section of the FPI identify specific tests needed for selection or monitoring of the patients who need the drug and describe, if available, information on the approximate kind, degree, and duration of improvement to be anticipated.

(Comment 46) One comment requested that the ''Indications and Usage'' section specify the type of clinical trial that has been conducted to support each indication (e.g., placebo-controlled, active-controlled).

The agency believes that the ''Clinical Studies'' section is the appropriate section of labeling to discuss the details (e.g., trial design, outcome) of clinical trials, not the ''Indications and Usage'' section. The agency has concluded that greater clarity about the scope of the information to be included in the ''Indications and Usage'' section is warranted and has revised proposed § 201.57(c)(2) accordingly. This revision is consistent with having, as stated in the preamble to the proposed rule, a more focused ''Indications and Usage'' section (65 FR 81082 at 81091).

(Comment 47) FDA received one comment that strongly supported the proposed modification of the ''Indications and Usage'' section to require that limitations in usefulness or in data supporting approval be specified. One comment stated that the requirement should be modified to specifically require discussion of differential drug effects in subpopulations with varying genetic characteristics.

FDA agrees that the ''Indications and Usage'' section must discuss differences in drug effectiveness in subgroups for which there is substantial evidence for such differences. The proposed language was not intended to limit the scope of the requirement to particular subgroups. The provision applies to any identifiable subgroup with a clearly different response to a drug. The agency believes the language in final § 201.57(c)(2)(i)(B) and (c)(2)(i)(D) makes clear that the section must discuss differential drug effects for all types of patient subgroups for which there is substantial evidence establishing differences in effects. If dosage modification is necessary based on genetic characteristics, this must be described in the ''Dosage and Administration'' section. FDA has revised proposed § 201.57(c)(3) accordingly (see § 201.57(c)(3)(i)(H) of final rule).

(Comment 48) One comment requested that FDA make clear when the ''Indications and Usage'' section must include specific tests needed for selection and monitoring of patients who need a drug (e.g., microbe susceptibility testing). The comment stated that it is not practical to recommend specific microbial susceptibility testing when empirical diagnosis is common.

Specific tests for selecting and monitoring patients would be described when they are necessary for safe and effective use. Therefore, the requirement in final § 201.57(c)(2)(i)(C) that the ''Indications and Usage'' section identify specific tests needed for selecting and monitoring patients does not require that the ''Indications and Usage'' section routinely state that microbial susceptibility testing must be done. The requirement addresses situations in which a drug is indicated for a specific therapeutic niche that can be identified by microbe susceptibility testing. For example, the ''Indications and Usage'' section might specify that a drug is indicated to treat penicillin-resistant pneumococci. The description of the drug's activity provides critical prescribing information.

• *Indications and usage—lack of evidence statement (proposed § 201.57(c)(2)(iv)(D))*

FDA proposed to revise then-current § 201.57(c)(3)(iv), which provided that in situations where there is a common belief that a drug may be effective for a certain use or condition or the drug is commonly used for that condition but the preponderance of the evidence shows the drug is ineffective, the ''Indications and Usage'' section must state that the drug is ineffective (proposed § 201.57(c)(2)(iv)(D)). The revision proposed to expand this requirement to situations in which a drug may be effective for a use but the preponderance of the evidence shows that the therapeutic benefits of the product do not generally outweigh its risks. In such situations, under sections 201(n) (21 U.S.C. 321) and 502(a) of the act, the agency can require that the ''Indications and Usage'' section state that there is a lack of evidence that the drug is effective or safe for that use.

(Comment 49) One comment requested that the agency provide examples to clarify what it intends by this new requirement.

Anti-arrhythmia drugs are an example of a category of drugs to which the new requirement in final § 201.57(c)(2)(ii) could apply. They are typically effective in restoring or maintaining normal sinus rhythm for a variety of types of rhythm disturbances, but because of the potential for pro-arrhythmic effects, they are typically indicated for only the more serious clinical situations in which their benefits outweigh their risks. For example, an anti-arrhythmic

drug may be indicated for sustained ventricular arrhythmia, but specifically not indicated for premature ventricular contractions.

• *Dosage and administration (proposed § 201.57(c)(3))*

FDA proposed to require that the ''Dosage and Administration'' section of the FPI (proposed § 201.57(c)(3)) contain the same information as required in then-current § 201.57(j), except that the section must include efficacious or toxic drug or metabolite concentration ranges and therapeutic concentration windows for drug or metabolite(s) where established and when clinically important. FDA proposed to require information on therapeutic drug concentration monitoring (TDM), when clinically necessary. The proposed provision also specified that dosing regimens must not be implied or suggested in other sections of labeling if not included in this section. FDA has retained this provision in the final rule with some editorial revisions (§ 201.57(c)(3)).

(Comment 50) One comment asked the agency to clarify whether the language in proposed § 201.57(c)(3), ''upper limit beyond which safety and effectiveness have not been established,'' is referring to maximum tolerated dose.

The language does not refer to the maximum tolerated dose. The upper limit beyond which safety and effectiveness have not been established would ordinarily refer to: (1) The largest dose demonstrated to be safe and effective in controlled clinical trials, (2) the largest dose evaluated that showed an increase in effectiveness (i.e., where studied larger doses provided no additional benefit), or (3) the largest dose beyond which safety has not been established or an unacceptable risk has been demonstrated.

(Comment 51) One comment requested that the agency make it clear that any dosage adjustments discussed in the ''Drug Interactions'' section should also be presented in the ''Dosage and Administration'' section.

The agency agrees that when there is specific information about how to adjust dosage because of a drug interaction, this information must be included in the ''Dosage and Administration'' section. The ''Dosage and Administration'' section should also refer the reader to the more detailed discussion of the drug interaction in the ''Drug Interactions'' and ''Clinical Pharmacology'' sections. In response to this comment, FDA has modified proposed § 201.57(c)(3) to require that information on dosage adjustments needed because of a drug interaction be included in the ''Dosage and Administration'' section.

(Comment 52) One comment requested that all intravenous dosing regimens in labeling be expressed in rates of milligrams per hour. The comment pointed out that rates are expressed in milligrams per minute and milligrams per hour. The comment maintained that expressing all such rates in milligrams per hour would avoid the need to recalculate rates and thus reduce the likelihood of medication errors.

The agency does not agree that always requiring rates of administration for intravenous medications to be expressed in milligrams per hour would avoid the need to recalculate rates of infusion and thus reduce medication errors. The agency believes that these rates should be expressed per time unit that is most appropriate to the interval over which a medication is to be administered. This approach will eliminate, to the extent possible, the need to recalculate rates and should, therefore, minimize error.

(Comment 53) One comment stated that, with respect to clinically important effectiveness and/or toxic drug and/or metabolite concentration ranges and therapeutic concentration windows in the ''Dosage and Administration'' section, effectiveness information other than information on TDM would more appropriately be placed in the ''Clinical Pharmacology'' section. The comment further stated that, if the concentration range concerned safety, it would more appropriately be included in the ''Warnings and Precautions'' section.

The ''Dosage and Administration'' section must identify efficacious or toxic concentration windows of the drug or its metabolites, if established and clinically significant, and information on TDM, when TDM is necessary. Clinically relevant background information supporting the need for TDM could appear in other sections of labeling as appropriate (e.g., ''Clinical Pharmacology,'' ''Clinical Studies,'' ''Adverse Reactions'').

(Comment 54) Two comments recommended including instructions on the appropriate time of day to take a drug and other dosing conditions (e.g., take with food, take on an empty stomach) in the ''Dosage and Administration'' section of the labeling. One comment requested that the labeling include a section concerning the importance of compliance with the dosage regimen and instructions on what to do about missed doses and noncompliance in general. The comment requested that, in the absence of data to support instructions on what to do about noncompliance, the labeling include a statement indicating that there is no such information.

The agency agrees that information about appropriate time of day to take a medication or other dosing considerations must be included in the ''Dosage and Administration'' section if this information is necessary for safe and effective use (e.g., if a significant amount of a therapeutic effect is lost if the drug is not taken on an empty stomach). Therefore, the agency has revised proposed § 201.57(c)(3) to require that clinically significant dosing information (e.g., clinically significant food effects) be included in the ''Dosage and Administration'' section. Similarly, the agency has revised proposed § 201.57(c)(13)(i)(B) of the ''Clinical Pharmacology'' section to clarify that certain recommendations regarding pharmacodynamic effects included in other sections of labeling, such as the ''Dosage and Administration'' section, must not be repeated in the ''Clinical Pharmacology'' section.

The agency agrees that rigid compliance with the dosage regimen can be critical to safe and effective drug therapy and information about how to manage noncompliance is important for practitioners. Therefore, FDA has revised proposed § 201.57(c)(3) to make clear that important considerations concerning compliance with the dosage regimen must be included.

The agency believes that the labeling should not include a separate section devoted to the importance of compliance with a drug's dosage regimen or information on what to do about missed doses, because this information is most appropriately contained in other sections of the labeling (e.g., ''Dosage and Administration,'' ''Clinical Pharmacology,'' ''Patient Counseling Information''). The agency believes that it would not be useful to include a statement in the labeling indicating that there is no information available about management of noncompliance (e.g., missed doses).

• *How supplied/storage and handling (proposed § 201.57(c)(4))*

FDA proposed to require that the ''How Supplied/Storage and Handling'' section of the FPI (proposed § 201.57(c)(4)) contain the same information as required at then-current § 201.57(k), except that a new provision was added at proposed § 201.57(c)(4)(v). Proposed § 201.57(c)(4)(v) would require a statement specifying the type of container to be used by pharmacists in dispensing the product. Comments pertaining to proposed § 201.57(c)(4)(v) are addressed in section VI.J of this document (''Comments on Revisions to

Container Labels''; see comments 106 through 110). Comment 41 addresses relocation of the ''How Supplied/ Storage and Handling'' section to § 201.57(c)(17) and the retention of critical prescribing information in the ''Dosage Forms and Strengths'' section at § 201.57(c)(4). A comment pertaining to the format for and type of information contained in these sections is discussed here.

(Comment 55) One comment recommended including product identity markings in this section. The comment also recommended bulleted or tabular presentation of product identity markings, color, flavor, package sizes, strengths, storage conditions, etc., to make such information more accessible.

FDA agrees with the comment that product identity markings are useful for practitioners and, therefore, now includes imprinting as an example of an identifying characteristic in both the ''Dosage Forms and Strengths'' and the ''How Supplied/Storage and Handling'' sections of the final rule. FDA also agrees that presenting information about product identity markings, color, flavor, package sizes, strengths, storage conditions, and other identifying information in a bulleted or table format will make the information more accessible, particularly where the product has many dosage forms and strengths. However, because the amount and content of information can vary significantly from product to product, FDA is not requiring a specific format.

• *Warnings and precautions (proposed § 201.57(c)(6))*

FDA proposed to revise the content of the ''Warnings'' and ''Precautions'' sections. First, FDA proposed to require that information on drug interactions, information on specific populations (i.e., pregnancy, labor and delivery, nursing mothers, pediatric, and geriatric use information), and information for patients be moved from the ''Precautions'' section to three new sections (described in proposed § 201.57(c)(7), (c)(8), and (c)(17) respectively). Second, FDA proposed to require that the remainder of the information in the ''Precautions'' section, with the information from the ''Warnings'' section, be combined into a new section entitled ''Warnings and Precautions'' (proposed § 201.57(c)(6)).

FDA also proposed to require that the ''Warnings and Precautions'' section include information on contacts for adverse reaction reporting (proposed § 201.57(c)(6)(v)). See comment 30 regarding deletion of proposed § 201.57(c)(6)(v).

Several comments supported reorganizing the ''Warnings and Precautions'' section. The comments agreed with FDA's findings, based on physician surveys and focus testing, that the distinction between warnings and precautions is not meaningful to practitioners who use labeling. The comments stated that the combined section would make the discussion of risk information in labeling less repetitive, less confusing, and more accessible.

(Comment 56) In the proposal, the agency specifically sought comment on whether there should be standardized headings for categories of adverse reactions in the proposed ''Warnings and Precautions'' section and, if there should be, what standardized headings would be appropriate.

Comments uniformly opposed standardized headings to categorize adverse reactions in the ''Warnings and Precautions'' section. Comments expressed concern that standardized headings would not provide sufficient flexibility to accommodate the diversity of risk information that might be appropriate for inclusion in the ''Warnings and Precautions'' section.

FDA agrees that standardized headings should not be required in the ''Warnings and Precautions'' section because a requirement to place risk information under prescribed headings could make the information less clear or more difficult to find.

(Comment 57) One comment requested clarification of the requirement in proposed § 201.57(c)(6)(iii) that the ''Warnings and Precautions'' section identify any laboratory tests that ''may be helpful'' in following a patient's response or identifying possible adverse reactions. The comment maintained that the language ''may be helpful'' is too vague and recommended that the language be changed to specify that only laboratory tests that ''have been shown to be helpful'' be required in the ''Warnings and Precautions'' section.

The agency is concerned that limiting the scope of laboratory testing recommendations identified in labeling to only those tests that have been ''shown to be helpful'' in monitoring patients could exclude sensible and potentially important laboratory testing recommendations. The agency agrees, however, that ''may be helpful'' is a vague standard and, therefore, has amended the provision to require identifying any laboratory tests ''helpful'' in following a patient's response or identifying possible adverse reactions.

(Comment 58) Several comments expressed concern about the proposal to change the criteria for inclusion of adverse reactions in the ''Warnings and Precautions'' section from ''serious'' to ''clinically significant'' adverse reactions. There was concern that the significance of the adverse reactions discussed in the ''Warnings and Precautions'' section would be diluted by the inclusion of less serious adverse reactions in the section, thus undermining the value of the section. Other comments expressed concern that ''clinically significant'' is subject to interpretation and could, in application, result in inconsistency across labeling for different products.

As discussed in the preamble accompanying the proposed rule (65 FR 81082 at 81092), ''serious'' was changed to ''clinically significant'' to expand the scope of the ''Warnings and Precautions'' section to allow for inclusion of adverse reactions that may not meet the regulatory definition of ''serious'' (§ 312.32(a)), but nonetheless have a significant impact on clinical use of the drug. The agency believes that information on both types of adverse reactions is necessary for practitioners to prescribe products safely and effectively and must, therefore, be included in the ''Warnings and Precautions'' section. The agency acknowledges that inclusion of less serious but clinically significant adverse reactions may add to the overall length of the ''Warnings and Precautions'' section of labeling for certain drugs. The agency does not agree, however, that the effect will be to dilute or deemphasize the importance of serious adverse reactions contained in the section. The agency believes that limiting inclusion of nonserious adverse reactions to only those that have significant impact on therapeutic decisionmaking (e.g., may reduce compliance with drug therapy) ensures that the intended scope of the ''Warnings and Precautions'' section is preserved.

(Comment 59) One comment recommended that the agency describe parameters upon which to base decisions about the sequence in which adverse reactions are presented in the ''Warnings and Precautions'' section.

There are multiple factors that could influence the sequence in which adverse reactions should be presented in the ''Warnings and Precautions'' section. The most significant include the relative seriousness of the adverse reaction, the ability to prevent or mitigate the adverse reaction, the likelihood the adverse reaction will occur, and the size of the population affected. In general, the sequence of the adverse reactions should reflect the relative public health significance, and the seriousness of the adverse reaction

should weigh more heavily than the likelihood of occurrence or the size of the affected population. The agency has added clarifying language to this requirement to assist in selecting and organizing information in this section. The agency is also making available guidance on the ''Warnings and Precautions'' section, which provides recommendations on sequencing of adverse reactions (see section IV of this document).

In addition, the final rule (§ 201.57(c)(6)(i)) states that FDA may require labeling to include a specific warning relating to a use that is not provided for under the ''Indications and Usage'' section if the drug is commonly prescribed for a disease or condition and such usage is associated with clinically significant risk or hazard. FDA deleted language from proposed § 201.57(c)(6)(i), (i.e., ''and there is a lack of substantial evidence of effectiveness for that disease or condition'') because the requirement for a warning is based on an assessment of risk. In addition, FDA also clarified that its authority under this provision must be exercised in accordance with sections 201(n) and 502(a) of the act.

• *Drug interactions (proposed § 201.57(c)(7))*

FDA proposed to require a ''Drug Interactions'' section (proposed § 201.57(c)(7)) containing the same information as required by the ''Drug interactions'' subsection of the ''Precautions'' section at then-current § 201.57(f)(4).

(Comment 60) Most comments supported creation of a distinct section for drug interactions. These comments maintained that the new section would improve the safety of drugs for patients on multiple medications. One comment asked FDA to clarify whether discussions of drug interaction pharmacokinetic studies should be repeated in the ''Clinical Pharmacology'' section.

How to divide information on drug interactions between the ''Clinical Pharmacology'' and ''Drug Interactions'' sections is a matter of judgment. Manufacturers must not include a detailed discussion of drug interaction pharmacokinetic studies in both the ''Drug Interactions'' and the ''Clinical Pharmacology'' sections. Ordinarily, clinically significant results and conclusions of such studies must appear in the ''Drug Interactions'' section and clinically significant information on dosing modifications in the ''Dosage and Administration'' section. If additional details about the design or conduct of the studies are relevant to the clinical use of the drug, the information must be included in the ''Clinical Pharmacology'' section. Thus, the agency has revised proposed § 201.57(c)(7)(i) and (c)(13)(i)(D) to provide this clarification (see § 201.57(c)(8)(i) and (c)(13)(i)(C)).

(Comment 61) One comment stated that the labeling example published with the proposed rule included recommended dosage adjustments for drug interactions that are not based on clinical experience and requested clarification about whether the manufacturer must include speculative interactions and dosage adjustments in this section. The comment also asked to what extent sponsors would be required to develop clinical data to support dosage adjustments for drug interactions.

Manufacturers must not speculate in labeling. Information from clinical experience is clearly the most persuasive, but other relevant data, such as pharmacokinetic data, in vitro data, and data from other drug products in the same pharmacologic or chemical class, may reliably predict the likelihood of an interaction with the drug or provide a basis for a dosage adjustment recommendation. Therefore, it would not be appropriate to limit the scope of the drug interactions and dosage adjustment information in labeling to only those interactions or dosage adjustments for which there are clinical data.

(Comment 62) One comment stated that including discussions of dosage adjustments to address drug interactions in both the ''Drug Interactions'' and ''Dosage and Administration'' sections would add unnecessarily to the length of the labeling.

FDA does not agree that discussing dosage adjustments for drug interactions in both the ''Drug Interactions'' section and the ''Dosage and Administration'' section would be unnecessary or repetitive because the purposes of the sections are distinct (see comment 51). The ''Drug Interactions'' section alerts the prescriber to the existence of interactions and provides a place for substantive discussion of the nature of the identified interactions, including practical advice about preventing or limiting interactions. The ''Dosing and Administration'' section provides specific information about how to modify the dose to minimize the risk of drug interactions when such information is available, but does not provide the details that are discussed in the ''Drug Interactions'' section.

(Comment 63) One comment recommended revising the ''Drug Interactions'' section to require the presentation of drug interaction data ranked by order of the strength of the data supporting the existence of an interaction.

FDA believes that relative clinical significance of the drug interaction would ordinarily be the most reasonable basis for determining the order of presentation of drug interactions. Because, for certain products, this section can be lengthy and complex, the agency will not designate a specific order in the regulations.

(Comment 64) One comment recommended that, in the following language from the proposed provision for the ''Drug Interactions'' section, the word ''patients'' be replaced with the word ''humans'': ''Information in this section must be limited to that pertaining to clinical use of the drug in patients.'' The comment maintained that drug interaction studies often involve healthy volunteers, rather than patients, and the language in the regulation should reflect the nature of the study participants.

The agency has revised final § 201.57(c)(8)(i) to clarify the scope of the information to be included in this section and this sentence was deleted.

(Comment 65) One comment requested that the agency clarify the requirement in the proposed ''Drug Interactions'' section to briefly describe the mechanism of interaction for drugs and drug classes that interact with a drug in vivo. The comment maintained that the mechanism is not always understood and requested that the rule specify that the requirement to describe the mechanism applies only if the mechanism is understood.

The agency agrees. Proposed § 201.57(c)(7) (§ 201.57(c)(8)(i) in this final rule) has been revised to state that the mechanism of an interaction must be briefly described, if it is known.

• *Use in specific populations (proposed § 201.57(c)(8))*

FDA proposed to require a new section entitled ''Use in Specific Populations'' (proposed § 201.57(c)(8)) to include the information on specific populations required in the ''Pregnancy,'' ''Labor and delivery,'' ''Nursing mothers,'' ''Pediatric use,'' and ''Geriatric use'' subsections of the ''Precautions'' section at then-current § 201.57(f)(6) through (f)(10). The agency also proposed to revise certain required warning language in the labeling of drugs in pregnancy categories D and X (proposed § 201.57(c)(8)(i)(A)(4) and (c)(8)(i)(A)(5)). The proposal would have replaced the following language from then-current § 201.57(f)(6)(i)(d) and (f)(6)(i)(e): ''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.'' The proposed alternative language, which was intended to address the concern that any woman with reproductive potential should be apprised of the risk associated with taking the category D and X drugs during pregnancy, read: ''If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.''

FDA also proposed some changes in terminology to the ''Nursing mothers'' subsection (proposed § 201.57(c)(8)(iii)). For example, FDA proposed to change the term ''nursing mothers'' to ''lactating women.'' Other proposed changes included making assessments based on ''clinically significant adverse reactions'' rather than ''serious adverse reactions.''

(Comment 66) Several comments supported creation of a section devoted to information about use in specific populations. The comments indicated that placing all the information on specific populations in one labeling section would make the information much easier to locate. However, one comment stated that the revised warning statement for drugs in pregnancy categories D and X no longer makes clear that a pregnant woman receiving the drug should be apprised of the potential hazard to the fetus. The comment expressed concern that the phrase ''women with reproductive potential'' could be interpreted as referring only to women with the potential to become pregnant and not to those who actually are pregnant.

The agency is developing a proposal that would revise the requirements for the ''Pregnancy,'' ''Labor and delivery,'' and ''Nursing mothers'' subsections of prescription drug labeling. For this reason, the agency has reconsidered the need to make minor, interim changes to the warning statements for pregnancy categories D and X in this final rule and has decided to retain the language at former § 201.57(f)(6)(i)(d) and (f)(6)(i)(e). This language clearly addresses use of the drug by pregnant women and obviates the need for the changes advocated by the comment.

FDA also decided not to make interim changes to the ''Nursing mothers'' subsection of the labeling and will retain the language at former § 201.57(f)(8) for this subsection. The agency believes that it is best to address all changes to the content of these subsections at one time.

(Comment 67) One comment requested that the agency combine the initiative to revise the requirements for the pregnancy labeling with this rulemaking to revise the requirements of prescription drug labeling generally. The comment maintained that the pregnancy labeling requirements need to be changed expeditiously to require that the labeling address the likelihood of harm to the fetus based on timing of exposure, pharmacokinetic changes in pregnant women, and the relevance of animal data to humans.

The agency does not agree that the two initiatives should be combined. The pregnancy labeling initiative focuses exclusively on revising the content requirements for the pregnancy subsection of labeling to meaningfully describe the risks associated with fetal and maternal exposure to a drug and the clinical implications of those risks. In contrast, this final rule is focused on revising the format and content of labeling to increase its usefulness for health care practitioners.

- *Adverse reactions—definition of adverse reaction (proposed § 201.57(c)(9))*

FDA proposed to revise the definition of ''adverse reaction'' to mean a ''noxious and unintended response to any dose of a product for which there is a reasonable possibility that the product caused the response, i.e., the relationship cannot be ruled out'' (proposed § 201.57(c)(9)).

(Comment 68) Several comments objected to the revised definition of an adverse reaction in proposed § 201.57(c)(9). The comments maintained that this definition would be too restrictive and could result in omission of important information. Comments expressed particular concern that the terms ''noxious'' and ''unintended'' could be applied to exclude important adverse reactions. They also stated that important information could be excluded from the ''Adverse Reactions'' section because manufacturers could narrowly construe whether the drug caused the event. Comments maintained, for example, that an adverse reaction that affects compliance could be considered clinically meaningful and thus merit discussion in the ''Warnings and Precautions'' section, but be excluded from the ''Adverse Reactions'' section because it is not considered noxious or unintended. Some comments requested clarification of elements of the definition—in particular ''noxious,'' ''unintended,'' and ''injurious to health.'' One comment recommended that ''unintended'' be changed to ''unexpected,'' stating that ''unexpected'' may more accurately reflect the intent of the definition. One comment requested that FDA issue guidance to clarify these concepts and conduct an educational campaign to explain the meaning and significance of the new definition. Several comments maintained that the definition of an adverse reaction in then-current § 201.57(g) is a more accurate description of the events that should be included in labeling.

One comment expressed concern that the proposed definition of adverse reaction could result in excluding adverse events that should be included in the labeling because there is a lack of guidance for determining ''reasonable causality'' to identify which adverse reactions to list. The comment said that it is commonly known that prescription drug labeling lists all adverse reactions that occurred in trials, with definite, probable, possible, and remote causality. The comment recommended that significant adverse reactions be listed in Highlights and reinforced in the full prescribing information. The comment also stated that all other events that occurred should still be listed, perhaps last in the comprehensive ''Adverse Reactions'' section, because the loss of a comprehensive listing of all reported events could be detrimental to patient safety.

Some comments stated that the proposed new definition for an adverse reaction was a marked improvement because it would narrow the scope of the ''Adverse Reactions'' section. These comments contended that narrowing the scope of events considered adverse reactions for purposes of the ''Adverse Reactions'' section would help address long-standing practitioner concerns that the section is not very informative because it contains excessively long lists of reactions, many of which are not relevant to clinical use of the drug.

The agency has reconsidered the proposed definition of an adverse reaction, which was intended to conform to the definition of adverse drug reaction for safety reporting in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance ''E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting'' (60 FR 11284 at 11285, March 1, 1995).

Upon consideration of the comments submitted in response to this proposal, the agency concluded that it should not require use of a new definition of adverse reaction for labeling of new and recently approved products. The agency believes that the language in the definition of adverse reaction at former § 201.57(g) (designated in the final rule

as § 201.57(c)(7)), in particular ''an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence'' is appropriate for labeling, but that it requires clarification, as described in the next paragraph, to minimize including information in labeling that does not help prescribers use the drug safely and effectively (i.e., adverse events that are not related to use of the drug), and that may result in diluting the usefulness of clinically meaningful information. Thus, FDA will, as recommended by several comments, continue to use its existing definition for adverse reaction.

The agency believes, as previously indicated, that the definition of adverse reaction at former § 201.57(g) requires clarification. For this purpose, FDA has revised this definition to make clear that it is specific to prescription drug labeling and does not include all adverse events observed during use of a drug, but only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. There are many factors to consider in assessing the association between a drug and a reported adverse event and determining whether a reported event is an adverse reaction that should be included in labeling. The agency has included clarifying language in this final rule to assist in selecting and organizing reactions. To further assist manufacturers and reviewers, FDA is making available the ''Adverse Reactions'' section guidance (see section IV of this document).

(Comment 69) One comment expressed concern that inclusion of an adverse reaction in the ''Adverse Reactions'' section under the proposed definition would be tantamount to an admission that the event was caused by a drug for product liability purposes. Another comment stated that having two definitions for adverse reactions (i.e., the definition in proposed § 201.57(c)(9) for new and recently approved drugs and the definition in redesignated § 201.80(g) for older drugs) may have implications for product liability. One comment stated that application of the proposed adverse reactions definition to drugs that have to revise their labeling to implement the new format would require reevaluation of clinical data and a new safety review by the agency. One comment requested the agency clarify whether manufacturers would now have to reclassify or otherwise reassess adverse reactions profiles of products with existing labeling.

The concerns expressed in these comments are based on the proposed adverse reaction definition. Because the agency is not adopting this definition for the purposes of labeling, FDA believes that the concerns expressed in these comments are no longer applicable.

- *Adverse reactions—characterization of adverse reactions (proposed § 201.57(c)(9)(ii))*

FDA proposed to retain the language from then-current § 201.57(g)(2) in proposed § 201.57(c)(9)(ii):

> 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.* * *

(Comment 70) One comment requested that the agency reconcile apparent inconsistencies between the draft of the ''Adverse Reactions'' section guidance in development and the language in the ''Adverse Reactions'' section of the proposed rule. The comment maintained that the recommended organization in the draft ''Adverse Reactions'' section guidance is not consistent with the organization of the ''Adverse Reactions'' section in the proposed rule. This comment advocated that important points regarding adverse reactions be discussed in both the proposed rule and the ''Adverse Reactions'' section guidance, with extensive detail provided in the guidance document.

Based on this comment and on comments received on the draft ''Adverse Reactions'' section guidance, the agency has revised the regulation on the ''Adverse Reactions'' section at proposed § 201.57(c)(9) (designated in this final rule as § 201.57(c)(7)) to clarify the scope of information for this section of labeling. See comments 71 through 75.

The agency recognizes that the ''Adverse Reactions'' section has evolved over time to a point where it now typically contains several different components (e.g., information from controlled clinical trials, uncontrolled clinical trials, and postmarketing experience). The agency also recognizes that there exists considerable inconsistency in how information in this section is organized and presented across different drug products. To address this problem, the agency recommends, in the ''Adverse Reactions'' section guidance, an organization for the typical components of the ''Adverse Reactions'' section.

Thus, FDA continues, as recommended by the comment, to provide general requirements in regulation and detailed recommendations in guidance. The ''Adverse Reactions'' section guidance provides recommendations for how to select information for inclusion in this section, how to characterize the information, and how to further organize it (see section IV of this document).

(Comment 71) One comment recommended that manufacturers be required to specify in the ''Adverse Reactions'' section what categorization scheme was employed for listing of the adverse reactions.

The agency believes that, in most cases, the basis for the categorization of ''Adverse Reactions'' section will be readily apparent to readers. In rare instances in which the basis for categorization is not apparent, it would be appropriate to identify the categorization scheme employed. The agency has, therefore, determined that it is not necessary to require in regulation that the basis for categorization of adverse reactions be identified for all labeling.

The agency has revised, for the reasons described in the response to comment 70, proposed § 201.57(c)(9)(ii) (designated in this final rule as § 201.57(c)(7)(ii)) to provide clarification for this part of the ''Adverse Reactions'' section. The agency changed the term ''organ system'' to ''body system.'' Although the two terms have been used interchangeably, currently, the term ''body system'' is used most often.

In addition, the agency deleted the option to categorize adverse reactions by toxicological mechanism. After reviewing the 1975 proposed and 1979 final rules, the agency concluded that the term is not clear; therefore, categorization by toxicological mechanism is not an appropriate option for the ''Adverse Reactions'' section.

The agency also made clear that, however categorized, adverse reactions must be listed in order of decreasing frequency.

FDA also removed the requirement that significantly more severe reactions be listed before other reactions regardless of frequency. In most cases, frequency information is paramount, but in other cases, severity information may be more important or a combination of

the two may be the best approach. The categorization scheme selected for the ''Adverse Reactions'' section should be appropriate to the drug's safety database and reflect the relative public health importance of the information.

The agency also clarified that if data are available and important for adverse reactions with significant clinical implications, details about the nature, frequency, and severity of the reaction must be included. This provision makes clear that, in many cases, in addition to lists of adverse reactions, descriptive information is appropriate for inclusion in the ''Adverse Reactions'' section.

(Comment 72) One comment requested that the agency require that adverse reactions identified from postmarketing experience be listed separately from adverse reactions identified from clinical trials.

The agency agrees that adverse reactions identified from domestic and foreign spontaneous reports after a drug is marketed should be listed separately from adverse reactions identified in clinical trials. Adverse reaction data from clinical trials and spontaneous reports communicate different information to practitioners. In clinical trials, subjects are specifically queried about and evaluated for occurrence of adverse events and clinical investigators have requirements for identifying and reporting such events (21 CFR 312.64(b)). Data from clinical trials inform practitioners about the range of adverse reactions that may occur. In addition, because there is typically a comparison to a control group, these data provide an estimate of the incidence and the ability to identify events that, because they are likely to be causally related, represent adverse reactions.

Postmarketing experience with a drug permits observation of suspected adverse reactions in a larger, often more diverse, patient population. This experience may provide an opportunity to identify low frequency reactions and reactions not previously observed because the susceptible population was either excluded from the controlled trials or only included in small numbers. But, to interpret this information accurately, a practitioner must be mindful that postmarketing experience, although more closely reflective of clinical practice, lacks the structure of a clinical trial setting that permits increased precision. For postmarketing reporting, the impetus for reporting, the frequency with which a suspected adverse reaction is reported, and the number of exposures to the drug compared to the number of suspected reactions reported are unknown, making estimation of incidence calculations difficult.

Because these differences significantly affect the interpretation of these complementary sets of data, the agency believes it is important to separate in labeling adverse reactions identified in clinical trials from adverse reactions identified from domestic and foreign spontaneous reports. For precisely these reasons, in the draft ''Adverse Reactions'' section guidance, FDA suggested segregating adverse reactions from spontaneous reports in this section of the labeling. Thus, the agency has revised proposed § 201.57(c)(9)(ii) (§ 201.57(c)(7) in this final rule) by creating a separate listing for each set of adverse reactions within the ''Adverse Reactions'' section.

The agency clarifies that this distinction is between adverse reactions identified in clinical trials and those identified from domestic and foreign spontaneous reports after a drug is marketed. Adverse reactions that are identified in clinical trials conducted after a drug is marketed would be listed under adverse reactions identified from clinical trials.

(Comment 73) One comment requested that, for drugs with multiple doses or indications, the ''Adverse Reactions'' section have a separate presentation of adverse reactions for each dose or indication.

The agency agrees that it is important for the ''Adverse Reactions'' section to call attention to adverse reactions for which there are clinically significant dose-response relationships.

Thus, the agency has revised proposed § 201.57(c)(9) (designated in this final rule as § 201.57(c)(7)) to require manufacturers to include details about the relationship of adverse reactions to drug dose where sufficient data are available and necessary to prescribe the drug safely and effectively. The agency does not believe, however, that it needs to require that separate presentations of adverse reactions always be included for different doses. If there are important differences in adverse reaction rates for different doses, the section can include a single table that directly compares the adverse reactions rates for different doses. Presenting rates for different doses side by side in a table, for example, is an effective way to make a dose-response relationship apparent.

The agency also does not believe that it needs to require a separate presentation of adverse reactions for each indication. Such information could be appropriate for a drug with multiple indications, however, when the adverse reaction profile differs substantially from one indication or population to another, the differences are drug related, and the data have important clinical implications. On the other hand, where differences are relatively minor and not clinically meaningful, separate presentations for multiple indications would not be informative and would detract from more important information.

(Comment 74) One comment requested that the ''Adverse Reactions'' section discuss differences in adverse reaction rates among different demographic subgroups (e.g., men, women, blacks, renally-impaired).

The agency agrees that the ''Adverse Reactions'' section must include information on differences in adverse reactions among demographic subgroups where sufficient data are available and important. Thus, the agency has revised proposed § 201.57(c)(9) (designated in this final rule as § 201.57(c)(7)) to require such information in the ''Adverse Reactions'' section.

• *Adverse reactions—frequency information (proposed § 201.57(c)(9)(ii))*

FDA proposed to retain the language from then-current § 201.57(g)(2) in proposed § 201.57(c)(9)(ii):

> 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.
>
> For biological products, such figures must be supported by substantial evidence.

(Comment 75) One comment asked the agency to clarify an apparent inconsistency between the proposed rule and the draft ''Adverse Reactions'' section guidance concerning how to characterize the incidence of adverse reactions. The comment pointed out that the proposed rule (which used the same language as in the 1979 final rule) recommended grouping adverse reactions by rough orders of magnitude and encouraged use of the terms ''frequent,'' ''infrequent,'' and ''rare'' in conjunction with orders of magnitude

appropriate for a given drug's safety database. The comment observed that agency guidance discouraged use of these terms when grouping by rough orders of magnitude.

The agency agrees that clarification is needed regarding presentation of incidence information for adverse reactions. The language in the proposed rule is not sufficiently precise to accurately reflect current practices in characterizing the incidence of adverse reactions associated with the use of a drug product. The preamble to the 1975 proposed rule indicates that precise percent figures would be appropriate if there is scientific evidence from well-controlled trials substantiating such figures and when inclusion of percent figures does not falsely imply a greater degree of accuracy than actually exists (40 FR 15392 at 15393, April 7, 1975). The science of clinical trials has progressed so substantially over time that ascertaining such rates is typically part of virtually all drug development programs.

Under current labeling practices, rates of incidence for most adverse reactions identified in controlled clinical trials are expressed as percentages. Current labeling also typically includes percentage rates for comparison groups in clinical trials (e.g., placebo group) where inclusion of such rates would not be misleading. Broader frequency ranges are used only when meaningful percentage rates cannot be determined. Therefore, the agency has revised proposed § 201.57(c)(9) (designated in this final rule as § 201.57(c)(7)) to make it clear that when meaningful adverse reaction rates can be derived (for drug treatment group and comparison groups) and presentation of comparator rates would not be misleading, they must be included in labeling.

The agency also believes it is inappropriate to use nonspecific terms such as ''frequent,'' ''infrequent,'' and ''rare'' when presenting adverse reaction information. The agency believes the science of clinical trials has evolved such that use of those terms in the manner recommended by the 1979 rule is confusing because the terms do not necessarily refer to the same frequency range across different drug products. For example, for product A, ''rare'' might mean an incidence of less than 1/500, but for product B, ''rare'' might mean an incidence of less than 1/1000. Moreover, the terms are imprecise and, even if precise meanings were defined, would reinforce the misconception that frequency is synonymous with seriousness.

The agency believes that identifying the numerical frequency range alone is a clearer way to communicate rough rates of incidence for a group of adverse reactions. Therefore, the agency has revised proposed § 201.57(c)(9) to require that adverse reactions for which meaningful percentage rates cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), be grouped within specified frequency ranges as appropriate to the safety database of the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined.

(Comment 76) One comment requested clarification on how percentages should be used to characterize the frequency of adverse reactions when percentages are derived from studies that evaluated greater doses than the approved dose. The comment asked whether, in this circumstance, rates of adverse reactions should be omitted from the ''Adverse Reactions'' section.

The agency will determine, during review of an application, whether adverse reaction rates derived from doses greater than recommended doses would be informative for practitioners and not misleading, and thus appropriate for inclusion in labeling. Where there are adverse reaction data from studies using different doses, including doses greater than recommended doses, the agency will evaluate whether pooling or otherwise combining adverse reaction data would more accurately describe the frequency of adverse reactions.

(Comment 77) One comment requested clarification on whether manufacturers are required to identify the total number of patients enrolled in clinical trials in the ''Adverse Reactions'' section.

FDA has revised proposed 201.57(c)(9)(i) (designated in this final rule as 201.57(c)(7)(i)) to clarify that the total number of subjects or patients exposed to the drug, and the extent of exposure, must be identified in the ''Adverse Reactions'' section, so that practitioners can interpret the significance of the data in this section. The ''Adverse Reactions'' section guidance provides recommendations on how to describe the database from which the adverse reaction data in this section are derived (see section IV of this document).

- *Clinical pharmacology (proposed § 201.57(c)(13))*

FDA proposed to require that the ''Clinical Pharmacology'' section (proposed § 201.57(c)(13)) contain three subsections—''Mechanism of action,'' ''Pharmacodynamics,'' and ''Pharmacokinetics.'' Proposed § 201.57(c)(13) also provided for an optional subsection for incorporation of other clinical pharmacology information that does not fit into one of the specified subsections.

(Comment 78) One comment recommended that the ''Clinical Pharmacology'' section be revised to require discussion of a drug's elimination half-life, indicate differences in elimination half-life as a function of age or other subpopulation, and specify the enzyme involved in metabolism (e.g., CYP450).

Under the final rule, elimination half-life of drugs and differences in the elimination half-life as a function of specific populations (including age-related populations) must be reported in the ''Pharmacokinetics'' subsection of the ''Clinical Pharmacology'' section of the labeling (§ 201.57(c)(13)(i)(C)). In addition, if there are clinically significant differences in elimination half-lives among specific populations and those differences require special monitoring or alternate dosing regimens, such information must be included in other sections, such as ''Use in Specific Populations,'' ''Warnings and Precautions,'' and ''Dosage and Administration.'' Information about drug metabolism, including metabolic pathways and the enzyme systems involved, is also required in the ''Pharmacokinetics'' subsection of the ''Clinical Pharmacology'' section.

(Comment 79) One comment requested that FDA clarify the statement in proposed § 201.57(c)(13)(i)(B): ''If pharmacokinetic/pharmacodynamic relationships are not demonstrated or are unknown, the labeling must contain a statement about the lack of information.'' The comment asked that FDA clarify whether the provision is referring to concentration versus response relationships generally.

In response to this comment, the agency has rephrased this provision, as follows: ''Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known.'' (See final § 201.57(c)(13)(i)(B).)

(Comment 80) One comment stated that the three new subsections in the ''Clinical Pharmacology'' section will make it easier to find information in the section.

One comment requested that in vitro data supporting the ''Mechanism of action'' subsection in the ''Clinical Pharmacology'' section be permitted to

be included in the subsection because such information is helpful in understanding a drug's physiologic activity and in differentiating a drug from other therapeutic agents.

The agency agrees that the three new subsections should make information easier to find. Because 201.56(d)(2) (proposed 201.56(d)(5)) permits additional nonstandard subsections, FDA deleted ''12.4 other clinical pharmacology information'' (proposed 201.57(c)(13)(i)(D)) from the final rule.

The ''Mechanism of action'' subsection must include information based on in vitro data if the information is essential to a description of the established mechanism of action and the information is clinically relevant. Where in vitro information about mechanism of action is included, the information must not be used as the basis for a clinical comparison (i.e., to differentiate the drug from other therapeutic agents).

(Comment 81) Many comments opposed the proposal (proposed § 201.57(c)(13)(ii) to revise the current ''Clinical Pharmacology'' section to require that in vitro data related to the activity or effectiveness of an anti-infective drug be included in the section only if a waiver is granted under § 201.58 or § 314.126(c) (21 CFR 314.126(c)). While comments conceded that in vitro data have their limitations, the comments maintained that in vitro data for anti-infective agents can be an important component of the total information available for making prescribing decisions in some situations, including: (1) In the absence of susceptibility testing, (2) in treating drug resistant pathogens (e.g., drug-resistant pneumococci), and (3) in treating rare infections. Some comments stated that preventing inclusion of in vitro data that indicate a drug is inactive against a microorganism could result in selection of inappropriate antibiotics and poor clinical outcomes. One comment maintained that some physician organizations effectively endorse use of in vitro data by having guidelines that recommend use of in vitro data as an adjunct to making educated empirical judgments about appropriate anti-infective therapy. Several comments stated that the absence of in vitro data will make it difficult for practitioners to identify appropriate broad spectrum agents when broad coverage is needed. One comment requested that in the event the agency decides to go forward and exclude in vitro data related to effectiveness unless a waiver has been granted, the agency explain in detail the process by which a waiver could be granted.

Several comments expressed concern about the implications of removing in vitro data for devising susceptibility tests for new anti-infective drugs. They stated that these data are relied on by FDA (the Center for Devices and Radiological Health) and by manufacturers of in vitro susceptibility tests in selecting appropriate organisms for which to devise tests. In addition, comments stated the data are used to develop quality control mechanisms for, and to help develop criteria for use in the review and clearance of, susceptibility test devices. Some comments maintained that removal of in vitro data would cause manufacturers not to develop susceptibility tests for organisms for which such tests would be desirable.

One comment supported exclusion of in vitro data from labeling. The comment stated that exclusion of in vitro data that are not adequate to support therapeutic decisionmaking will improve anti-infective therapy and help prevent inappropriate use of antibiotics.

The agency has reconsidered its proposal to exclude from the ''Clinical Pharmacology'' section in vitro data for anti-infectives that are not supported by clinical data. The agency is considering a broad range of issues concerning the development and labeling of anti-infective products, including the types of data that should be obtained to support indications, the way that indications and anti-infectives data should be presented in labeling, and ways to meaningfully address resistance to anti-infective drugs. The agency believes a comprehensive and coordinated approach is needed to address these issues. Thus, FDA is deferring any action on the in vitro data proposals in the ''Clinical Pharmacology'' section of labeling at §§ 201.57(c)(13)(ii) and 201.80(b)(2) until the agency has developed a comprehensive plan. At that time, the agency may repropose changes to the way in which in vitro data are presented in labeling.

(Comment 82) Several comments maintained that the algorithm in the agency's current guidance for industry (''Clinical Development and Labeling of Anti-Infective Drug Products,'' 1992) for determining when it is appropriate to include in labeling in vitro data not supported by clinical data contains adequate safeguards and should continue to be used for determining when to include such data. One comment suggested that labeling users be educated about the criteria for inclusion in labeling of in vitro data not supported by clinical data and how to use such data in making prescribing decisions.

At this time, the agency will continue to rely on the algorithm in its current guidance on clinical development and labeling of anti-infectives for determining when to include in vitro data in the ''Clinical Pharmacology'' section of labeling. As part of the comprehensive evaluation of the way in which anti-infective therapies are currently developed and labeled (see response to comment 81), the agency may reconsider use of the algorithm and make any changes that may be needed. For this reason, the agency will not at this time undertake an educational campaign to educate prescribers about the basis for inclusion of in vitro data in labeling.

(Comment 83) Several comments recommended retaining in vitro data for anti-infective drugs in the ''Clinical Pharmacology'' section and strengthening the current in vitro disclaimer statement that indicates that the clinical significance of the in vitro data is unknown.

Until FDA has developed a comprehensive plan to address the broad range of issues confronting development and labeling of anti-infective products, the agency will defer any decisions about the content of the disclaimer that accompanies in vitro data indicating that the clinical significance of the data is unknown.

(Comment 84) One comment requested that the agency clarify the scope of the proposed exclusion of in vitro data to make clear that it does not encompass in vitro data with clinical substantiation. The comment maintained that in vitro susceptibility data from large scale clinical trials would provide some basis for making an informed decision about possible effectiveness in the absence of susceptibility testing (e.g., while awaiting such testing) and that this information is especially important for antiviral drugs.

In vitro data that are supported by clinical data have certain problems in common with in vitro data not supported by clinical data (e.g., antimicrobial susceptibilities are constantly changing and vary by location). In vitro and animal data not supported by clinical data were the focus of the agency's proposal to exclude in vitro and animal data from the ''Clinical Pharmacology'' section (§ 201.57(c)(13)(ii)). As discussed previously, the agency has reconsidered its proposal to exclude such data from

labeling and will defer any action until it has developed a comprehensive plan.

(Comment 85) Several comments recommended that in vitro susceptibility data for anti-infectives be retained in labeling and be placed in a new labeling section entitled ''Clinical Microbiology.''

The agency believes that a labeling section devoted specifically to clinical microbiology data is not needed at this time. As a result of its ongoing comprehensive evaluation of anti-infectives drug development and labeling practices, the agency may reconsider the need for a separate section on clinical microbiology.

• *Nonclinical toxicology (proposed § 201.57(c)(14))*

FDA proposed to require a new section in the FPI entitled ''Nonclinical Toxicology'' (proposed § 201.57(c)(14)) to contain information from then-current § 201.57(f)(5) (the ''Carcinogenesis, mutagenesis, impairment of fertility'' subsection) and then-current § 201.57(l) (the ''Animal Pharmacology and/or Animal Toxicology'' section).

(Comment 86) One comment requested that FDA provide guidance clarifying when it would be appropriate to omit the ''Nonclinical Toxicology'' section.

Although the final rule provides that any section of labeling would be omitted if it is clearly inapplicable (see § 201.56(d)(4)), it is unlikely that the ''Nonclinical Toxicology'' section, in its entirety, would ever be inapplicable. Animal data are often the only practical and ethical means to understand a product's potential for certain kinds of toxicity (e.g., carcinogenicity, mutagenicity, reproductive and developmental toxicity). In addition, even if carcinogenicity data are not available, the labeling must state that these studies were not done (§ 201.57(c)(14)(i)). The final rule provides, however, that the ''Animal toxicology and/or pharmacology'' subsection must include certain data that do not appear elsewhere in the labeling. This means that this subsection would be omitted if all the required information appears in one or more of the other labeling sections (§ 201.57(c)(14)(ii)).

• *Clinical studies (proposed § 201.57(c)(15))*

FDA proposed to require a section in the FPI entitled ''Clinical Studies'' (proposed § 201.57(c)(15)). The section would be required to contain a discussion of clinical studies that are important to a prescriber's understanding of the basis for approval of the drug product, including the extent and limitation of the product's benefits, how the drug was used in clinical trials, who was studied, and critical parameters that were monitored.

(Comment 87) One comment requested that the agency clarify the extent to which secondary endpoint data, quality of life data, and pharmacoeconomic data would be permitted in the ''Clinical Studies'' section.

The ''Clinical Studies'' section must describe those studies that facilitate an understanding of how to use a drug safely and effectively. Generally, this means those studies that were essential to establishing the drug's effectiveness for the purpose of obtaining marketing approval.

If studies were appropriately designed to evaluate secondary endpoints, it may be appropriate to include a discussion of these secondary endpoints in the section.

The agency would evaluate the appropriateness of including quality of life and pharmacoeconomic data according to the same standard. The data could be appropriate for inclusion in the section if all of the following apply: (1) The data are from adequate and well-controlled trials that incorporated quality of life or pharmacoeconomic endpoints in their design and carried out appropriate analyses, (2) for pharmacoeconomic studies, the findings are reasonably generalizable to most clinical environments, not just the ones studied, and (3) the information would be important to a practitioner's understanding of how to use the drug in a clinical setting. The ''Clinical Studies'' section guidance contains FDA's recommendations on what studies are appropriate for inclusion in the ''Clinical Studies'' section (see section IV of this document).

(Comment 88) Some comments requested that the agency reconsider its proposal to bar, in the ''Clinical Studies'' section, inclusion of data concerning indications and doses that are not consistent with the approved indications and dosing regimens. Comments maintained that such information can be important to a practitioner's understanding of a product's clinical and safety profile, as well as to an understanding of the approved indication. Some comments stated that all studies that are scientifically sound and provide medically relevant information should be included in the ''Clinical Studies'' section. One comment stated that practitioners understand that data presented in the ''Clinical Studies'' section, as opposed to the ''Indications and Usage'' or ''Dosage and Administration'' sections, are intended for informational purposes only (i.e., not to suggest claims).

One comment asked that the agency make clear that the limitation on inclusion of information in labeling about unapproved doses and regimens would not preclude discussion of a dose ranging study that supports approval and includes dosage regimens that were not approved for use.

One comment agreed with the proposed revision to exclude from the ''Clinical Studies'' section data and information concerning indications and dosing that are not consistent with the information in the ''Indications and Usage'' and ''Dosage and Administration'' sections. The comment maintained that inconsistent information about indications and dosing creates confusion and contributes to uncertainty and distrust of information in the labeling.

Some comments stated that if the agency has concerns about the implications of labeling on product promotion, these can be addressed through its existing legal authority and should be addressed as a separate issue.

The agency requires that claims in any section of labeling, expressed or implied, be supported by substantial evidence (§ 201.56(a)(3)). This requirement would not preclude discussing in labeling an adequate and well-controlled clinical study, including a dose ranging study that has treatment arms with dosing regimens that are not recommended, if the data for the use of such regimens are important to a practitioner's understanding of how to use the drug safely and effectively. For instance, it might be important to include such data if the data indicate that a particular dosage regimen is not effective, is minimally active, provides no benefit compared to lower doses, or is associated with an unacceptable level of toxicity. If data that include dosage regimens other than recommended regimens are discussed in the ''Clinical Studies'' section, the data must be accompanied by a statement appropriately qualifying the data and indicating that those dosage regimens have not been found safe and effective by FDA, if such a statement is necessary for the labeling to be truthful and not misleading.

The agency agrees that advertising and promotional labeling regulations address product promotion issues and that this final rule is not an appropriate context for discussion of these issues.

• *References (proposed § 201.57(c)(16))*

FDA proposed to permit references to be included in labeling in place of a detailed discussion of a subject that is of limited interest, but nonetheless important (proposed § 201.57(c)(16)). The proposed provision stated that the reference must be based on an adequate and well-controlled clinical investigation under § 314.126(b) or, for a biological product, upon substantial evidence of effectiveness.

(Comment 89) One comment maintained that requiring that all information contained in the ''References'' section be based on adequate and well-controlled trials will result in omission of important references for many anti-infective products, including references for standardized test methodology in in vitro studies.

The agency believes that inclusion of a reference to clinical data will be unusual. Any clinical data that are important to a prescriber's understanding of the safe and effective use of the drug must be summarized in the ''Clinical Studies'' section, rather than referenced in the ''References'' section. The ''References'' section may cite an authoritative scientific body, standardized methodology, scale, technique, or similar material important to prescribing decisions that are mentioned in another section of labeling, but cannot readily be summarized. The agency has revised proposed §§ 201.57(c)(16) and 201.80(l) to make this clear and to delete the requirement that limits the ''References'' section to references to adequate and well-controlled clinical studies.

(Comment 90) One comment noted that, even though the conditions for including references in the proposed rule are essentially the same as in the requirements for old labeling, there are substantial differences in the way these conditions are applied across new drug reviewing divisions.

As discussed in the response to the previous comment, in this final rule, the agency has clarified the conditions under which it is appropriate to include a reference in prescription drug labeling. The agency appreciates the comment's concern about inconsistent application of the criteria for inclusion of references across different new drug review divisions. As part of its internal efforts to implement this final rule and related labeling initiatives, the agency intends to make considerable efforts to ensure consistent application of the requirements.

• *Patient counseling information (proposed § 201.57(c)(17))*

FDA proposed that the ''Information for patients'' subsection of the ''Precautions'' section (required under then-current § 201.57(f)(2)) be made a separate section entitled ''Patient Counseling Information'' (proposed § 201.57(c)(17)). The section would be placed at the end of the FPI.

The agency also proposed to require in proposed § 201.57(c)(17) that any approved printed patient information or Medication Guide be referenced in the ''Patient Counseling Information'' section and that the full text of the approved printed patient information or Medication Guide be reprinted immediately following the section.

(Comment 91) One comment supported the proposal to put information for patients in its own section and change the name from ''Information for patients'' to ''Patient Counseling Information.'' The comment stated that the name change is important because it emphasizes the need to counsel patients on their medications and not just provide printed materials.

As described in the proposed rule, FDA determined to change the heading of the information required under then-current § 201.57(f)(2) from ''Information for patients'' to ''Patient Counseling Information'' to clarify that the information under this section is not intended to be distributed to patients, but is intended to help practitioners communicate important drug information to patients.

(Comment 92) Some comments requested that the agency clarify the meaning of ''any approved printed patient information.'' One comment also asked that the agency clarify ''Medication Guide.''

FDA has revised the terminology in the final rule to clarify the meaning of ''any approved printed patient information'' and ''Medication Guide.'' The term ''FDA-approved patient labeling'' refers to any labeling that has been reviewed and approved by the agency that provides information for patients and is for distribution to patients who are prescribed a drug. This term includes approved printed patient information specifically required by regulation (e.g., for oral contraceptives (21 CFR 310.501) and estrogens (21 CFR 310.515)) and patient labeling that is submitted voluntarily to FDA by manufacturers and approved by the agency. FDA-approved patient labeling may have different functions reflected in the type of information conveyed to patients. For example, some FDA-approved patient labeling contains risk information, and some contains only detailed instructions about how to administer a drug product.

Medication Guides are a specific category of FDA-approved patient labeling. Under part 208 (21 CFR part 208), FDA can require a Medication Guide for a prescription drug product that FDA determines poses a serious and significant public health concern requiring distribution of FDA-approved patient information (§ 208.1(a)). Medication Guides are subject to specific content and format requirements (§ 208.20).

(Comment 93) Some comments supported the proposed requirement to reprint FDA-approved patient labeling at the end of the ''Patient Counseling Information'' section so that this information is readily accessible for healthcare practitioners. Other comments requested that the agency reconsider the proposal to require that FDA-approved patient labeling be printed at the end of the FPI. Some comments asked whether attaching prescription drug labeling without FDA-approved patient labeling to trade packaging and attaching the FDA-approved patient labeling separately would satisfy the requirement. Some comments expressed concern that prescription drug labeling with the FDA-approved patient labeling reprinted at the end may make it more difficult for patients to find and read the patient information. One comment stated that patient information typically uses larger fonts and may use color and illustrations, making it difficult and costly to reprint in the prescription drug labeling. Some comments also expressed concern that inclusion of FDA-approved patient labeling would make the labeling too long and impose additional costs because it could necessitate redesign and enlarging of trade packaging. One comment asked whether it would be sufficient to provide only a reference to FDA-approved patient labeling in the ''Patient Counseling Information'' section instead of reprinting the information in the section.

FDA believes that it is crucial that prescribers have ready access to FDA-approved patient labeling so that they are aware that the information exists, can familiarize themselves with the content of that information, and can explain the information to their patients. The agency believes this objective can best be accomplished by requiring that this information be reprinted at the end of prescription drug labeling. Thus, it would be insufficient to provide only a reference to FDA-approved patient labeling in the ''Patient Counseling Information'' section.

However, the agency is persuaded that reprinting the FDA-approved patient labeling at the end of the

labeling is not the only approach that would successfully address the need to familiarize prescribers with this information. Therefore, the agency has revised the requirements at §§ 201.57(c)(18) and 201.80(f)(2) to require that FDA-approved patient labeling either accompany the prescription drug labeling or be reprinted at the end of such labeling (i.e., immediately following the ''Patient Counseling Information'' section of the FPI for products subject to § 201.57(c)(18) or after the last section of labeling for products subject to § 201.80(f)(2)).

The agency acknowledges that, in cases for which FDA-approved patient labeling is included with prescription drug labeling, additional costs will be incurred by the manufacturer. To help minimize the added cost, FDA has revised proposed § 201.57(c)(18) to specify that the same type size requirements that apply to prescription drug labeling (§ 201.57(d)(6)) also apply to FDA-approved patient labeling that is printed at the end of the labeling or accompanies labeling, unless a Medication Guide is to be distributed to patients in compliance with § 208.24 (see table 7 of this document). In most cases, this will be a minimum type size of 8 points. For trade labeling, this will be a minimum type size of 6 points (see response to comment 102 for discussion of 6-point minimum type size for trade labeling for products subject to § 201.57). For Medication Guides to be distributed to patients, the type size requirements set forth at § 208.20 apply. With regard to the labeling for products subject to § 201.80, the agency clarifies at § 201.80(f)(2) that the font size requirement for Medication Guides in § 208.20 does not apply to a Medication Guide that is printed in prescription drug labeling unless it is intended to comply with § 208.24 (i.e., the requirement to distribute Medication Guides to patients). Thus, for these products, there is no minimum font size requirement for FDA-approved patient labeling that is included with labeling but not for distribution to patients (see table 7).

TABLE 7.—TYPE SIZE REQUIREMENTS FOR LABELING AND FDA-APPROVED PATIENT LABELING INCLUDED WITH LABELING

Labeling	Type Size Requirements for Labeling	FDA-Approved Patient Labeling Included with Labeling	Type Size Requirements for FDA-Approved Patient Labeling
New Format (§ 201.57)			
Trade Labeling (i.e., labeling on or within the package from which the drug is to be dispensed)	Minimum 6-point type	FDA-approved patient labeling that is not for distribution to patients	Minimum 6-point type
		Any FDA-approved patient labeling except a Medication Guide that is for distribution to patients	Minimum 6-point type
		Medication Guide that is for distribution to patients	Minimum 10-point type
Other Labeling (e.g., labeling accompanying promotional materials)	Minimum 8-point type	FDA-approved patient labeling that is not for distribution to patients	Minimum 8-point type
		Any FDA-approved patient labeling except a Medication Guide that is for distribution to patients	Minimum 8-point type
		Medication Guide that is for distribution to patients	Minimum 10-point type
Old Format (§ 201.80)			
Trade Labeling and Other Labeling	No minimum requirement	FDA-approved patient labeling that is not for distribution to patients	No minimum requirement
		Any FDA-approved patient labeling except a Medication Guide that is for distribution to patients	No minimum requirement
		Medication Guide that is for distribution to patients	Minimum 10-point type

(Comment 94) One comment asked whether the agency meant for the prescription drug labeling with the FDA-approved patient labeling reprinted at the end to replace the stand-alone FDA-approved patient labeling required to be distributed to patients. The comment asked if the combined document would satisfy the requirement to distribute the FDA-approved patient labeling to patients who have been prescribed the drug. Other comments asked whether FDA-approved patient labeling attached to prescription drug labeling in a way that would facilitate it being torn off (e.g., along a perforation line) would satisfy these requirements. One comment noted that if the FDA-approved patient labeling is appended to the prescription drug labeling as a perforated attachment, it might be more difficult for the patient to receive information at the pharmacy because the pharmacist would have to separate the patient information from the prescription drug labeling.

The agency does not mean for prescription drug labeling with the FDA-approved patient labeling reprinted at the end to replace the stand-alone FDA-approved patient labeling required to be distributed to patients. FDA has long stressed the importance of providing such information to consumers.

However, if the FDA-approved patient labeling is appended to the prescription drug labeling (e.g., as a perforated attachment that can be torn off and given to patients) and is formatted as

required for distribution to patients (§ 208.20), it would meet the requirement to provide information to patients. For example, for a product subject to § 201.57 with a Medication Guide, trade labeling for the product would be required to be in at least 6-point type (see comment 102 of this document), while the Medication Guide, if reprinted as a perforated attachment to the labeling for distribution to patients, would be required to be in a minimum 10-point type (see table 7). For products subject to § 201.80 with a Medication Guide, there is no minimum font size requirement for the labeling, while the Medication Guide, if reprinted as a perforated attachment to the labeling for distribution to patients, would be required to be in a minimum 10-point type (see table 7). The agency does not agree that distributing prescription drug labeling with the FDA-approved patient labeling appended as a perforated attachment will make it more difficult for the patient to receive information at the pharmacy because the pharmacists would have to detach the patient information.

(Comment 95) One comment sought clarification of what information should be included in the ''Patient Counseling Information'' section. The comment expressed concern about how the information in this section is to be communicated to patients.

The ''Patient Counseling Information'' section contains information that the practitioner may decide to convey to the patient at the time of prescribing for the drug to be used safely and effectively (e.g., warnings about driving if the product causes drowsiness, or the concomitant use of other substances that may have harmful additive effects). The information in this section will vary depending on the safety and efficacy characteristics of the product and how it is taken.

FDA believes that requiring a separate ''Patient Counseling Information'' section and a reminder message in Highlights directing practitioners to this section will make patient counseling information in labeling more accessible to health care practitioners. These requirements will increase the accessibility of the section and should reinforce the need for practitioners to counsel their patients, thereby fostering communication between practitioners and patients about prescribed drugs.

(Comment 96) One comment asked whether including the FDA-approved patient labeling in the ''Patient Counseling Information'' section would be sufficient to meet the content requirements for the section.

Including only the FDA-approved patient labeling in the ''Patient Counseling Information'' section is not sufficient to meet the requirements of this section. This section, like the other sections of prescription drug labeling, is specifically written for health care practitioners. Its purpose is to inform practitioners about what information is important to convey to the patient at the time of prescribing for the drug to be used safely and effectively. FDA-approved patient labeling, in contrast, is specifically written for a lay audience and is intended to be read by patients.

The agency emphasizes how important it is that prescribers be informed about what they should communicate to their patients. On the basis of a series of national telephone surveys conducted by FDA to assess how patients receive information about their prescription medicines, the agency determined that the prescribing physician is the primary source of drug information for patients (Ref. 5). The most recent survey, conducted in 1998, showed that more patients received verbal prescription medicine information at their physician's office (69 percent) than at the pharmacy (43 percent) (Ref. 5). In addition, although 74 percent of patients reported receiving written information at the pharmacy, of those who received written information at the pharmacy, 85 percent received instruction sheets and 83 percent received stickers on the medicine container, but only 38 percent received brochures about the medicine. These results indicate that most consumers who receive product information, other than instructions for use or the sticker information, receive it orally from their physicians during an office visit.

(Comment 97) One comment asked whether products with existing labeling that will be required to convert to the new labeling format will be required to have a ''Patient Counseling Information'' section if the product's existing labeling does not contain an ''Information for patients'' subsection in its ''Precautions'' section.

If a product that does not have an ''Information for patients'' subsection becomes subject to the new content and format requirements at § 201.57, the product's manufacturer would be required to develop a ''Patient Counseling Information'' section for the product's prescription drug labeling unless a ''Patient Counseling Information'' section would be clearly inapplicable (see § 201.56(d)(4)) and thus not required. The agency anticipates that few products would qualify for such an exception. The agency believes that the vast majority of products that will be required to have a ''Patient Counseling Information'' section will already have an ''Information for patients'' subsection in their existing labeling on which to base the ''Patient Counseling Information'' section. Thus, this new requirement is anticipated to impose minimal burdens on manufacturers.

I. Comments on the Format Requirements (Proposed § 201.57(d))

FDA proposed new format requirements for prescription drug labeling (proposed § 201.57(d)). The proposed provisions set forth minimum standards and requirements for many of the key graphic elements of labeling (e.g., type size, letter and line spacing, and contrast).

(Comment 98) Some comments recommended implementation of the proposed changes solely or primarily as part of the electronic labeling initiative. Some comments requested that the new format requirements not be implemented for prescription drug labeling required to be distributed with a drug in trade packaging. They pointed out that using an electronic format would permit use of larger print size, hypertext linking to all sections of labeling, links to newly revised sections of labeling, key word searches, and links to patient information without affecting the size of trade packaging. The comments maintained that larger trade packaging will be required to accommodate larger labeling that will result from the new format requirements.

The agency agrees that use of the required format in conjunction with an electronic medium may have benefits over paper labeling. As discussed in section V of this document, the agency believes that, in the future, the Internet and other electronic sources for labeling will most likely be the primary means for delivering drug information to practitioners. At the present time, however, some practitioners may not have the requisite computer equipment or skills to access prescription drug labeling in an electronic format. The agency anticipates that it will be several years before the phase-out of paper labeling as the major source of prescribing information can begin. Therefore, the agency believes that it is important to establish minimum format requirements for paper labeling.

(Comment 99) One comment recommended the use of more blank space among sections of Highlights. The comment expressed concern that, because Highlights contains a significant amount of information in a constrained space and uses a variety of

formatting techniques, the overall effect would be confusing. One comment stated that the placement of the ''Patient Counseling Information Statement'' above the ''Highlights Limitation Statement'' in Highlights is not ideal because it appears that the ''Patient Counseling Information Statement'' is the title of the limitation statement. The comment also requested that the FPI be required to be in a two-column format because such a format enables users to stay better aware of the overall information structure, as well as read individual sections more easily.

The agency believes that use of more blank space in Highlights would not be feasible because additional blank space would increase the length of Highlights and of labeling generally. The one-half page length limitation for Highlights is based on the strong preferences of physicians surveyed in developing the prototype for the new labeling format in the proposed rule. Physicians reacted negatively to prototype Highlights that were one or one and one-half pages long. They indicated that the utility of Highlights decreased significantly as its length increased. In addition, there was significant concern from manufacturers about the costs associated with adding to the length of labeling.

The agency also believes that the formatting techniques used in Highlights help make the information accessible, notwithstanding the density of the section. Therefore, the agency does not believe that it is necessary to include more blank space in Highlights.

The agency agrees that the formatting and placement of the ''Patient Counseling Information Statement'' and the ''Highlights Limitation Statement'' in Highlights could be improved to better communicate the discrete information provided by each statement. For this reason, and in response to comments recommending greater prominence for the ''Highlights Limitation Statement,'' the agency moved this statement to appear at the beginning of Highlights (see comment 35). The agency also removed the requirement at proposed § 201.57(d)(3) that the ''Patient Counseling Information Statement'' be presented in the center of a horizontal line, so that it does not appear to be a section title.

The agency agrees that a two-column format is effective, but believes other formats may be equally effective in conveying prescription drug information and, therefore, is not requiring a two-column format for the FPI.

• *Bolding (Proposed § 201.57(d)(5))*

In the proposal, the agency specifically sought comment on whether the requirement in proposed § 201.57(d)(5) to bold the information required by proposed § 201.57(a)(1) through (a)(4), (a)(11), and (a)(15) (i.e., the following information in Highlights: Drug names, dosage form, route of administration, and controlled substance symbol; the inverted black triangle symbol; the prescription drug symbol; boxed warnings or contraindications; adverse reaction reporting contacts; and Highlights limitation statement) would ensure the visual prominence of the bolded information or whether different highlighting methods would be more effective.

(Comment 100) Most comments expressed satisfaction that bolding was adequate to ensure the visual prominence of the specified information. Some comments stated that capitalization, italics, and underlining, also effective methods of ensuring prominence and flexibility, should be maintained. Some comments expressed concern that possible alternative methods of ensuring visual prominence (e.g., color printing) would add unnecessary costs. One comment requested that, if color is required, specific Pantone colors be assigned to specific types of information to ensure consistency in all product labeling.

The agency recognizes that use of different methods to ensure prominence may decrease their impact and significance. Therefore, FDA concludes that bolding alone is adequate to achieve visual prominence for the specified information in Highlights. The agency also agrees that color printing would add cost and impose an additional burden on manufacturers that would not be offset by meaningful improvement in visual prominence. Therefore, § 201.57(d)(5) requires the following Highlights information to be in bold type: Highlights limitation statement; drug names, dosage form, route of administration, and controlled substance symbol; the initial U.S. approval statement and year of this approval; boxed warnings; adverse reaction reporting contacts; and the patient counseling information statement.

(Comment 101) One comment requested that the agency revise the format of Contents to make it easier to read and use. The comment stated that the information in Contents is not as accessible as it could be because it uses straight columns, which make it hard to distinguish the major labeling sections (e.g., ''Use in Specific Populations'') from subsections (e.g., ''Pregnancy''). The comment recommended use of contrasting font types and sizes for the section titles and subheadings in each section, underlining section titles, indenting subheadings under each section title, and providing more blank space between each section. Another comment also recommended indenting the subheadings under the major sections to more readily distinguish between the major sections and the subheadings within the sections.

The agency agrees that all the recommended revisions to the format of Contents could make the information easier to read and use. Because of cost and space constraints, however, the agency believes that it is impractical to implement all of the recommended changes. FDA has revised the format requirements at proposed § 201.57(d) to now require that the subheadings under each section heading in Contents be indented (§ 201.57(d)(10). In addition, the final rule now requires that only the headings in Contents be bolded, not the subheadings (§ 201.57(d)(10)). The agency believes these changes make the Contents easier to read and use without increasing its length or attendant costs.

(Comment 102) In the proposal, the agency specifically sought comment on whether the proposed requirement (proposed § 201.57(d)(6)) for a minimum type size of 8 points for all typeface information in labeling is sufficient or whether a minimum type size of 10 points would be more appropriate. Currently, prescribing information is usually printed in 6- or 7-point type.

One manufacturer stated that 6-point type was generally adequate for prescribing information, and another manufacturer stated that it typically uses 4- to 6-point type. Some manufacturers were concerned that a minimum 8-point type would increase the length of labeling to such an extent that trade packaging would have to increase in size to accommodate the longer labeling and the increase in size would impose substantial costs. One comment recommended that prescribing information that accompanies trade packaging not be subject to the 8-point type minimum, while prescribing information that is distributed in other contexts, where it is more likely to be referenced by the prescriber (e.g., prescribing information in electronic format, prescribing information accompanying promotional materials and product samples), be required to be in at least 8-point type. Some manufacturers stated that 8-point type was adequate for prescribing information included in trade packaging, but that a minimum 10-point type would increase the length of labeling to such an extent that trade packaging would have to increase in

size to accommodate the larger prescribing information.

Some consumers and health care advocacy organizations requested that the agency reconsider whether the increase to an 8-point minimum type size was sufficient to achieve the agency's goal of improving the readability of the prescribing information. They stated that, to improve readability, labeling should be printed in a type size larger than 8 points and with more white space. They urged the agency to test prototypes to compare the relative readability of 8-point versus 10-point type. Some comments advocated that the minimum type size should be at least 10 points, and preferably 12 points, for all patient information.

In the preamble accompanying the proposed rule, FDA summarized studies that demonstrated the importance of type size in evaluating readability of written information and its effect on visibility and reading speed (see 65 FR 81082 at 81096 and Refs. 6 through 9). Type size combined with other graphical elements (e.g., letter and line spacing, contrast, print and background color, and type style) also affect readability (Ref. 10).

The agency carefully considered the literature, the comments submitted in response to the font size proposal, and the estimated costs of using various font sizes for labeling, and has determined that permitting different font sizes for trade labeling (i.e., labeling on or within the package from which the drug is to be dispensed) and labeling disseminated in other settings (e.g., labeling that accompanies prescription drug promotional materials) best achieves the agency's objective of ensuring an acceptable base level of readability for prescription drug labeling while, at the same time, minimizing costs to manufacturers. Even though a larger font size may improve readability, the agency believes that an 8-point minimum type size, combined with other required graphical elements (e.g., bold type, bullets, demarcation lines), is adequate for prescription drug labeling disseminated in settings where it is likely to be referred to by prescribers (e.g., labeling that accompanies drug promotional materials). The agency believes that the 8-point minimum type size reasonably balances the agency's objective of improving the readability of labeling with the costs associated with the resultant increase in the length of the labeling.

The agency also agrees with the comments requesting that there be an exception for trade labeling. FDA believes that a minimum 6-point type size requirement is satisfactory for such labeling. FDA's telephone survey of office-based physicians showed that the prescribing information in trade labeling is referred to by physicians substantially less frequently than other sources of prescribing information (Ref. 11, p. 30). Because manufacturers could incur substantial costs in converting trade labeling to 8-point type and the public health benefits of such conversion may not justify these costs, the agency believes it is reasonable to allow a 6-point minimum type size for trade labeling (see comment 124). Thus, proposed § 201.57(d)(6) was revised to permit a 6-point minimum type size for trade labeling.

The agency disagrees with the comment that recommended use of type sizes smaller than 6 points because such labeling would not be sufficiently readable. The final rule on OTC drug labeling requirements summarized research on smaller font sizes, noting that a significant portion of the adult population is not able to read OTC drug product labeling with 4.5-point type size (see 64 FR 13254 at 13264 and 13265, March 17, 1999).

The agency acknowledges those comments that urge even larger minimum type sizes to further increase readability. The agency agrees that, absent any cost or space constraints, a 10- or 12-point minimum type size would be preferable to 8-point. However, the agency believes that the 8-point minimum type size requirement for all labeling except trade labeling and the variety of formatting techniques incorporated into the new labeling format will substantially improve the readability of labeling without imposing unreasonable costs on manufacturers. Moreover, this final rule establishes minimum type sizes, but does not prevent manufacturers from printing labeling in larger type sizes.

(Comment 103) One comment requested that the agency require Roman typeface in labeling for optimal legibility. The comment stated that Roman is a major improvement over currently used sans serif, and that sans serif is only appropriate in applications where appearance is more important than legibility (e.g., advertising).

The agency does not agree that FDA should require a specific typeface for all prescription drug labeling. The agency believes that any typeface that is clear and legible should be acceptable in labeling.

(Comment 104) In the proposal, the agency specifically sought comment on whether the requirement in proposed § 201.57(d)(8) for a one-half page limit on Highlights is adequate or whether there are alternatives that would be more appropriate and under what circumstances such alternatives should be considered.

Some comments stated that the one-half page length restriction should be required for all products (i.e., there are no circumstances in which the limitation should be waived). Other comments maintained that it might be difficult to consistently accommodate the information required to be in Highlights within one-half page. These comments stated that the final rule should allow for some flexibility in the length of Highlights in those cases where one-half page may not be practical or possible. These comments indicated that some manufacturers had done mockups of Highlights and had been unable to get the required information on one-half page. Some comments stated that the length restriction should be flexible enough to accommodate as many disclaimers and qualifying messages as are necessary to guide the physician to the more detailed discussion of the desired information in the FPI. These comments maintained that the limitation on length could result in increased medication errors because important information would be too compressed or might be excluded from Highlights.

The agency believes that a one-half page Highlights is adequate for the vast majority of products. As discussed previously, Highlights provides introductory information to the more detailed FPI. The agency does not agree that multiple disclaimers or qualifying statements would be useful or appropriate.

The agency acknowledges, however, that there may be situations in which it may not be possible to accommodate all the information that should go into Highlights within one-half page. In such cases, the agency may waive the one-half page requirement and approve the labeling with slightly longer Highlights. Accordingly, FDA has revised § 201.58 in this final rule to make clear that FDA can waive any of the requirements under § 201.56 or § 201.57.

The agency strongly believes that limiting the length of Highlights is critical to preserving its usefulness. In the physician surveys relied on by the agency in developing and refining the new labeling format, 80 percent of physicians indicated that a summary or highlights section should be no more than one-half page. The surveys found that the perceived usefulness of Highlights declined considerably with increasing length. Accordingly, the labeling format was designed to accommodate, on a single page, a one-

half page Highlights and a one-half page Contents. To test the feasibility of limiting Highlights to one-half of a page, the agency did numerous mockups of Highlights for a wide range of products and found that the one-half page limit provided adequate space in each case. Thus, the agency anticipates that the length restriction will be feasible in the vast majority of cases.

(Comment 105) In the proposal, the agency specifically sought comment on whether there are means other than a vertical line that would facilitate access to, and identification of, new labeling information in the FPI.

Some comments agreed that it was highly desirable to call attention to new information in the FPI and that the vertical line is adequate to identify the new information. Other comments stated that it was desirable to call attention to new information, but that a vertical line in the FPI might not be the best mechanism because it might not be understood as a revision mark by practitioners. Some comments maintained that use of a vertical line would make the printing and graphics process for labeling more complex and costly. One comment recommended italicizing new or revised text in the FPI. One comment recommended use of an asterisk to identify changes, along with a footnote explaining what was changed. Some comments maintained that identifying recent changes in narrative in a section of the FPI devoted to labeling changes or in the proposed ''Recent Labeling Changes'' section in Highlights (now called ''Recent Major Changes'') would alone be adequate to call attention to changes in the FPI. Some comments stated that the vertical line will call unnecessary attention to minor changes. Some comments stated that, by stressing labeling changes, the identification of changes in the FPI could dilute the significance of unmarked text.

The agency has retained the proposed requirement at § 201.57(d)(9) to mark major changes in the FPI with a vertical line in the left margin. The agency agrees that it is highly desirable to call attention to new information in the FPI and that the vertical line is adequate to identify the new information. The agency considered bolding, underlining, and italicizing as means to emphasize changes. These formatting techniques are all currently used in labeling to add emphasis for purposes other than identifying new information, so they would not be readily understood as identifying labeling changes. Asterisks are also used in labeling for purposes other than identifying labeling changes. The agency believes that use of an explanatory footnote with the asterisk would not overcome the confusion arising from use of an asterisk for multiple purposes in labeling.

The agency acknowledges that a vertical line in the margin might not be universally understood as an indication that the text adjacent to the mark has been changed. The agency believes, however, that a significant percentage of practitioners have had some experience with commercial word processing software and thus some exposure to revision marks, including the use of the vertical line to identify changed text. The agency also intends to develop for practitioners a comprehensive educational campaign to accompany the introduction of the revised labeling format. This educational campaign will address, among other issues, the significance of the vertical line in the margin.

The agency does not believe the vertical line will unnecessarily call attention to minor changes in labeling. The vertical line will be applied only to substantive changes that are identified in the ''Recent Major Changes'' (''Recent Labeling Changes'' in the proposed rule) section in Highlights. In response to comments requesting that the agency clarify what is meant by substantive changes, the agency specified in the final rule that only significant changes in the ''Boxed Warning,'' ''Indications and Usage,'' ''Dosage and Administration,'' ''Contraindications,'' and ''Warnings and Precautions'' sections of the FPI be listed in the ''Recent Major Changes'' section. Nonsubstantive changes such as typographical or editorial changes should not be identified. The agency believes that focusing on substantive changes in only these sections will avoid calling unnecessary attention to minor changes and will ensure that the significance of unmarked text is not diluted.

The agency believes that it would not be adequate to identify labeling changes only in a section of the labeling devoted to changes. The agency believes it is important to also identify the specific text that has been changed so that practitioners will be able to locate changes and access the complete text.

J. Comments on Revisions to Container Labels

In addition to revising its regulations governing the content and format of labeling for prescription drugs, the agency also proposed certain revisions to the information required to appear on prescription drug product labels (proposed § 201.100). The proposed revisions were intended to lessen overcrowding on prescription drug labels by removing certain information from the container label.

Current § 201.100(b)(2) requires that the label on a prescription drug container bear a statement of the recommended or usual dosage. Where it is not possible to present an informative or useful statement about the recommended or usual dosage in the space available on the container label, current § 201.55 states that the requirements of § 201.100(b)(2) may be met by including the statement ''See package insert for dosage information.'' The agency proposed to eliminate § 201.55. The agency also proposed to eliminate the requirement in § 201.100(b)(5) that the label of a prescription drug for other than oral use must bear the names of all inactive ingredients. The agency proposed to eliminate the requirement in § 201.100(b)(7) that the container label bear a statement directed to the pharmacist specifying the type of container to be used in dispensing the product to maintain its identity, strength, quality, and purity. The agency proposed to require instead that these instructions be placed in the ''How Supplied/Storage and Handling'' section of prescription drug labeling (proposed § 201.57(c)(4)(v)).

(Comment 106) Several comments opposed the proposal to eliminate the requirement that the label of a prescription drug product for other than oral use bear the name of all inactive ingredients. The comments stated that identification of inactive ingredients is important because of their potential to be allergens. Some comments maintained that manufacturers should be able to list on product labels selected inactive ingredients (e.g., ingredients that are known allergens or are associated with adverse reactions). One comment recommended listing the diluent that should be used for admixture or those diluents that are contraindicated. Two comments supported eliminating the list of inactive ingredients from the container label of products for other than oral use. They agreed that the presence of such information in the ''Description'' section of prescription drug labeling would be sufficient and that eliminating the information from the container label could make other information on the label more accessible and legible.

Several comments also opposed the proposal to eliminate the requirement that the label of a prescription drug product bear a statement directed to the pharmacist specifying the type of container to be used in dispensing the product to maintain its identity,

strength, quality, and purity. The comments maintained that eliminating dispensing information from the container label, and placing it in prescription drug labeling, would make the information less accessible to pharmacists and would thus be inefficient and frustrating for pharmacists. The comments were concerned that making information on storage and handling less accessible could lead to inappropriate storage and handling. Some comments urged that the label at least be required to state any special or unusual conditions for storage. One comment recommended mandatory use of a symbol that signifies when a product requires special handling. Two comments supported removal of information on storage and handling from product labels, agreeing that less information on the container label could make other information on the label more accessible and legible.

One comment maintained that manufacturers should be able to remove from the label the statement referring practitioners to the full prescribing information for dosage information before the manufacturer is required to revise its label in accordance with this final rule.

The agency has reconsidered its proposals to eliminate from container labels: (1) The list of inactive ingredients for products other than for oral use, (2) the statement directed to the pharmacist concerning the type of container in which a product should be dispensed, and (3) the statement referring practitioners to the package insert for dosage information in situations in which it is not possible to include information about the recommended or usual dose on the label. The agency decided to withdraw these proposed revisions to container labels. The agency believes that what is appropriate content for product container labels and how to make that information as accessible as possible need to be further evaluated. The agency intends to conduct a comprehensive evaluation of information required to be included on container labels and, if necessary, will propose changes to these requirements at that time.

At this time, the agency will not require placement of a symbol on the container label indicating that the product has special storage and handling requirements. The agency will consider this possibility during its evaluation of the content of product labels. It would be premature to adopt such a symbol at this time.

(Comment 107) One comment requested that the proposed requirement to specify in the ''How Supplied/Storage and Handling'' section the type of container to be used in dispensing a product to maintain a product's identity, strength, quality, and purity (information formerly presented on the product label) should apply only if the product cannot be dispensed in the standard amber vial. The comment maintains that limiting the scope of the requirement to situations in which exceptional storage conditions are required would serve to highlight the need for special considerations when dispensing.

As discussed in the previous comment, the agency has reconsidered its proposed changes to the container label, including the proposal to remove from the container label information directed at the pharmacist concerning the appropriate container in which to dispense a product. The agency will continue to require that dispensing instructions appear on the container label. Accordingly, proposed § 201.57(c)(4)(v) was deleted from the final rule. Storage and special handling conditions have to be specified in labeling consistent with the requirements of § 201.57(c)(17)(iv) of this final rule.

(Comment 108) One comment requested that the container label also be required to disclose when the container or some component of the container contains latex or polyvinyl chloride (PVCs).

As discussed in the response to comment 106, the agency intends to conduct a comprehensive evaluation of the product label and may repropose changes in the content of the product label at a later time, including changes concerning the presence of latex and PVCs in drug containers.

(Comment 109) One comment urged that there be a mandatory location for the ''Rx Only'' symbol on the main part of the label and that there be a specified minimum font size for the symbol.

In rulemaking (initiated under section 126 of the Food and Drug Administration Modernization Act of 1997), the agency amended its regulation requiring that container labels contain the statement ''Caution: Federal law prohibits dispensing without prescription'' by replacing the statement with the symbol ''Rx Only'' (67 FR 4904, February 1, 2002). Comments submitted to the agency in response to this proposed change requested that FDA specify the font size and the location of the symbol on the container label. The agency declined this request in the final rule of February 1, 2002, and declines it again in this final rule. As discussed in the preamble to the February 2002 final rule, existing statutory (section 502(c) of the act) and regulatory provisions (§ 201.15) requiring that information on product labels be prominent and conspicuous so as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use provide the agency adequate authority to ensure that the symbol is visually accessible. The agency does not believe it is necessary to specify the location of the symbol or its font size to ensure that the symbol achieves adequate prominence.

(Comment 110) One comment expressed concern about the proliferation of artwork on label containers and the potential for that artwork to make the label more difficult to read and cause medication errors.

The agency acknowledges the potential for artwork to obscure important information on the label. The agency believes, however, that its existing authority under 502(c) of the act and § 201.15 is adequate to ensure that artwork does not compromise the prominence and conspicuousness of information required to be on the label.

K. Miscellaneous Comments

(Comment 111) One comment requested that the agency clarify how the content and format of the brief summary required to accompany prescription drug advertising under § 202.1 would be affected by the proposed revisions to prescription drug labeling. Another comment suggested that the agency entertain the idea that Highlights could serve as an alternative to the brief summary because the agency has noted that Highlights contains the most important information about drug-related risks.

The proposed regulations were not designed to affect either the content or the format of the brief summary of prescribing information required to accompany prescription drug advertisements under § 202.1 (21 U.S.C. 352(n)). As discussed in the proposed rule (65 FR 81082 at 81087), statements made in promotional labeling and advertisements must be consistent with all information included in labeling under proposed § 201.57(c) to comply with current §§ 201.100(d)(1) and 202.1(e).[9] The agency does believe, however, that Highlights communicates important information about a drug. The agency therefore will explore further, in conjunction with other prescription drug advertising initiatives, the concept

[9] This requirement at proposed § 201.57(a) has been removed because it is not pertinent to the contents of § 201.57 and is redundant with provisions at §§ 202.1 and 201.100.

that Highlights could serve as a brief summary (see also FDA's response to comment 112 about the brief summary for consumer directed advertisements).

(Comment 112) Some comments stated that prescription drug labeling should be written in language that a lay audience can comprehend. The comments noted that consumers need to be able to read and understand the labeling because it accompanies the product, and because it is often used to provide information for direct-to-consumer (DTC) advertisements.

The purpose of prescription drug labeling is to provide health care practitioners information necessary for safe and effective use. The agency believes that use of medical and scientific terminology is necessary to effectively communicate to practitioners information about a product's risks and benefits as required under 21 U.S.C. 352(n) and § 201.100. Requiring that language used in prescription drug labeling be tailored to a lay audience would result in a loss of the clarity and precision needed to effectively communicate to practitioners a product's benefits and risks. For example, if a drug is associated with a risk of a specific type of blood disorder, the disorder must be identified by its technical name (e.g., thrombotic thrombocytopenic purpura) so the practitioner can more quickly diagnose and treat the disorder when symptoms present. Scientific terminology may help to identify types of patients that might be at increased risk or otherwise manage the risk of that blood disorder. If the risk can only be described in terms that a lay audience can comprehend (e.g., blood disorder), the labeling would lack the precision needed to communicate the specific risk to prescribers.

For many products, the final rule will improve the usefulness of the brief summary to consumers and health care practitioners by improving the usefulness of the prescription drug labeling, on which the brief summary is based. To this end, FDA has issued a draft guidance document entitled ''Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements'' that describes various options for presenting this information in DTC print advertisements (69 FR 6308, February 10, 2004). By providing recommendations on use of alternatives to prescription drug labeling to fulfill the brief summary requirement, FDA is encouraging manufacturers to develop brief summaries for use in consumer-directed advertisements using language they can understand.

L. Comments on the Proposed Implementation Plan

For new and more recently approved drugs, FDA proposed a staggered implementation schedule for the labeling requirements, with revised labeling required for newer products first (proposed § 201.56(c)). The schedule is being finalized as proposed (see table 5 in section III of this document). Revised labeling for ANDA products depends on the labeling for the reference listed drug. The agency proposed to implement no later than 1 year after the effective date of the final rule the revised content requirements regarding unsubstantiated claims in labeling for newer and older drugs. The agency also proposed to implement by 1 year after the effective date of the final rule the requirement that any FDA-approved patient labeling be reprinted immediately following the ''Patient Counseling Information'' section of the FPI for newer products or immediately following the last section of the labeling for older products. The agency also proposed to implement by 1 year after the effective date of the final rule the requirement that in vitro or animal data related to activity or efficacy of a drug that have not been shown by adequate and well-controlled studies to be pertinent to clinical use be removed from the labeling unless a waiver is granted.

In the proposal, the agency specifically sought comment on whether the revised content and format requirements should be applied, as proposed, to drug products with an NDA, BLA, or efficacy supplement that is pending at the effective date of the final rule, that was 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.

(Comment 113) Several comments agreed with the categories of prescription drugs that would be subject to the new labeling content and format requirements in the agency's proposed implementation plan. Other comments expressed concern that the proposed implementation plan is too narrow. These comments maintained that the new format is superior to the old format and the scope of the proposed implementation of the new format would leave large numbers of products with inferior labeling. Some comments requested that the revised content and format requirements eventually be applied to all marketed prescription drugs. One comment recommended that the implementation plan also apply to all drugs that are among the 150 most frequently prescribed drugs that would not otherwise be covered by the implementation plan. The comment maintained that under the proposed implementation plan only 1 of the current top 15 drugs used in the elderly would be required to implement the revised content and format.

Some comments expressed concern that having different labeling formats would be confusing to physicians. One comment expressed concern that having two different formats might impact prescribing behavior, arguing that prescribers might favor newer, more expensive drugs. Some comments maintained that a single standard format is needed to facilitate access to labeling in electronic formats. One comment also questioned FDA's underlying assumption that there is a lesser need for improved labeling for older products because practitioners are more familiar with older products and refer to older product labeling less frequently than newer product labeling. The comment maintained that newer practitioners would need to refer to the labeling of older drugs to the same extent as for newer drugs. One comment suggested that manufacturers be given the option to revise labeling for older products.

Some comments from manufacturers maintained that it would be most practical to apply the new format requirements only to products whose applications are submitted on or after the effective date of the final rule. They stated that broader implementation would place a substantial burden on FDA resources and could interfere with review of new drugs. One comment stated that the new format should apply only to drugs that are not a member of an existing drug class (i.e., products that would be considered the original member of a drug class) or that are a new and novel member of an existing drug class and whose applications are submitted on or after the effective date of the final rule. The comment maintained that having different labeling formats for similar drugs within the same drug class would be a competitive disadvantage for one format or the other.

The agency believes the implementation plan as proposed for new and more recently approved drug products is the best option for implementing the new format requirements. The agency agrees that it is desirable for all prescription drugs to be subject to the same labeling rules. However, the agency has carefully considered the costs and benefits of implementing the revised labeling

format and determined that requiring broader implementation (e.g., to all prescription drugs) of the new format requirements would be an excessive regulatory burden.

This initiative will require substantial resource allocation by the agency and industry for a period of several years. The agency's proposed implementation plan, which is being finalized in this rule as proposed, is intended to make the best use of these resources. As discussed in the preamble to the proposed rule (65 FR 81082 at 81098), the plan targets newer products because practitioners are more likely to refer to the labeling for newer products. In FDA's survey of physicians, newness of the product was a reason rated by 87 percent of physicians as very likely to trigger a labeling referral for a drug (Ref. 11, p. 35). In addition, the labeling for newer products is typically longer and more complex and, thus, more likely to benefit from a new format that makes the information more accessible. The implementation plan will also capture many older products that would not otherwise be covered by the plan when manufacturers seek new indications for their products (i.e., submit an efficacy supplement). For these reasons, the agency believes the implementation as proposed is the most reasonable approach to maximizing the public health benefit and best utilizing available resources in requiring the new content and format for labeling. In addition, manufacturers of older products not covered by the implementation plan may voluntarily revise, and submit for review, labeling for their products in the new format at any time.

The agency does not believe that an implementation plan based on volume of prescriptions would be prudent. Prescription volume can fluctuate considerably over time, and the agency is not aware that there are standardized prescription volume data that are generally accepted as accurate. Thus, the agency believes it would be very difficult to fairly implement and enforce an implementation plan based on prescription volume.

The agency also acknowledges that the existence of two different labeling formats may lead to some frustration among practitioners. The agency believes, however, that any potential confusion can be minimized. Practitioners are already aware of the content and format of existing labeling. The agency intends to engage in a comprehensive educational campaign to educate practitioners about the major features of the new format and why the implementation plan did not encompass all prescription drugs.

FDA is cognizant that the presence of two labeling formats will present important challenges when implementing electronic labeling but is confident that these challenges can be successfully addressed. For example, the ways in which information will be formatted, tagged, and stored in the contemplated electronic format will permit access to labeling information in both the old and new labeling formats.

The agency does not agree that the new format should be applied only prospectively or that it should be optional for the currently approved drugs that would be subject to the new format requirements under the proposed implementation plan. This narrower application of the new format requirements would fail to reach a significant number of products whose labeling is frequently referenced and could benefit from the new format requirements.

(Comment 114) Several comments objected to the proposed requirement that, within 1 year of the effective date of the final rule, manufacturers review all existing labeling and remove any express or implied unsubstantiated claims from the ''Indications and Usage,'' ''Dosage and Administration,'' ''Clinical Pharmacology,'' and ''Clinical Studies'' sections. Some comments maintained that this requirement would be very burdensome for industry and the agency. They disagreed with the agency's contention in the preamble to the proposed rule that the labeling changes to remove unsubstantiated claims could usually be accomplished without prior approval by the agency (i.e., with a ''Changes Being Effected'' labeling supplement). They stated that these changes would more often than not require prior approval and extensive negotiations between the agency and a manufacturer. Some comments maintained that there would be a substantial number of requests for waivers under § 201.58 or § 314.126(c) and these requests would also be a burden on the agency. Some comments agreed with the requirement to remove unsubstantiated claims from existing labeling, but stated that 1 year was not enough time for manufacturers to accomplish the task. One comment maintained that the burden on the agency would compromise the drug approval process. One comment requested that the agency clarify what types of statements would have to be removed.

The agency has reconsidered the proposed requirement to have manufacturers scrutinize all existing labeling for unsubstantiated claims and remove all such claims from labeling within 1 year of the effective date of the final rule. The agency agrees that a requirement to scrutinize all existing labeling within that timeframe would place substantial burdens on manufacturers and the agency and that such burdens might not be justified. In the preamble to the proposed rule, the agency estimated that no more than 25 percent of labeling for drugs other than antibiotics might contain unsubstantiated claims. Based on a recent review of a sample of prescription drug labeling, however, the agency believes the percentage of products whose labeling might contain such claims is considerably lower than 25 percent and not high enough to justify a requirement that manufacturers scrutinize all existing labeling to identify those claims, particularly in a short timeframe.

The agency is eliminating only the requirement that manufacturers scrutinize all labeling for the presence of unsubstantiated claims within 1 year of the effective date of the final rule. The language in proposed § 201.57(c)(2), (c)(3), and (c)(15) and § 201.80(c)(2), (j), and (m)(1) remains in the final rule, requiring that the ''Indications and Usage,'' ''Dosage and Administration,'' and ''Clinical Studies'' sections must not imply or suggest uses not supported by substantial evidence and/or dosing regimens not included in the ''Dosage and Administration'' section. This language accurately reflects the existing regulatory standard for claims presented in prescription drug labeling.

While the agency will not require a systematic evaluation of all existing labeling to identify unsubstantiated claims within 1 year of the effective date of the final rule, the agency wishes to make it clear that manufacturers have an ongoing obligation to ensure that claims in labeling have adequate substantiation and are not false or misleading. When new information comes to light that causes information in labeling to become inaccurate, manufacturers must act to change the content of their labeling, in accordance with §§ 314.70 and 601.12 (21 CFR 314.70 and 21 CFR 601.12). To clarify this obligation, the agency has revised § 201.56 to specify that manufacturers must act to correct labeling that, in light of new information, has become inaccurate (see § 201.56(a)(2)).

(Comment 115) One comment recommended an implementation period of 3 years, rather than 1 year as proposed, to append any FDA-approved patient labeling to the end of the labeling for trade packages. The

comment maintained that additional time was needed for reconfiguration and replacement of packaging equipment.

The agency believes that the proposed implementation plan is appropriate and in the best interest of public health. Including the FDA-approved patient labeling in prescription drug labeling ensures that this information is available to health care practitioners to reinforce the discussions they have with their patients concerning the risks and benefits of prescription drugs. The agency considers improving physician-patient communication crucial for public health. Furthermore, the agency believes that this requirement should not place an undue burden on manufacturers because of the approximately 200 products that would be affected by this provision of the final rule, the labeling of more than 60 percent of them already conform with the requirement (see section XI.C.1 of this document).

(Comment 116) Manufacturers of products subject to an ANDA (generic products) expressed concern that NDA holders will use the rule's implementation provisions as a mechanism to delay approval of generics. The specific concern was that NDA holders will obtain approval for a new indication near the end of their marketing exclusivity for their drug's original indication, revise the labeling for the drug to the new format, and receive 3 years' marketing exclusivity for the new indication. The comments asked FDA to make it clear that, in such situations, manufacturers of generic products would be permitted to base their labeling on the old format until the marketing exclusivity for the new indication has expired.

The agency wishes to make clear that the requirement to revise the labeling of a reference listed drug in the new format does not have any impact on the duration of exclusivity for the drug and, therefore, does not prevent a manufacturer of a generic product from using the revised labeling of the reference listed drug. Under section 505(j)(2)(A)(v) of the act (21 U.S.C. 355(j)(2)(A)(v)) and §§ 314.94(a)(8) and 314.127(a)(7) (21 CFR 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 (§ 314.93), because the generic drug product and the reference listed drug are produced or distributed by different manufacturers, or because aspects of the listed drug's labeling are protected by patent or exclusivity. This final rule does not change the requirement to exclude any condition of use or indication from the labeling of a generic product when necessary (e.g., when the reference listed drug has patent protection or market exclusivity for an indication), nor does it prevent, as described at § 314.127(a)(7), approval of an ANDA when the reference listed drug has protected labeling.

In the scenario described, the reference listed drug and the generic product would both be required to use the new labeling format. The NDA holder could not prevent the manufacturer of the generic product from using the new labeling format of the reference listed drug, but the NDA holder would still have exclusivity for the new indication.

(Comment 117) One comment recommended that all generic drugs pending approval or approved on or after the effective date of the final rule be required to submit labeling based on the new format. The comment maintained that the content of labeling is not significantly changed, just reordered, so this requirement would not be burdensome for manufacturers of generic products and the information in the labeling of the reference listed drug product and the generic product would still be essentially the same.

The agency does not believe that manufacturers of generic products should be required to provide labeling in the new format when seeking approval for their product if the reference listed drug product is not required to have its labeling in the new format. As discussed in the response to comment 115, the act and regulations currently require that a generic product have the same labeling as the reference listed drug product. Moreover, the agency believes that, to avoid confusion, the labeling of a generic product should be in the same format as the labeling of the reference listed drug.

(Comment 118) One comment urged FDA to compile a list of products that would be subject to the new format requirements and make the list publicly available.

FDA does not believe that it is necessary to compile such a list. Manufacturers can readily determine whether their products are subject to these requirements by referring to the implementation plan and the effective date of the rule (see section III of this document).

(Comment 119) Some comments requested that the agency clarify whether this final rule has implications for labeling that is distributed with prescription drug samples. One comment requested that the agency amend the rule to include labeling that is distributed with prescription drug samples. The comment maintained that free prescription drug samples do not contain adequate information in their packaging to keep consumers safe from harm.

FDA has often emphasized the importance of providing patients with useful written prescription drug information (e.g., FDA-approved patient labeling) in a variety of settings (see e.g., 63 FR 66378, December 1, 1998; 68 FR 33724, June 5, 2003). Prescription drug samples must be accompanied by trade labeling (§ 201.100(c)), which is subject to this final rule. If FDA-approved patient labeling for a product is required to be distributed to the patient, the manufacturer or distributor of that product must provide it with the samples.

M. Comments on Environmental Impact

(Comment 120) One comment maintained that FDA failed to adequately consider the environmental impact of the additional paper that will be required for labeling and the increase in size of packaging and shipping containers.

As stated in section IX of the proposed rule (65 FR 81082 at 81103), the agency determined that it is not required to do an environmental assessment or an environmental impact statement. This is an action excluded under § 25.30(h) and (k) (21 CFR 25.30(h) and (k)) (i.e., does not individually or cumulatively have a significant effect on the human environment). The changes made to the proposal in this final rule do not change this conclusion. Therefore, neither an environmental assessment nor environmental impact statement is required.

VII. Legal Authority

In this rule, FDA is addressing legal issues relating to the agency's action to revise the regulations prescribing content and format requirements for prescription drug labeling.

A. Statutory Authority

FDA's revisions to the content and format requirements for prescription drug labeling are authorized by the act and by the Public Health Service Act (the PHS Act). Section 502(a) of the act deems a drug to be misbranded if its labeling is false or misleading ''in any particular.'' Under section 201(n) of the act, labeling is misleading if it fails to reveal facts that are material with respect to consequences which may result from the use of the drug under the

conditions of use prescribed in the labeling or under customary or usual conditions of use. Section 502(f) of the act deems a drug to be misbranded if its labeling lacks adequate directions for use and adequate warnings against use in those pathological conditions where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users. Section 502(j) of the act deems a drug to be misbranded if it is dangerous to health when used in the dosage or manner, or with the frequency or duration, prescribed, recommended, or suggested in its labeling.

In addition, the premarket approval provisions of the act authorize FDA to require that prescription drug labeling provide the practitioner with adequate information to permit safe and effective use of the drug product. Under section 505 of the act, FDA will approve an NDA only if the drug is shown to be both safe and effective for use under the conditions set forth in the drug's labeling. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Under 21 CFR 314.125, FDA will not approve an NDA unless, among other things, there is adequate safety and effectiveness information for the labeled uses and the product labeling complies with the requirements of part 201. Under § 201.100(d) of FDA's regulations, prescription drug products must bear labeling that contains adequate information under which licensed practitioners can use the drug safely for their intended uses. This final rule amends the regulations specifying the format and content for such labeling.

Section 351 of the PHS Act (42 U.S.C. 262) provides legal authority for the agency to regulate the labeling and shipment of biological products. Licenses for biological products are to be issued only upon a showing that they meet standards ''designed to insure the continued safety, purity, and potency of such products'' prescribed in regulations (section 351(d) of the PHS Act). The ''potency'' of a biological product includes its effectiveness (21 CFR 600.3(s)). Section 351(b) of the PHS Act prohibits false labeling of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

B. First Amendment

FDA's requirements for the content and format of prescription drug labeling are constitutionally permissible because they are reasonably related to the government's interest in ensuring the safe and effective use of prescription drug products and because they do not impose ''unjustified or unduly burdensome'' disclosure requirements. (See *Zauderer* v. *Office of Disciplinary Counsel*, 471 U.S. 626, 651 (1985); see also *Ibanez* v. *Florida Dep't of Bus. and Prof'l Regulation*, 512 U.S. 136, 146 (1994).) The information required by the final rule to appear in labeling is the information necessary to provide facts that are material with respect to consequences which may result from the use of the drug under the conditions of use prescribed in the labeling or under customary or usual conditions of use (sections 201(n) and 502(a) of the act); adequate directions for use and adequate warnings (section 502(f) of the act); and information on the conditions of use in which the product would be dangerous (section 502(j) of the act). In addition, pursuant to section 505 of the act, the labeling sets forth information on the conditions in which the product is safe and effective. By its terms, the final rule requires disclosure of the essential scientific information necessary for safe and effective use of the labeled drug product. Consequently, FDA believes the final rule passes muster under the First Amendment.

In *Central Hudson Gas & Electric Corporation* v. *Public Service Commission* 447 U.S. 557 (1980), the Supreme Court established a four-step analysis for assessing the constitutionality of government restrictions on the content of commercial speech.

> [First,] we must determine whether the expression is protected by the First Amendment. For commercial speech to come within that provision, it at least must concern lawful activity and not be misleading. [Second,] we ask whether the asserted governmental interest is substantial. If both inquiries yield positive answers, we must determine [third] whether the regulation directly advances the government interest asserted, and [fourth,] whether it is not more extensive than is necessary to serve that interest.

This rule also survives scrutiny under the four-part test in *Central Hudson*. FDA believes that much information required to appear in prescription drug labeling is necessary for labeling to be nonmisleading. The risk information contained in such labeling, for example, constitutes material facts within the meaning of sections 201(n) and 502(a) of the act. Risk information can also qualify as warnings compelled by section 502(f) and (j) of the act. Other information, such as information on indications for the product, dosage and administration information, and how supplied information, is necessary because it provides adequate directions for use. Because not all of the information required in labeling clearly is necessary to prevent the labeling from being false or misleading, it is necessary for FDA to apply the remaining parts of the *Central Hudson* analysis.

FDA's interest in protecting the public health has been previously upheld as a substantial government interest under Central Hudson. (See *Pearson* v. *Shalala*, 164 F.3d 650, 656 (D.C. Cir. 1999) (citing *Rubin* v. *Coors Brewing Co.*, 514 U.S. 476, 484–85 (1995).) The final rule's labeling requirements directly advance this interest, thereby satisfying the third part of *Central Hudson*, because by requiring disclosure of complete information on the conditions under which a product can be used safely and effectively, the requirements help to ensure that prescription drug products will be prescribed properly by health care practitioners and will be used safely and effectively by patients.

Finally, under the fourth part of the *Central Hudson* test, there are not numerous and obvious alternatives (in fact, there are no reasonable alternatives) (*Cincinnati* v. *Discovery Network*, 507 U.S. 410, 418 n.13 (1993)) to the content and format requirements of this final rule that directly advance the government's interest but are less burdensome to speech. Health care practitioners are accustomed to looking to the prescription drug labeling as their primary source of information about a product, and patients rely for their drug information primarily on practitioners. Neither a public education campaign, nor encouraging sponsors to provide information on the risks and benefits of drugs but not requiring such information, would ensure that practitioners have the information they need about the conditions in which prescription drugs can be used safely and effectively. Requiring disclosures meets the fourth part of the test.

Accordingly, the agency believes it has complied with its burdens under the First Amendment to support the content and format requirements for prescription drug labeling.

VIII. Paperwork Reduction Act of 1995

The final rule contains information collection provisions that are subject to review by the OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description and respondent description of the information collection provisions are shown below with an estimate of the reporting burdens. 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 information. The OMB and FDA received no comments concerning the information collection provisions of the proposed rule.

Title: Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products

Description: The final rule amends FDA's regulations governing the format and content of labeling for human prescription drug products. It revises current regulations to require that the labeling of new and recently approved products contain highlights of prescribing information, a table of contents for prescribing information, reordering of certain sections, minor content changes, and minimum graphical requirements. The final rule does not subject older drugs to the revised labeling requirements. However, it does require, as for new and recently approved products, that FDA-approved patient labeling accompany or be reprinted immediately following the last section of prescription drug labeling.

As discussed in section VII of this document, FDA's legal authority to amend its regulations governing the content and format of labeling for human prescription drugs derives from sections 201, 301, 502, 503, 505, and 701 of the act and from section 351 of the PHS Act.

A. Summary of Prescription Drug Labeling Content and Format Requirements in this Final Rule That Contain Collections of Information

Section 201.56 requires that prescription drug labeling contain certain information in the format specified in either § 201.57 or § 201.80, depending on when the drug was approved for marketing. Section 201.56(a) sets forth general labeling requirements applicable to all prescription drugs. Section 201.56(b) specifies the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in §§ 201.56(d) and 201.57. Section 201.56(c) sets forth the schedule for implementing these revised content and format requirements. Section 201.56(e) specifies the sections and subsections, required and optional, for the labeling of older prescription drugs not subject to the revised format and content requirements.

Section 201.57(a) requires that prescription drug labeling for new and more recently approved prescription drug products include ''Highlights of Prescribing Information.'' Highlights provides a concise extract of the most important information required under § 201.57(c) (the FPI), as well as certain additional information important to prescribers. Section 201.57(b) requires a table of contents to prescribing information, entitled ''Full Prescribing Information: Contents,'' consisting of a list of each heading and subheading along with its identifying number to facilitate health care practitioners' use of labeling information. Section 201.57(c) specifies the contents of the FPI. The final rule reorders information required at former § 201.57, makes minor content changes, and provides standardized identifying numbers for the required information. Section 201.57(d) mandates new minimum specifications for the format of prescription drug labeling and establishes minimum requirements for key graphic elements such as bold type, bullet points, type size, and spacing.

In accordance with the final rule, older drugs not subject to the revised labeling content and format requirements in § 201.57 remain subject to labeling requirements at former § 201.57, which is redesignated as § 201.80 by this final rule. Section 201.80 contains minor clarifications. In addition, § 201.80(f)(2) requires that within 1 year, any FDA-approved patient labeling be referenced in the ''Precautions'' section of the labeling of older products and either accompany or be reprinted immediately following the labeling.

B. Estimates of Reporting Burden

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

The reporting burdens for the general requirements in § 201.56(a) are the same as those for former § 201.56(a) through (c) and are estimated in tables 8a and 8b as part of the burdens associated with § 201.57. Section 201.56(b) and (c) sets forth the categories of affected drugs and their implementation schedule, generating no reporting burdens. Section 201.56(d) sets forth the required sections and subsections associated with the revised format in § 201.57; therefore, its associated reporting burdens are estimated in tables 8a and 8b under the requirements at § 201.57. Sections 201.56(e) and 201.80 codify former labeling requirements at §§ 201.56(d) and (e) and 201.57, with minor clarifications, for older prescription drugs. The requirements in these sections impose no new reporting burdens (except those accounted for in section VIII.B.6 of this document), as they were previously incurred to produce existing labeling.

2. Annual Burden for Labeling Design, Testing, and Submitting to FDA for NDAs Submitted on or After the Effective Date of the Final Rule (§§ 201.56 and 201.57)

New drug product applicants must: (1) Design and create prescription drug labeling containing Highlights, Contents, and FPI, (2) test the designed labeling (e.g., to ensure that the designed labeling fits into carton-enclosed products), and (3) submit it to FDA for approval.

Based on information received from the pharmaceutical industry, FDA estimated that it took applicants approximately 3,200 hours to design, test, and submit prescription drug labeling to FDA as part of an NDA or BLA under former labeling requirements (see row 1 of table 8a). FDA estimates that it will take an additional 149 hours to generate Highlights and Contents and otherwise comply with the additional requirements of the final rule (see row 2 of table 8a). Therefore, it will take a total of approximately 3,349 hours to design, test, and submit new labeling. Approximately 85 applicants would submit approximately 107 new applications (NDAs and BLAs) to FDA per year, totaling 358,343 hours (see Total of table 8a).

3. Burden Associated with Labeling Supplements for Applications Approved Within 5 Years Prior to the Effective Date of the Rule (§ 201.57)

The final rule requires that prescription drug applications approved during the 5 years before, or pending on, the effective date conform to format and content requirements at § 201.57. For these products, applicants must redesign and negotiate the labeling, including Highlights and Contents, test the redesigned labeling, and prepare and submit that labeling to FDA for approval. Based on information provided in the ''Analysis of Economic Impacts'' (economic analysis) (see section XI.D.2.a of this document), labeling supplements for a total of approximately 344 innovator products would be submitted to the FDA over a 5-year period (beginning in year 3 and ending in year 7 after the effective date of the rule). Approximately 172 applicants would submit these labeling supplements. The time required for redesigning, testing, and submitting the labeling to FDA is estimated to be approximately 196 hours per application, totaling 67,424 hours (see row 1 of table 8b).

4. Burden Associated with Revised Labeling Efficacy Supplements Submitted on or After the Effective Date of the Rule (§§ 201.56(d) and 201.57)

Efficacy supplemental applications for older drugs submitted on or after the effective date of the final rule are subject to the content and format requirements at §§ 201.56(d) and 201.57. To meet these requirements, applicants must revise the existing labeling for these products. Each year an increasing number of innovator drug labeling will have been revised, and over time, very few efficacy supplements independently will generate labeling revisions as a result of this final rule. According to information in the economic analysis, the total number of affected efficacy supplements over 10 years is estimated at 324, with a decreasing number each year over the 10-year period (see section XI.D.2.a. of this document). For purposes of this analysis, the total burden for efficacy supplements is summarized in row 2 of table 8b. Over 10 years, approximately 172 applicants will trigger approximately 324 efficacy supplements, each one requiring approximately 196 hours to revise the labeling in the application, totaling 63,504 hours. In addition to this burden, a minimal annual reporting burden, probably even lower than the 7 per year estimated in year 10 of table 13 of this document, will continue indefinitely.

5. Burden Associated with Revised Labeling for Efficacy Supplements for Generic Drug Products (§ 201.57)

The reporting burden for generic products subject to the requirements of the final rule has only been estimated for those products requiring revisions to their existing labeling. Reporting burdens for generating newly approved labeling for generic products (§ 314.94(8)) is already approved under OMB control number 0910–0001. According to the data in the economic analysis, beginning in year 3 and continuing throughout the 10-year period analyzed, approximately 42 generic applications per year must submit labeling supplements to comply with the final rule (see section XI.D.2.a of this document). For purposes of this analysis, approximately 336 already approved generic drug applications must submit labeling supplements over the 10-year period after the effective date of the rule (see section XI.D.2.a of this document). The time required to revise and submit this labeling to FDA would be approximately 27 hours per application, totaling 9,072 hours (see row 3 of table 8b). In addition to this burden, a minimal reporting burden associated with a very small number of generic applications referencing older drugs may continue indefinitely.

6. Requirement That FDA-Approved Patient Labeling Accompany Prescription Drug Labeling Within 1 Year (§§ 201.57 and 201.80)

Within 1 year, all FDA-approved patient labeling must either accompany or be reprinted immediately following the prescription drug labeling (§§ 201.57(c)(18) and 201.80(f)(2)). As indicated in the economic analysis (section XI.D.1 of this document), an estimated 80 products will need to revise labeling as a result of this requirement. Approximately 18 applicants would be subject to this requirement. The agency estimates approximately 38 hours per product as a one-time labeling revision, totaling 3,040 hours (see row 4 of table 8b).

C. Capital Costs

A small number of carton-enclosed products may require new packaging to accommodate longer inserts (see section XI.D.2.c and comment 124 of this document). As described in more detail in the economic analysis (section XI.D.2.c.ii), up to 5 percent of the existing products affected by the rule (i.e., products with new efficacy supplements, products approved in the 5 years prior to the effective date of the rule, and affected ANDAs) may require equipment changes at an estimated cost of $200,000 each product. As shown in table 17, the estimated value of equipment changes totals $7.2 million and $8.7 million over 10 years discounted at 7 and 3 percent, respectively.

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

TABLE 8A.—ESTIMATED REPORTING BURDEN FOR NEW DRUG APPLICATIONS[1]

Category (21 CFR section)	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours
Annual burden associated with former labeling requirements (former 201.56(d) and 201.57)	85	1.26	107	3,200	342,400
Additional annual burden associated with requirements of this final rule (201.56(d) and 201.57)	85	1.26	107	149	15,943
Total				3,349	358,343

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

TABLE 8B.—ESTIMATED REPORTING BURDENS FOR LABELING REVISIONS TO ALREADY-APPROVED DRUG PRODUCTS[1]

Category (21 CFR section)	Year(s) In Which Burdens Occur Following Rule's Effective Date	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours	Total Capital Costs
Burden associated with revised labeling for applications approved within 5 years prior to the rule's effective date (201.57)	Beginning year 3, ending year 7	172	2.0	344	196	67,424	$3.3 million
Burden associated with revised labeling for efficacy supplements submitted on or after the rule's effective date (201.56(d) and 201.57)	Beginning year 1, diminishing over time	172	1.88	324	196	63,504	$2.5 million
Burden associated with revised labeling for efficacy supplements for generic drug products (201.57)	Beginning year 3, continuing annually thereafter	42	8	336 (for years 1–10)	27	9,072	$2.5 million
Burden as a result of having FDA-approved patient labeling accompany drug labeling within 1 year (201.57(c)(18) and 201.80(f)(2))	Year 1 only	18	4.44	80	38	3,040	$400,000
Total						143,040	Up to $8.7 million (see table 17)

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

The information collection provisions in this final rule have been approved under OMB control number 0910–0572. This approval expires December 31, 2008. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Environmental Impact

The agency has determined under 21 CFR 25.30(h) and (k) 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.

X. Executive Order 13132: Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to ''construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.''[10] Here, FDA has determined that the exercise of State authority conflicts with the exercise of Federal authority under the act.

The act gives FDA comprehensive authority over drug safety, effectiveness, and labeling. FDA is the expert Federal agency charged by Congress with ensuring that drugs are safe and effective and that product labeling is truthful and not misleading (sections 505(d) and 903(b)(2)(B) of the act (21 U.S.C. 393(b)(2)(B))). According to the act, a manufacturer of a drug must submit an NDA containing ''full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use'' (section 505(b)(1)(A) of the act; see also 21 CFR 314.50; see also *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979) (''Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use'' (citations omitted))).

[10] Because we have determined that the act preempts State law because the exercise of State authority conflicts with the exercise of Federal authority under that statute, we need not construe our statutory rulemaking authority as required by section 4(b) of the Executive order.

An NDA must include the ''proposed text of the labeling,'' together with ''annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling * * *'' (21 CFR 314.50(c)(2)(i)). The proposed labeling must also provide ''adequate directions for use'' (section 502(f) of the act). FDA by regulation has defined this to mean ''directions under which the layman can use a drug safely * * *'' (21 CFR 201.5). Because a prescription drug, by definition, cannot be used safely by a layperson without professional supervision, FDA regulations afford an exemption from the statutory requirement of adequate directions for use for a prescription drug whose labeling includes ''any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended * * *'' (§ 201.100(c)(1)). If labeling lacks this information, or is otherwise false or misleading in any particular, FDA is authorized to refuse to approve the NDA (section 505(d) of the act; 21 CFR 314.125(b)(6) and (b)(8)).

The FDA review process for an NDA is thorough and scientifically rigorous. An NDA must contain proposed labeling and all information about the

drug (whether favorable or unfavorable) that is pertinent to evaluating the application and that is received or otherwise obtained by the applicant from any source (21 CFR 314.50 and 601.2(a)). FDA scientists evaluate this information, and may request additional information as necessary to provide a complete and accurate picture of the product. FDA may supplement the expertise of its in-house scientific personnel with advice from scientific advisory committees of outside experts (21 CFR 14.171).

Under the act and FDA regulations, the agency determines that a drug is approvable based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's benefits and risks under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d) of the act). FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to use of the product in day-to-day clinical practice, such as the nature of the disease or condition for which the product will be indicated, and the need for risk management measures to help assure in clinical practice that the product maintains its favorable benefit-risk balance. The centerpiece of risk management for prescription drugs generally is the labeling, which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively in accordance with the act.

FDA carefully controls the content of prescription drug labeling, because such labeling is FDA's principal tool for educating health care practitioners about the risks and benefits of the approved product to help ensure safe and effective use. As FDA noted in the preamble accompanying the December 2000 proposed rule amending the 1979 physician labeling regulations:

> The part of a prescription drug product's approved labeling directed to health care practitioners * * * 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 * * * . [T]he 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.

(65 FR 81082 at 81082 and 81083). What distinguishes the prescription drug labeling from other information available to practitioners about a prescription drug is that the prescription drug labeling ''is intended to provide physicians with a clear and concise statement of the data and information necessary for the safe and effective use of the drug.'' Moreover, the act ''permits labeling statements with respect to safety only if they are supported by scientific evidence and are not false or misleading in any particular'' (44 FR 37434 at 37435 and 37441).

Under this final rule, risk information must appear in different sections of the prescription drug labeling in a particular order and must be based on data derived from human experience whenever possible. For example, information included in the contraindications section of prescription drug labeling must include only ''[k]nown hazards and not theoretical possibilities'' (§ 201.57(c)(5)). The adverse reactions section must include those adverse events for which there is some basis to believe there is a causal relationship between the event and the drug (§ 201.57(c)(7)).

The act and FDA regulations prescribe several procedures to ensure that FDA receives information about risks that become apparent after approval. Because clinical trials involve time-limited administration of the investigational product to a relatively small and homogeneous population of study subjects, adverse events that were not observed during clinical trials may be recognized or identified following approval. The act provides that a manufacturer must establish and maintain such records, and make such reports, as FDA may require by regulation (section 505(k) of the act). To implement this provision, FDA has issued regulations requiring prompt reports of serious, unexpected drug experiences and periodic reports of all information relating to the safety and effectiveness of the drug (21 CFR 314.80 and 314.81). Manufacturers may also commit to conduct additional safety and effectiveness studies following approval and submit data from these studies to the agency. (See section 506B of the act (21 U.S.C. 356b).)

The statutory and regulatory requirements for the submission of information to FDA are accompanied by statutory provisions addressing the failure of a sponsor to comply with these requirements. A manufacturer that introduces a new drug into interstate commerce without having submitted the required premarket information has violated the act (section 505(a) of the act) and is subject to FDA enforcement action. Similarly, if a manufacturer fails to submit information required by 21 CFR 314.80 and 314.81, it is subject to enforcement action under 21 U.S.C. 331(e). FDA is authorized to investigate suspected fraud using its general statutory investigative authority (section 702 of the act (21 U.S.C. 372)). The agency is also empowered to address fraud by seeking injunctive relief and civil penalties (21 U.S.C. 332, 333(g)(1)(A)), and has authority to invoke the general federal prohibition on making false statements to the Federal Government (18 U.S.C. 1001). In sum, FDA has a variety of enforcement options that allow it to make a calibrated response to suspected violations of the act's information submission requirements.

The agency carefully reviews all the information submitted by a sponsor in a marketing application to make its statutorily required judgment as to whether the product is safe and effective and otherwise in compliance with the act. It also reviews adverse event information submitted after marketing approval and determines what action, if any, should be taken. In rare cases, FDA finds that the information supports a determination to withdraw the product from the market (section 505(e) of the act; 21 CFR 601.5(b)(1)). In other instances, FDA uses other risk management techniques. One such technique is incorporating additional risk information into, or otherwise modifying, the prescription drug labeling (§ 201.57(e)). In many cases, review of the submitted reports does not lead to any change, e.g., because FDA determines that the event reported is not causally related to the product.

Changes to prescription drug labeling typically are initiated by the sponsor, subject to FDA review, but are sometimes initiated by FDA. Under FDA regulations, to change prescription drug labeling (except for editorial and other minor revisions), the sponsor must submit a supplemental application fully explaining the basis for the change (§§ 314.70 and 601.12(f)). FDA permits two kinds of labeling supplements: (1) Prior approval supplements, which require FDA approval before a change is made (§§ 314.70(b) and 601.12(f)(1)), and (2) CBE supplements, which may be implemented before FDA approval, but after FDA notification (§§ 314.70(c) and 601.12(f)(2)). Labeling changes to the FPI to add or strengthen a warning, precaution, contraindication, or adverse reaction statement are within the

category of changes for which CBE supplements are required by FDA regulations (§§ 314.70(c)(6)(iii) and 601.12(f)(2)(i)) (see comment 5). While a sponsor is permitted to add risk information to the FPI without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading under section 502(a) of the act. To mitigate this risk, manufacturers often consult with FDA before adding risk information to labeling. As noted in response to comment 5, however, a sponsor may not use a CBE supplement to make most changes to Highlights.

As FDA has long recognized, its role is not to regulate medical practice. The agency's actions nevertheless affect medical practice in a variety of ways. For example, FDA approval decisions affect the availability of drugs and medical devices. Also, FDA decisions as to the content and format of prescription drug labeling affect health care practitioners' communications with patients, to the extent such labeling is relied upon by such practitioners to guide their discussions of risk with patients. FDA strongly believes that health care practitioners should be able to rely on prescription drug labeling for authoritative risk information and that health care practitioners should not be required to convey risk information to patients that is not included in the labeling.

If State authorities, including judges and juries applying State law, were permitted to reach conclusions about the safety and effectiveness information disseminated with respect to drugs for which FDA has already made a series of regulatory determinations based on its considerable institutional expertise and comprehensive statutory authority, the federal system for regulation of drugs would be disrupted. Where a drug has not been reviewed by FDA and decisions with respect to safety, effectiveness, and labeling have not been made by the agency, expert determinations would not yet have been made by FDA, and such disruption would not occur.

Section 4(c) of Executive Order 13132 instructs us to restrict any Federal preemption of State law to the ''minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated.'' This final rule meets the preceding requirement because, as discussed in more detail above, it preempts state law only to the extent required to preserve Federal interests. Section 4(d) of Executive Order 13132 states that when an agency foresees the possibility of a conflict between State law and federally protected interests within the agency's area of regulatory responsibility, the agency ''shall consult, to the extent practicable, with appropriate State and local officials in an effort to avoid such a conflict.'' Section 4(e) of Executive Order 13132 adds that, when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency ''shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.''

FDA sought input from all stakeholders on new requirements for the content and format of prescription drug labeling through publication of the proposed rule in the **Federal Register**. Although the proposed rule did not propose to preempt state law, it did solicit comment on product liability issues. FDA received no comments on the proposed rule from State and local governmental entities.

Officials at FDA consulted with a number of organizations representing the interests of state and local governments and officials about the interaction between FDA regulation of prescription drug labeling (including this rule) and state law.

In conclusion, the agency believes that it has complied with all of the applicable requirements under Executive Order 13132 and has determined that this final rule is consistent with the Executive order.

XI. Analysis of Economic Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (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, unless the agency certifies that the rule is not expected to have significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize any significant impact of the rule on small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement 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 rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. The final rule would amend current requirements for the format and content of human prescription drug product labeling. Although the effectiveness of the revised labeling in achieving time savings and reductions in adverse reactions is uncertain, based on the following analysis as summarized in table 9, FDA projects that the present value of the quantifiable benefits of the final rule over 10 years range from $330 million to $380 million and from $420 million to $480 million at a 7 and 3 percent discount rate, respectively. Direct costs of the final rule are projected to range from approximately $7 million to $17 million in any one year, for a total present value of approximately $90 million and $120 million over 10 years at a 7 and 3 percent discount rate, respectively. The agency thus concludes that the benefits of this final rule outweigh the costs. Furthermore, the agency has determined that the final rule is not an economically significant rule as described in the Executive order, because annual impacts on the economy are substantially below $100 million. Because the rule does not impose any mandates on State, local or tribal governments, or the private sector that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act. The current inflation-adjusted statutory threshold is about $115 million.

The agency believes that this rule would not have a significant impact on most small entities. However, it is possible that some small firms that produce several affected drugs, or small firms that might be required to undertake packaging modifications, may be significantly affected by this rule. Therefore, the following analysis, in conjunction with the preamble, constitutes the agency's final regulatory flexibility analysis as required by the Regulatory Flexibility Act.

TABLE 9.—SUMMARY OF PROJECTED QUANTIFIABLE BENEFITS AND COSTS OVER 10 YEARS[1]

	Total ($ million)	Present Value ($ million)	
		3 percent	7 percent
Benefits:			
Health Care Practitioner Time Saved	150	120	90
Cost of Adverse Drug Events Avoided	360 to 430	300 to 360	240 to 290
Total Potential Benefits	510 to 580	420 to 480	330 to 380
Costs:			
Design and Produce Trade Labeling; Modify Packaging Equipment	42	36	29
Reformat and Produce Labeling Not Accompanying Drug Products	36	30	25
Print Longer PDR	59	49	39
Total Costs	140	120	90

[1] Numbers may not sum due to rounding.

A. Purpose of the Final Rule

The purpose of the final rule is to make it easier for health care practitioners to find and read information important for the safe and effective use of prescription drugs. As described elsewhere in this preamble, the agency has found that the current format of prescription drug labeling can be improved to more optimally communicate important drug information (see section I of this document). Enhanced communication of drug information to physicians should make them better informed prescribers. The final rule is designed to achieve these objectives by amending the current content and format of the labeling for certain human prescription drug products to, among other things, highlight frequently accessed and new information, include a table of contents for the detailed information in labeling, and reorder this detailed information.

B. Comments on the Economic Impact Analysis

Most comments on the economic analysis of the proposed rule came from pharmaceutical manufacturers. Although many manufacturers expressed concerns that the agency had significantly underestimated the costs to industry, especially the additional packaging costs that would be necessary with labeling printed in 8 points, only a few provided detailed information about the potential burden they expected the rule to impose. The agency welcomes these comments and, whenever possible, has incorporated data from these examples in the final analysis of economic impacts.

(Comment 121) Several comments argued that manufacturers would incur significant administrative costs when negotiating the content of Highlights with FDA.

Although our analysis did not separate administrative costs from other labeling design costs, the agency anticipated that manufacturers would require some ''detailed discussions and drug-specific decisions'' during the design phase of labeling (e.g., regarding exactly which adverse reactions should be listed in Highlights) (65 FR 81082 at 81106). Currently, manufacturers submitting new applications (i.e., NDAs and BLAs) and efficacy supplements have to negotiate the content of labeling as part of the review process. Because any information in Highlights is also in the FPI, the agency does not agree that negotiating the content of Highlights will impose significant administrative costs beyond what is currently incurred by these manufacturers. As noted, to facilitate this process, the agency is making available guidance to assist manufacturers in selecting information for inclusion in Highlights (section IV of this document).

On the other hand, manufacturers of recently approved innovator drugs (i.e., approved within 5 years prior to the effective date of the final rule) will incur costs to: (1) Prepare and submit their redesigned labeling to FDA for approval, which may include negotiations concerning the content of Highlights, and (2) replace existing labeling with redesigned labeling. To account for these additional actions, the one-time design costs for labeling of recently approved products are estimated to be about 50 percent higher than for labeling of new products (see section XI.D.2 of this document).

(Comment 122) The agency sought specific comment on 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. One comment stated that because the proposal has the potential to substantially affect larger companies (could double the length of labeling and require extensive re-engineering and re-design of packaging lines and ancillary equipment), its impact would be even greater on smaller companies.

Although the agency had requested input from small companies that might be affected by the rule, all comments on this question came from large companies. FDA believes it is difficult to predict the effect of the rule on small firms. While small firms may have lower sales volume over which to spread the fixed costs of compliance, some industry consultants have found that small pharmaceutical firms have less organizational layers and incur lower costs for the same activity than large pharmaceutical firms (Ref. 12). Table 22 in section XI.E.2 of this document illustrates the potential impact that the final rule might have on small firms.

(Comment 123) One comment maintained that there is no support for FDA's identified benefit of reducing the time it takes a prescriber to use labeling by 15 seconds. The comment argued that Highlights, because it contains incomplete information, would actually increase physician reading time and asserts that FDA's assumption would be true only if physicians read just Highlights.

The agency acknowledges that there is not direct empirical support for the estimate of 15 seconds time savings, but is persuaded based on consultation with physicians that the labeling changes would save time. The agency consulted physicians in a national survey, focus groups, and a public meeting to design labeling that provides easier and faster access to the most important and commonly referenced prescribing

information (65 FR 81082 at 81083 through 81085; see also Ref. 11). Using a standard format with frequently accessed sections at the beginning of labeling will help physicians find important information quickly and retain that information. Inclusion of Contents and references in Highlights to the full prescribing information that is cited or concisely summarized will speed access to detailed information in the FPI. In the absence of quantitative evidence suggesting a different estimate of time savings, the agency is retaining 15 seconds as a conservative estimate of the amount of time health care practitioners can save when seeking drug product information in labeling.

(Comment 124) Some comments argued that FDA's estimate significantly underestimates increased costs for trade packaging, shipping containers, and new packaging and shipping equipment to accommodate the larger labeling that will result from the new format. Some comments argued that the agency's initial estimate of $200,000 to adjust or retool existing packaging equipment underestimates the impact on industry by almost fourfold. Moreover, one comment stated it could cost large manufacturers with many product lines up to $40 million to change all packaging lines. Several comments stated that increases of this magnitude will require retooling or replacing existing equipment, increasing containers to accommodate longer outserts, or, in some cases, adding a carton. Comments also stated that longer labeling would increase administrative costs.

FDA allows each manufacturer some flexibility to determine the size and shape of a product's trade labeling and packaging. A survey of labeling printed in the Physicians' Desk Reference (PDR) for 200 products showed that, on average, labeling requires 200 square inches of surface area when printed in 6.5-point type size. Since prescription drug labeling is printed on both sides of the paper, these findings suggest that current trade labeling averages 100 square inches. From this baseline, the agency calculates that about an additional 92.6 square inches of paper would be needed to print labeling in 8-point type size and to add Highlights and Contents to the labeling.

To reduce the burden on industry, the final rule requires that trade labeling be printed in at least 6-point type size (see comment 102), similar to the size of the baseline case used in the original analysis and a size generally supported by industry comments on the proposed rule. Even though some trade labeling is currently printed in a size as small as 4 points, on average, trade labeling is in 6 points, and thus requiring a minimum type size of 6-point will not increase the size of most trade labeling. However for the few products currently printed in 4 points, labeling will require approximately 33 percent more paper to conform with the 6-point minimum size requirement at § 201.57(d)(6). The agency believes that the additional resources associated with longer labeling are warranted by the ease of use and speed of comprehension by having labeling printed in 6 rather than 4 points.

Highlights and Contents will increase trade labeling by approximately 40 square inches, requiring an additional 20 square inches of paper. Manufacturers submitting NDAs and BLAs have not yet designed product labeling or packaging. Thus, the agency does not agree that the final rule will impose additional packaging costs on these manufacturers. In contrast, manufacturers submitting efficacy supplements or having existing labeling for drug products affected by the final rule will need to determine if their redesigned trade labeling fits on or within existing packaging.

The final rule will affect less than 15 percent of existing products in the United States.[11] The agency agrees that some packaging lines of these products will require adjustment to accommodate longer trade labeling, but disagrees that this will be necessary for all packaging lines. Based on an analysis of ophthalmic products, the agency increased the proportion of existing products expected to incur one-time production costs from 1 to 5 percent (see section XI.D.2.c.ii of this document).

(Comment 125) One comment insisted that FDA's estimate of 92.6 square inches of additional labeling space is not sufficient to accommodate the proposed new labeling sections, increase in white space, increase in type size, and inclusion of patient information in the FPI. The comment suggested that FDA's presentation of how much additional labeling space would be needed was confusing.

The implementation schedule to add FDA-approved patient labeling to prescription drug labeling differs from the implementation schedule for the formatting and content changes affecting labeling for new and recently approved products (i.e., approved within 5 years of the effective date of the final rule). Consequently, the agency analyzed the impact of each of these requirements separately.

Within 1 year of the effective date of the final rule, any FDA-approved patient labeling must either be reprinted immediately following the end of labeling or accompany the labeling (§§ 201.57(c)(18) and 201.80(f)(2)). An estimated 150-square inches of surface area would be needed to print this information, adding an additional 75-square inches to the size of the labeling (65 FR 81082 at 81109). The agency identified up to 200 products with some form of FDA-approved patient labeling that will be affected by the final rule. A sample of these affected products shows that the labeling of more than 60 percent already conforms to this provision of the final rule. For the final analysis, the agency increased the estimate of the number of affected products from 50 to 80, thus increasing the incremental printing costs for this provision of the final rule to $0.4 million annually (see section XI.D.1 of this document).

More space will be needed to print longer trade labeling and labeling distributed with promotional materials for new and recently approved products. The length will depend on the minimum type size requirements for the labeling. For trade labeling printed in a minimum of 6 points, an estimated 20 square inches of paper is necessary to accommodate Highlights and Contents. In contrast, product labeling distributed with promotional materials must be printed in a minimum 8-point type size, requiring about 93 square inches of paper (65 FR 81082 at 81107). Furthermore, for labeling with FDA-approved patient labeling which is not currently appended to the product labeling, after all provisions of the final rule are implemented, product labeling will be approximately 168 square inches or 65 square inches longer when printed in 8-point or 6-point type, respectively.

(Comment 126) One comment asked the agency to consider the impact of the increased number of calls on companies, and possible increases in personnel to process calls, as a result of requiring companies to include their phone number in the package inserts. Another comment raised concerns that requiring corporate telephone numbers for reporting of serious adverse reactions in Highlights would require companies to change their labeling with each change of their corporate telephone number.

The agency believes that health care practitioners have varied access to company information via the Internet and other sources, thus including the phone number is unlikely to overly burden a company's ability to handle

[11] Data derived from information in ''Approved Drug Products with Therapeutic Equivalence Evaluations,'' December 2001.

incoming calls. The agency believes that changes in corporate phone numbers are an ordinary business expense.

C. Benefits of Regulation

The expected economic benefits of this final rule are the sum of the present values of: (1) The reduced time needed by health care practitioners to seek desired information in prescription drug labeling; (2) the increased effectiveness of drug treatment; and (3) the avoided costs of treating drug-related errors due to misunderstood or incorrectly applied drug information.

We acknowledge that the information to estimate the benefits of this rule is quite limited. In particular, we do not have direct estimates of how much time practitioners might save by using the new labeling, or how the new labeling might improve doctors' understanding of risks of prescription drugs. There is no formal study that tested how alternative labeling formats affect physicians' speed or quality of comprehension of information related to potential adverse effects of drugs.

1. Decreased Health Care Practitioner Time

Prescription drug labeling is a major source of information about the risks and benefits of prescription drugs. Each year health care practitioners spend considerable time seeking medical knowledge about the therapeutic risks and benefits of the drugs prescribed to treat patients. However, only a few studies have focused on the information-seeking behavior of health care practitioners. Four studies using family practice physicians reported that the PDR, a compilation of prescription drug labeling, was the most frequently used reference book in a clinical setting (Refs. 13 through 16). In one study published in 1990, physicians reported using the PDR almost daily (Ref. 13). In addition to the PDR, physicians receive prescription drug labeling directly from drug manufacturers and their representatives.

A 1994 FDA survey of physicians found that 42 percent referred to prescription drug 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 (Ref. 11, pp. 30–31). These findings suggest that a physician seeks drug information from prescription drug labeling on average 212 times each year.[12] Moreover, comments from a pharmacy association, submitted in response to the proposed rule, reported that a recent informal survey of pharmacists found that 30 percent refer to prescription drug labeling several times each day, 36 percent refer at least once per day, and 34 percent refer at least once per week. If representative, these findings suggest that the average pharmacist in the United States seeks information from prescription drug labeling at least 257 times each year.[13] To put this estimate in perspective, approximately 2.85 billion prescriptions were dispensed by retail pharmacies in 2001 (Ref. 17). About 60 percent of the 212,660 pharmacists in the United States work in retail pharmacies (Refs. 18 and 19) and cumulatively seek information from prescription drug labeling about 32.8 million times each year (212,660 pharmacists x 0.6 x 257 labeling consultations per year), approximately 12 times for every 1,000 prescriptions dispensed.

For the analysis of the proposed rule, FDA was aware of no data estimating the total time physicians spend reading prescription drug labeling. It also had no estimates of how much time savings might result from possible changes in drug labeling. It therefore conservatively assumed that physicians could save an average of 15 seconds each time they refer to prescription drug labeling in the new format (65 FR 81082 at 81104). One comment from a pharmaceutical manufacturing organization requested justification for this assumption (see comment 123). The comment stated that rather than save time, the new format with Highlights would lengthen the time practitioners spend looking for information.

The agency disagrees it will take health care practitioners more time to find information with the new format compared to the old format. As described elsewhere in the preamble, the agency solicited input from health care practitioners to develop a format that presents complex drug information in a manner that will enable them to find information more rapidly, improving the communication of the risks and benefits of the drug (see section I of this document). In comments on the proposed rule, organizations representing health care practitioners and consumer groups strongly supported the new format as being easier and quicker to use (see comment 2). Comments from many drug manufacturers agreed that including a comprehensive table of contents and reordering of the detailed information would improve clarity of the labeling and quickly direct the reader to the appropriate section of the FPI, but expressed reservations about the utility of Highlights (see comment 2).

Comments, including one by an expert in human cognition, supported Highlights as a way to improve the accessibility of the most heavily used information (see comment 2). Moreover, by including references in Highlights to specific sections of the FPI, Highlights will also enhance the effective use of the information in the detailed sections of the labeling. Therefore, based on comments from health care practitioners, professional organizations and consumer groups, the agency believes that the new format will reduce the time physicians, pharmacists, and other practitioners must spend seeking specific information in prescription drug labeling and increase the extent they rely on labeling for drug information.

A recent study in Oregon found that primary care physicians on average will consult two sources of information, one of which is usually the PDR, and spend an average of 12 minutes seeking information to answer patient questions (Ref. 16). Another study in Finland logged the time physicians spent searching a computerized set of guidelines, the ''Physicians' Desk Reference and Database,'' and found the average time needed to find and read an article was 4.9 minutes (Ref. 20).

Although these studies may not be representative of the average practitioner in the United States, they suggest that the agency's estimate of a 15-second time savings with the new format (once drug labeling is at hand) is plausible and conservative in that it is only a small improvement relative to time currently spent for most labeling referrals. If the new format were implemented for all prescription drug products, the nation's 625,100 physicians active in patient care (Ref. 21) could save a total of about 552,100 hours per year (625,100 physicians x 212 labeling consultations per year x 15 seconds saved per labeling consultation/ 3600 seconds per hour). Likewise, pharmacists could save an additional 227,700 hours per year (212,660 pharmacists x 257 labeling consultations per year x 15 seconds saved per labeling consultation/ 3,600 seconds per hour).

The final rule only applies to new and recently approved products. Moreover, implementation for recently approved products is phased in over several years.

[12] On average, physicians work 47 weeks per year and consult prescription drug labeling 4.51 times each week [(7 consultations per week x 42 percent) + (4 consultations per week x 33 percent) + (1 consultation per week x 25 percent)] (65 FR 81082 at 81104 through 81105).

[13] On average, it is assumed that pharmacists work 50 weeks per year and consult labeling 5.14 times per week [(10 consultations per week x 30 percent) + (5 consultations per week x 36 percent) + (1 consultation per week x 34 percent)].

Thus, the final rule will initially apply only to a small percentage of prescription drug labeling. The rule's focus on newer products includes the prescription drug labeling that health care practitioners consult most 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 (Ref. 11, p. 35). Similarly, the pharmacy association's survey found that pharmacists were most likely to consult labeling if the drug was recently approved (48 percent).

Although the average practitioner regularly prescribes from 40 to 100 pharmaceutical products (Ref. 24), the proportion of these that are new drugs is unknown. Because the agency received no comments and has no other information on the percentage of reformatted labeling that practitioners will consult, the initial assumptions remain unchanged (65 FR 81082 at 81104). This analysis, therefore, assumes that the rule will begin affecting the length of time needed for prescription drug labeling consultations in the second year of implementation, only affecting 5 percent of all consultations in that year. The percentage of reformatted prescription drug 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, reaching 50 percent in year 10. Thus, in year 10, the time savings for physicians and pharmacists is projected to equal about 276,000 and 113,900 hours, respectively. 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 (see section V of this document).

To estimate the monetary value of the time saved, an hourly loaded wage for physicians is calculated using data from the American Medical Association (AMA) on the average net annual income of all non-Federal physicians (excluding residents), the average weekly workload, average number of weeks worked per year and benefits adjusted by the proportion of self-employed physicians (Refs. 22 and 23). The loaded wage for pharmacists is calculated from Bureau of Labor Statistics data (Ref. 18). At $88.16 per hour for physicians ([$194,400 x (1 + 0.2)] / [47 weeks x 56.3 hours / week]) and $46.75 per hour for pharmacists ($33.39 / hour x (1 + 0.4)), table 10 shows the annual monetary value of time saved and indicates that the present value over 10 years equals approximately $90 million or $120 million using a 7 or 3 percent discount rate, respectively.

TABLE 10.—VALUE OF HEALTH CARE PRACTITIONER TIME SAVED[1]

Year	Current Value ($ million)			Present Value ($ million)	
	Physicians	Pharmacists	Total	Total Discounted at 3 percent	Total Discounted at 7 percent
1	0	0	0	0	0
2	2	1	3	3	3
3	5	1	6	5	5
4	7	2	9	8	7
5	12	3	15	13	11
6	15	3	18	15	12
7	17	4	21	17	13
8	19	4	24	19	14
9	22	5	27	20	15
10	24	5	30	22	15
Total	120	30	150	120	90

[1] Numbers may not sum due to rounding.

2. Improved Effectiveness of Treatment

The final rule will improve prescription drug labeling to make it easier to find and use information about the product. More effective communication of drug information will better inform practitioners about the risks and benefits of drugs prescribed to patients. Prescription drug labeling can contain hundreds of facts about a drug, increasing the time needed to find specific information, relative to simpler labeling. For example, labeling of the drug cisapride contains over 470 facts (Ref. 24). Under the final rule, Highlights would emphasize those characteristics of drugs that physicians report are the most important for decisionmaking. With the Contents and references to the FPI in Highlights, practitioners can more quickly find all relevant facts about the drug that are specific to their patients. Each format change required by the final rule is intended, therefore, to present the complex drug information contained in labeling in a way that will improve the ability of practitioners to select and prescribe drugs to their patients safely and effectively.

The initial U.S. approval date will alert practitioners to newer products that should be used with greater vigilance. There are over 100 NDAs, including about 30 new molecular entities, approved every year in the United States. Initial approval is based on data from clinical trials conducted to determine the safety and effectiveness of a product. These trials typically include only enough subjects to detect 1 adverse reaction in every 300 to 500 patients (Ref. 25). It is not uncommon for drugs to have significant adverse effects that occur at lower frequencies than can be

detected in premarketing clinical trials. Adding contact information where practitioners can report suspected adverse reactions will facilitate the collection of drug safety information and make it easier for the agency and manufacturers to identify significant safety concerns that can emerge after a drug is marketed and a much larger population is exposed to the product. Moreover, by identifying those sections of the labeling in which there have been important recent changes, the new format will also alert practitioners to significant new safety concerns and other significant changes to labeling once a product has been approved.

In addition, any FDA-approved patient labeling must be printed at the end of the labeling, or accompany the labeling, regardless of when the product was approved. Including patient information enhances the likelihood that physicians will communicate important information to patients, improving patient understanding and adherence to treatment recommendations. 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 Costs to Treat Avoidable Adverse Reactions

Although there are multiple causes of adverse reactions, some are potentially preventable and can result from misunderstood or incorrectly applied drug 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). According to a 2000 GAO report on adverse drug events, standardized packaging is one of many approaches that can be adopted to reduce medication errors (Ref. 26). Requiring that prescription drug labeling follow a standardized format will better inform health care practitioners about the drugs that are prescribed to patients, improve the effectiveness of treatment, and reduce the number of preventable adverse reactions experienced by patients.

No national study on the incidence or associated costs of adverse reactions has been conducted. Furthermore, it is difficult to compare published studies because they are either too limited in scope or differ in methodology. Nevertheless, studies of hospitalized patients suggest that the rate of preventable adverse events that occur during hospitalization is approximately 1.2 to 1.8 adverse events per 100 patients admitted (Refs. 27 through 29). Moreover, 1 of these studies conducted in the early 1990s in the northeastern United States found that a majority of preventable adverse events (about 1 adverse event 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 (Ref. 28). A more recent study conducted in the southwestern United States reported 4.2 adverse events per 100 patients, of which only 15 percent where deemed preventable (Ref. 29). Given the approximately 36 million annual hospitalizations in the United States (Ref. 30), these data suggest that between 229,000 and 364,000 adverse reactions among hospitalized patients are potentially preventable each year.

A number of studies show that the occurrence of an adverse event in a hospitalized patient increases the costs of caring for the patient by an average of between $2,162 and $2,595 (Refs. 28, 29, and 31). Costs associated with preventable adverse events were even higher, averaging about $4,685 per patient (Ref. 31), or $6,075 in 2000 dollars. If all hospitals incur similar costs for preventable adverse events, the potentially preventable annual costs from this source could total from between $1.4 billion to $2.2 billion nationally (in 2000 dollars).

Few studies on adverse reactions in outpatient or long-term care settings have been conducted. A report from a multidisciplinary conference held in 2000 to discuss a national research agenda for ambulatory patient safety described a diverse and complex outpatient system that was prone to the same types of errors observed in hospital studies (Ref. 32). In 1995, FDA estimated that hospitalizations associated with outpatient adverse reactions cost $4.4 billion per year (60 FR 44182 at 44232; August 24, 1995), equaling $5.2 billion in 2000 dollars. If the causes of errors in the outpatient setting are similar to the causes in hospitals, half of these costs are related to physician ordering errors. Thus, about $2.6 billion (in 2000 dollars) per year in additional hospital costs result from errors likely to be influenced by improved prescribing information.

FDA lacks data to estimate the actual proportion of the adverse reaction costs that would be prevented under the final rule. Combining the projected hospital costs attributable to preventable in-hospital and outpatient adverse reactions, from $4.0 billion to $4.8 billion per year may be potentially avoided through measures that provide better information to doctors, such as prescription drug labeling. If the final rule reduced these costs by even 1 percent, between $40 million and $48 million of the costs of hospitalization could be prevented each year. Over 10 years, the present value of these avoided costs would total from $240 million to $290 million with a 7 percent discount rate, and from $300 to $360 with a 3 percent discount rate (table 11).

Table 11.--Annual Avoided Health Care Costs of Treating Patients for Preventable Adverse Drug Events [1, 2]

Year	Current Value ($ mil)					Present Value ($ mil)			
	Outpatient ADEs	In-Hospital ADEs		Total		Total Discounted at 3 percent		Total Discounted at 7 percent	
		From:	To:	From:	To:	From:	To:	From:	To:
1	0	0	0	0	0	0	0	0	0
2	26	14	22	40	48	38	45	35	42
3	26	14	22	40	48	37	44	33	39
4	26	14	22	40	48	35	43	30	37
5	26	14	22	40	48	34	42	28	34
6	26	14	22	40	48	33	40	27	32
7	26	14	22	40	48	32	39	25	30
8	26	14	22	40	48	32	38	23	28
9	26	14	22	40	48	31	37	22	26
10	26	14	22	40	48	30	36	20	24
Total	230	130	200	360	430	300	360	240	290

[1] Numbers may not sum due to rounding.
[2] Assumes the rule will avoid 1 percent of the preventable hospitalization costs from in-hospital and outpatient adverse drug events.

As illustrated in table 12, the magnitude of the potential benefits of the final rule will be sensitive to the assumed level of effectiveness. At 0.4 percent, the total present value of avoided hospital costs for preventable in-hospital and outpatient adverse drug events will exceed the total present value of the compliance costs for the final rule at both 3 and 7 percent discount rates.

TABLE 12.—IMPACT OF DIFFERENT EFFECTIVENESS LEVELS ON THE TOTAL PRESENT VALUE OF AVOIDED HOSPITAL COSTS TO TREAT PREVENTABLE ADVERSE DRUG EVENTS[1]

Effectiveness Estimate (percent)	Discounted at 3 percent ($ million)		Discounted at 7 percent ($ million)	
	From:	To:	From:	To:
0.1	30	36	24	29
0.4[2]	120	140	97	120
0.5	150	180	120	150
1.0	300	360	240	290
5.0	1,500	1,800	1,200	1,500

[1] Numbers may not sum due to rounding.
[2] Corresponds to the breakeven point where over 10 years, the total present value of hospital costs avoided exceeds the total present value of the compliance costs of the final rule.

When compared with other published studies, the agency's estimate of the cost of adverse reactions is likely less than the total social cost of such events. In particular, FDA's estimates include only hospital costs, and exclude the willingness to pay of patients to reduce these risks. Because these risks include fatality risks, the willingness to pay may be quite large. Using a restrictive definition of adverse events and including direct and indirect costs, a large study of hospital discharge records conducted by Thomas and others in Utah and Colorado was published in 1999 and estimated that preventable adverse events cost society at least $17 billion (in 1996 dollars) each year (Ref. 33). In contrast, a 2001 revision of the 1995 Johnson and Bootman cost-of-illness model used current costs whenever possible and predicted that drug-related illness occurring in ambulatory care settings cost about $177.4 billion each year, or more than 40 times the estimate of avoided costs that was used in the rest of this analysis

(Refs. 34 and 35). While we acknowledge that we have no direct evidence about how the rule would reduce preventable adverse reactions, if the final rule avoided at least one-tenth of a percent of the costs predicted by the Thomas study, annual benefits of the rule would approximately equal annual costs.

D. Costs of Regulation

Except as noted below, the methods used to estimate costs for the proposed rule remain the same for the final impact analysis (65 FR 81082 at 81103 through 81112). When possible, unit costs have been updated.

The proposed rule would have required two broad types of changes to the labeling of prescription drug products. First, labeling of approximately one-third of products already approved for marketing would have been revised to delete or add information within 1 year. Several comments argued that these changes would be quite costly relative to the limited benefits that would be derived and difficult to accomplish in the proposed implementation period (see comment 114). In response to these comments, the agency removed the requirements to delete certain information from all existing prescription drug labeling. Only those products with existing labeling that have FDA-approved patient labeling will be required to revise the labeling within 1 year.

Second, the proposed rule would have revised the content and established format requirements for labeling of new and recently approved applications. Although the agency modified some specific content and format requirements, the staggered implementation schedule and most provisions were retained for the final rule. Therefore, direct costs incurred to change prescription drug labeling include the costs of: (1) Designing or revising prescription drug labeling and submitting the new labeling to FDA, (2) producing longer trade labeling including any equipment adjustments, (3) layout and artwork for labeling not accompanying drug products, (4) producing longer labeling for labeling not accompanying drug products, and (5) printing longer labeling in the PDR.

1. Labeling Changes for All Approved Prescription Drug Products

a. *Affected products.* The agency will require that FDA-approved patient labeling accompany the prescription drug labeling, or be printed following the last section of the prescription drug labeling within 1 year after the effective date of the final rule. The agency identified up to 200 products with some form of FDA-approved patient labeling that will be affected by the final rule. A sample of these affected products shows that the labeling of more than 60 percent already conforms to this provision of the final rule. Therefore, the labeling of an estimated 80 products will need to be revised.

b. *Prescription drug labeling design costs.* On average, prescription drug manufacturers will incur about $2,220 per product in design and implementation costs to append FDA-approved patient labeling to existing prescription drug labeling. Because changes must be made within 1 year of the effective date of the final rule, not all firms will have sufficient time to deplete their inventories of existing prescription drug labeling. With a 12-month implementation period, FDA consultants estimate per product inventory losses of approximately $630. Thus, including excess inventory losses, the cost to change prescription drug labeling is estimated at $2,850 per product (65 FR 81082 at 81109; and 68 FR 6062 at 6074, reflecting updated costs). As shown in table 13, in the first year firms may incur one-time costs of $0.2 million to add FDA-approved patient labeling to the labeling of the affected products.

c. *Incremental printing costs for prescription drug labeling.* Printed patient information would add an estimated 2 pages or about 75-square inches to the length of trade labeling when printed on two sides (65 FR 81082 at 81109). Updating the unit printing costs for inflation, this additional length would increase the incremental printing costs by approximately $6.84 for 1,000 pieces of labeling (75-square inches per piece x $0.0000912 per square inch x 1,000 pieces) (68 FR 6062 at 6074). For the final analysis, FDA estimates that for affected products, up to 650,000 pieces of trade labeling would be distributed each year (section XI.D.2.c.i of this document). For each of the affected products, manufacturers will incur annual incremental costs averaging about $4,440 to print the longer trade labeling (650,000 pieces per product per year x $6.84 per 1,000 pieces). For all 80 affected products, annual incremental printing costs for trade labeling will increase by $0.4 million. Furthermore, manufacturers distributing longer prescription drug labeling with promotional materials and samples will spend up to an additional $5,125 in annual incremental printing costs each year for 3 years (750,000 pieces per year x $6.84 per 1,000 pieces (approximation based on information in footnote 17 in section XI.D.2.e of this document)). Therefore, industry will incur additional printing costs with a present value of approximately $3.6 million or $4.2 million over 10 years at a 7 or 3 percent discount rate, respectively (table 13).

d. *Physicians' Desk Reference (PDR) Costs.* The agency estimates that 75 percent of prescription drug products have labeling already printed in the PDR. In 2002, an additional page in the PDR costs manufacturers $9,750.[14] Thus, the per product annual cost to print two additional pages is about $19,500 ($9,750 x 2). For the estimated 60 affected products (80 products x 0.75), the annual PDR costs would increase by $1.2 million ($19,500 x 60), equaling a present value of approximately $8.2 million or $10.0 million over 10 years with a 7 or 3-percent discount rate, respectively (table 13).

TABLE 13.—COSTS TO INCLUDE FDA-APPROVED PATIENT LABELING WITH LABELING OF EXISTING PRESCRIPTION PRODUCTS[1, 2]

Year	One-Time Labeling Revision Costs ($ million)	Annual Incremental Printing Costs ($ million)	Annual PDR Costs ($ million)	Total Costs ($ million)
1	0.2	0.8	1.2	2.2
2	0.0	0.8	1.2	1.9

[14] Not all of these costs to manufacturers are social costs, as the PDR publisher is presumably selling additional pages at more than its true opportunity cost. The excess is a transfer, but we do not know its magnitude.

TABLE 13.—COSTS TO INCLUDE FDA-APPROVED PATIENT LABELING WITH LABELING OF EXISTING PRESCRIPTION PRODUCTS[1, 2]—Continued

Year	One-Time Labeling Revision Costs ($ million)	Annual Incremental Printing Costs ($ million)	Annual PDR Costs ($ million)	Total Costs ($ million)
3	0.0	0.8	1.2	1.9
4	0.0	0.4	1.2	1.5
5	0.0	0.4	1.2	1.5
6	0.0	0.4	1.2	1.5
7	0.0	0.4	1.2	1.5
8	0.0	0.4	1.2	1.5
9	0.0	0.4	1.2	1.5
10	0.0	0.4	1.2	1.5
Total Cost	0.2	4.8	11.7	16.7
Present Value of Total Discounted at 3 percent	0.2	4.2	10.0	14.4
Present Value of Total Discounted at 7 percent	0.2	3.6	8.2	12.0

[1] Numbers may not sum due to rounding.
[2] This estimate assumes that products with Medication Guides already conform to this requirement of the final rule.

2. Labeling Changes for New and Recently Approved Prescription Drug Products

a. *Affected products.* The final rule would require that prescription drug labeling conform to format and content requirements for three categories of products: (1) All NDAs, BLAs, and efficacy supplements submitted to FDA on or after the effective date, (2) NDAs, BLAs, and efficacy supplements approved over the 5 years preceding the effective date or pending on the effective date of the final rule, and (3) any ANDA that references a listed drug with labeling conforming to the requirements of the final rule. For the first category of products, the prescription drug labeling requirements would apply when a sponsor files an NDA, BLA or efficacy supplement. Products in the second category must file supplemental applications within 3 to 7 years of the issuance of the rule, according to the implementation plan described in the preamble (see Table 5). For ANDA products (generic products), the implementation schedule for the affected reference listed drug applies. This rule does not cover labeling for OTC products (including those approved under an NDA).

Estimates of the number of new applications that would be affected by the rule are updated and based on application approvals since 1997. During this period, an average of 97 NDAs and 10 BLAs were approved each year. FDA assumes that this average rate will continue. The number of affected products approved within 5 years before the effective date are estimated as the number of NDAs approved during the 5-year period from 1997 through 2001 without subsequent efficacy supplements.

Most efficacy supplements are filed and approved within 5 years of the approval date of their original application. Over time, prescription drug labeling of most products affected by the final rule will already conform to the requirements of the final rule when an efficacy supplement is submitted. Beginning in year 3, therefore, the number of labeling revisions as a result of an efficacy supplement will decline over time.

The initial analysis of impacts did not include estimates of the number of generic products that would be affected because the period of exclusivity for most innovator products covered by the rule would extend beyond the 10-year horizon. However, a subsequent analysis of data from ''Approved Drug Products with Therapeutic Equivalence Evaluations'' (the Orange Book) found that some older innovator products with generic equivalents have recent approvals of efficacy supplements or NDAs for new dosage strengths that could trigger revision of the labeling of some reference listed drugs. Although the overall number of older innovator products affected by the final rule is anticipated to be small, normally there are multiple generic products for each reference listed drug. Therefore, beginning in year 3, the final rule is estimated to affect an average of 42 generic products annually. Table 14 shows the number of products projected to be affected by the final rule during the 10-year period following the effective date.

TABLE 14.—ESTIMATED NUMBER OF AFFECTED PRODUCTS BY APPLICATION TYPE

Year	New NDAs and BLAs	Efficacy Supplements	Approvals 5 Years Prior to Effective Date	ANDAs	Total
1	107	69	0	0	176

TABLE 14.—ESTIMATED NUMBER OF AFFECTED PRODUCTS BY APPLICATION TYPE—Continued

Year	New NDAs and BLAs	Efficacy Supplements	Approvals 5 Years Prior to Effective Date	ANDAs	Total
2	107	69	0	0	176
3	107	52	69	42	270
4	107	39	69	42	257
5	107	29	68	42	246
6	107	22	69	42	240
7	107	16	69	42	234
8	107	12	0	42	161
9	107	9	0	42	158
10	107	7	0	42	156
Total	1,070	324	344	336	2,074

b. *Prescription drug labeling design costs.* The cost of designing prescription drug labeling that conforms to the final 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 prescription drug labeling that otherwise would 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 prescription drug labeling changed to the new format or for generic drug labeling. Costs for currently marketed products that would be undergoing relabeling for other reasons (e.g., related to an efficacy supplement) will be in between these extremes.

FDA has previously estimated that it takes about 2 months of full-time effort to design a novel patient information guide (for the first prescription drug in a therapeutic class), but less than 1 week to redesign a guide following a previously approved prototype (i.e., innovator drugs in the same therapeutic class for which patient information was already developed) (60 FR 44232). The final rule requires reordering of the detailed information in the prescription drug labeling and addition of Highlights and Contents. Although FDA designates the new order, detailed discussion and drug-specific decisions (e.g., regarding exactly what should be listed in Highlights) may be necessary. Because negotiation of labeling is a routine part of the review process, including Highlights and Contents does not increase this time burden on manufacturers or the agency. Therefore, the time required to revise labeling conforming to the requirements of the final rule will fall between the time required to design a novel patient information guide and time required to redesign a guide. Although sponsors of new applications and efficacy supplements would incur many of the same design costs as sponsors of existing innovator products, they would experience no additional testing, preparation, and application costs. For the initial analysis, it was anticipated that manufacturers would incur one-time costs up to $5,000 for each new product and $7,500 for each existing product to conform to the format and content provisions of the rule (65 FR 81082 at 81106 through 81107). These one-time per product costs are updated to $6,190 and $8,700, respectively. Modifying prescription drug labeling for ANDAs is anticipated to cost generic drug manufacturers about $1,300 per product, including $830 in labor costs and $470 in material costs for artwork and scrap (68 FR 6062 at 6074).

Once product labeling contains Highlights, any substantive revisions of key sections of the labeling must be listed in the recent major changes section along with the month and year the revision was incorporated. However, the final rule also requires that after 1 year, the information about recent major changes must be removed the next time the labeling is reprinted. Manufacturers voluntarily change drug product labeling frequently during the first 5 years a product is marketed. During this period, the agency anticipates that manufacturers would remove recent major changes from Highlights at the same time they voluntarily change labeling and, thus, would incur no additional costs. After 5 years on the market, however, some manufacturers would incur additional costs to remove recent major changes in the timeframe specified by the final rule. The earliest this might occur is in year 7 after the initial redesign of the labeling.[15] Based on the agency's experience with products that have been on the market for more than 5 years, up to 10 percent of the products affected by the final rule might be required to remove recent major changes in year 7 or later, at a per product cost of approximately $1,600. Over 10 years, the present value of these costs could equal about $0.1 million with either a 7 percent or 3 percent discount rate.

As shown in table 15, the total first-year costs would amount to $1.1 million. Costs increase to a high of $1.6 million in years 3 and 4. After the seventh year, when all products approved within 5 years prior to the rule's effective date or pending on the effective date have redesigned prescription drug labeling, the costs decline to about $0.8 million per year. As a result, the estimated total present value of the costs of redesigning prescription drug labeling over 10 years is about $8.8 million and $10.5 million with a 7 and 3 percent discount rate, respectively.

[15] Recent major changes must remain in the Highlights for at least 1 year. Any major change after year 5 would therefore remain on the labeling through year 6 or later.

TABLE 15.—ESTIMATED PRESCRIPTION DRUG LABELING DESIGN COSTS[1]

Year	Current Value ($ million)					Present Value ($ million)	
	NDAs and BLAs	Efficacy Supplements	Approvals 5 Years Prior to Effective Date	ANDAs	Total	Total Discounted at 3 percent	Total Discounted at 7 percent
1	0.7	0.4	0.0	0.0	1.1	1.1	1.0
2	0.7	0.4	0.0	0.0	1.1	1.0	1.0
3	0.7	0.3	0.6	0.1	1.6	1.5	1.3
4	0.7	0.2	0.6	0.1	1.6	1.4	1.2
5	0.7	0.2	0.6	0.1	1.5	1.3	1.1
6	0.7	0.1	0.6	0.1	1.5	1.2	1.0
7	0.7	0.1	0.6	0.1	1.5	1.2	0.9
8	0.7	0.1	0.0	0.1	0.8	0.7	0.5
9	0.7	0.1	0.0	0.1	0.8	0.6	0.4
10	0.7	0.0	0.0	0.1	0.8	0.6	0.4
Total	6.7	2.0	3.0	0.4	12.2	10.5	8.8

[1] Numbers may not sum due to rounding.

c. *Costs associated with producing longer labeling accompanying drug products and drug samples (trade labeling).* The proposed rule would have required that trade labeling be printed in 8-point minimum type size, almost doubling the current average length for the labeling. Several comments from pharmaceutical manufacturers stated that the agency had underestimated the retooling and packaging line costs that would be incurred to include this longer trade labeling (see comment 124). A few large firms estimated that new equipment would cost between $135,000 and $700,000 per packaging line and could total up to $40 million for a large firm if trade labeling of all products were affected. As discussed in section XI.F of this document (''Alternatives Considered''), the agency recognized that including all products in the final rule would substantially increase costs to industry and, therefore, limited the final rule to new and recently approved products (see section XI.F.3 of this document). Furthermore, approximately half of the affected products shown in table 14 will be new approvals that have not yet established packaging. Nevertheless, based on the potential economic impact the larger type size might have on pharmaceutical manufacturers, for the final rule the agency reduced the minimum size requirement for trade labeling to 6 points, a size generally reported as acceptable in comments from manufacturers (see comment 102). Thus, the new format and content requirements of the final rule will lengthen trade labeling by approximately 20 square inches when printed on two sides. Longer prescription drug labeling increases the cost of paper, ink, and other ongoing incremental printing costs. As discussed below, even in 6 points, a small number of products are still expected to incur some equipment costs (e.g., different insert-folding machinery).

i. *Incremental printing costs for trade labeling.* U.S. retail pharmacies dispense about 3.3 billion prescriptions per year, of which an estimated 790 million are for unit-of-use products that include prescription drug labeling within the package (65 FR 81082 at 81107, updated using IMS data at *http://www.ims-health.com*). If the non-unit-of-use prescriptions average one piece of labeling per 3.3 prescriptions, the total number of labelings accompanying retail products equals roughly 1.5 billion. Further, adding hospital pharmaceutical volume, estimated at approximately 54 percent of retail volume, yields an annual total of 2.4 billion pieces of trade labeling accompanying prescribed products. Allowing 10 percent for wastage indicates that manufacturers distribute roughly 2.6 billion pieces of labeling with prescribed products each year. Since 60 percent of all prescriptions are for branded products, about 1.6 billion pieces of labeling are currently included with about 2,440 branded products and about 1.0 billion pieces are included with 2,900 generic products.[16] Using 650,000 pieces per innovator product and 370,000 pieces per generic product, at a cost of $0.18 and $0.19 per 100 pieces, respectively, yields annual per product cost estimates of $1,165 and $700, respectively. Table 16 shows the estimated number of revised labelings and annual incremental printing costs over 10 years.

Trade labeling must also accompany drug product samples. However, the number of samples distributed for a specific product depends on a manufacturer's marketing strategy and may vary from year to year. Although IMS Health (IMS) reported that the volume of samples distributed in the United States between 1997 and 2000 ranged from 860 million to 920 million (Ref. 36), sales representatives normally leave one piece of labeling for every 10 samples they distribute. Even though new products are sampled more often than older products, some manufacturers continue to distribute samples throughout the life cycle of their product. While the actual number of samples including reformatted trade labeling is uncertain, we anticipate that manufacturers may spend up to $0.2

[16] Derived from ''Approved Drug Products with Therapeutic Equivalence Evaluations,'' CDER, FDA, 2001. The estimate is a count of all branded products marketed under an NDA and differentiated by active ingredient, therapeutic equivalence, dosage form, or manufacturer, not including multiple dosage strengths. Although not counted, adding biologicals would not significantly alter results.

million annually to print longer trade labeling to accompany drug samples (table 16).

Table 16.--Incremental Annual Printing Costs for Longer Trade Labeling in 6-Point Minimum Type Size[1]

Year	Number by Type (million)			Current Value ($ mil)				Present Value ($ mil)	
	NDA, BLA, and ES	ANDA	Samples	NDA, BLA, and ES	ANDA	Samples	Total	Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	110	0	90	0.2	0.0	0.2	0.4	0.4	0.3
2	230	0	90	0.4	0.0	0.2	0.6	0.5	0.5
3	380	16	90	0.7	0.0	0.2	0.9	0.8	0.7
4	520	31	90	0.9	0.1	0.2	1.1	1.0	0.9
5	650	47	90	1.2	0.1	0.2	1.4	1.2	1.0
6	780	62	90	1.4	0.1	0.2	1.7	1.4	1.1
7	900	78	90	1.6	0.1	0.2	1.9	1.6	1.2
8	980	93	90	1.8	0.2	0.2	2.1	1.7	1.2
9	1,100	110	90	1.9	0.2	0.2	2.3	1.7	1.2
10	1,100	120	90	2.0	0.2	0.2	2.4	1.8	1.2
Total	6,750	560	900	12.1	1.1	1.6	14.7	12.1	9.4

[1] Numbers may not sum due to rounding.

ii. *Equipment costs.* The original analysis estimated that 1 percent of affected existing products would be required to adjust packaging equipment with trade labeling printed in 8 points. According to several comments, trade labeling is currently printed in type sizes of 4.5 points and larger (see comment 102). Thus, it is unlikely that the minimum type size requirement of the final rule (i.e., 6 points for trade labeling) will require firms to purchase new packaging equipment. However, in a few cases where existing labeling is printed in type sizes between 4.5 points and 6 points, firms may need to adjust packaging lines for longer labeling. Since the labeling of many ophthalmic drug products is printed in type sizes smaller than 6 points, the proportion of recent approvals for ophthalmic products was used as a proxy for the proportion of affected products that will incur some equipment costs. For the final analysis, 5 percent of existing products affected by the rule (i.e., products with new efficacy supplements, products approved in the 5 years prior to the effective date of the rule, and affected ANDAs) will incur costs of $200,000 each product. As shown in table 17, the estimated present value of equipment changes totals $7.2 million and $8.7 million over 10 years discounted at 7 and 3 percent respectively.

TABLE 17.—COST OF ADJUSTMENTS TO PACKAGING LINES TO ACCOMMODATE LONGER TRADE LABELING[1, 2]

Year	Estimated Number of Affected Products	Total Cost ($ million)	Present Value ($ million)	
			Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	3	0.7	0.7	0.6
2	3	0.7	0.7	0.6
3	8	1.6	1.5	1.3
4	8	1.5	1.3	1.1
5	7	1.4	1.2	1.0
6	7	1.3	1.1	0.9
7	6	1.3	1.0	0.8
8	3	0.5	0.4	0.3
9	3	0.5	0.4	0.3
10	2	0.5	0.4	0.2

TABLE 17.—COST OF ADJUSTMENTS TO PACKAGING LINES TO ACCOMMODATE LONGER TRADE LABELING[1, 2]—Continued

Year	Estimated Number of Affected Products	Total Cost ($ million)	Present Value ($ million)	
			Total Discounted at 3 Percent	Total Discounted at 7 Percent
Total	50	10.0	8.7	7.2

[1] Numbers may not sum due to rounding.
[2] For products with labeling printed in type sizes smaller than 6 points, the final rule may require that some packaging lines be retooled. Based on NDA, ANDA or efficacy supplements approvals for ophthalmic drug products between 1997 and 2001, an estimated 5 percent of the existing products affected by the rule will require some change to packaging equipment at an average cost of $200,000 per product.

d. *Layout and design costs for prescription drug labeling not accompanying drug products*. The final rule specifies a minimum type size of 6 points for trade labeling and 8 points for all other prescription drug labeling distributed by a manufacturer (e.g., labeling required to be distributed with promotional materials or in promotional settings). Firms choosing to print all prescription drug labeling for a product in the same type size (8 points or larger) will incur no additional design costs. However, if trade labeling is printed in a type size smaller than 8 points, a firm will incur additional costs of $810 per product to change and proof read the layout, and to prepare artwork for the labeling not accompanying the drug product. It is uncertain how many firms will print labeling in different type sizes. However, if all new and recently approved innovator products are affected, the total present value of the additional design costs is approximately $1.0 million or $1.2 million over 10 years discounted at 7 or 3 percent respectively (table 18).

TABLE 18.—ESTIMATED ONE-TIME LAYOUT AND DESIGN COSTS FOR LABELING NOT ACCOMPANYING DRUG PRODUCTS[1,2]

Year	Number of Affected Products	Total Costs ($ million)	Present Value ($ million)	
			Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	176	0.1	0.1	0.1
2	176	0.1	0.1	0.1
3	228	0.2	0.2	0.2
4	215	0.2	0.2	0.1
5	204	0.2	0.1	0.1
6	198	0.2	0.1	0.1
7	192	0.2	0.1	0.1
8	119	0.1	0.1	0.1
9	116	0.1	0.1	0.1
10	114	0.1	0.1	0.0
Total	1,738	1.4	1.2	1.0

[1] Firms are expected to only print this type of labeling for 3 years after the launch of a new innovator drug product.
[2] Numbers may not sum due to rounding.

e. *Costs associated with producing longer prescription drug labeling not accompanying drug products*. In contrast to trade labeling, with the new content and format requirements the length of current labeling will increase an average of about 93 percent when printed in 8-point type size. At this length, the incremental printing costs will increase by $0.85 per 100 pieces. To calculate the annual cost to print prescription drug labeling not accompanying drug products, FDA estimated that pharmaceutical representatives detailing drug products would distribute approximately 50 million pieces of prescription drug labeling annually. Because most detailing involves relatively new products, the products most affected by this rule, FDA assumed that manufacturers would incur additional printing costs for all of this labeling, amounting to about $0.4 million annually.

Finally, FDA estimated that about 730,000 pieces of prescription drug labeling per approval would be distributed each year by mail or at conferences to physicians, other health care practitioners, consumers, retail pharmacy outlets, and hospital pharmacies for 3 years following approval of a new drug.[17] As shown in table 19, annual total costs peak at $4.4 million in year 5. Over 10 years with a 7 or 3 percent discount rate, the present value of the incremental printing costs

[17] For each approval, it was assumed that all physicians involved in primary care and 25 percent of physicians practicing a medical specialty would receive two mailings per year, or an estimated 646,150 pieces (i.e., (222,400 x 2) + (0.25 x 402,700 x 2)), for 3 years following product launch. An additional 10 percent or 64,615 pieces are estimated to be distributed annually for 3 years to other health care practitioners or consumers. Furthermore, FDA assumes that 55,581 retail pharmacy outlets and 8,020 hospital pharmacies would receive 1 mailing to announce the launch of a new innovator product in the year of approval (65 FR 81082 at 81108, updated).

for longer prescription drug labeling not accompanying drug products would be about $24 million or $29 million, respectively.

Table 19.--Annual Incremental Printing Costs for Longer Prescription Drug Labeling Not Accompanying Drug Products Printed in 8-Point Minimum Type Size[1]

Year	Number of Affected Innovator Products	Number of Pieces and Type of Delivery (million)		Current Value of Costs ($ mil)			Present Value ($ mil)	
		In-Person	Mailed	In-Person	Mailed	Total Cost	Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	176	50	140	0.4	1.2	1.6	1.5	1.5
2	176	50	260	0.4	2.2	2.6	2.5	2.3
3	228	50	430	0.4	3.6	4.0	3.7	3.3
4	215	50	450	0.4	3.8	4.3	3.8	3.3
5	204	50	470	0.4	4.0	4.4	3.8	3.2
6	198	50	450	0.4	3.8	4.2	3.6	2.8
7	192	50	430	0.4	3.7	4.1	3.3	2.6
8	119	50	370	0.4	3.1	3.6	2.8	2.1
9	116	50	310	0.4	2.6	3.1	2.3	1.7
10	114	50	260	0.4	2.2	2.6	1.9	1.3
Total	1,738	500	3,600	4.0	30.2	34.5	29.3	23.9

[1] Numbers may not sum due to rounding.

f. *Physicians' Desk Reference (PDR) Costs.* FDA estimates that the new Highlights, including any boxed warnings, and Contents would add about a half page to the PDR labeling of each affected prescription drug product. Based on conversations with Medical Economics (the publisher of the PDR) on the cost per printed page, FDA estimates that the annual publishing costs of the extra space required for printing the expanded prescription drug labeling would be about $5,550 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). FDA also 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 prescription drug 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 prescription drug labeling in the PDR would be about $1.2 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 costs of printing longer PDR listings are shown in table 20.

TABLE 20.—COST TO PRINT LONGER LISTINGS IN THE PDR[1, 2]

Year	Current Value ($ million)			Present Value ($ million)	
	PDR Bound	PDR Supplement	Total Costs	Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	0.7	0.5	1.2	1.2	1.1
2	1.5	0.5	2.0	1.8	1.7
3	2.4	0.5	2.9	2.6	2.4

TABLE 20.—COST TO PRINT LONGER LISTINGS IN THE PDR[1, 2]—Continued

Year	Current Value ($ million)			Present Value ($ million)	
	PDR Bound	PDR Supplement	Total Costs	Total Discounted at 3 Percent	Total Discounted at 7 Percent
4	3.3	0.5	3.8	3.3	2.9
5	4.2	0.4	4.6	4.0	3.3
6	5.0	0.4	5.4	4.5	3.6
7	5.8	0.4	6.2	5.0	3.9
8	6.3	0.4	6.7	5.3	3.9
9	6.8	0.4	7.2	5.5	3.9
10	7.2	0.4	7.6	5.7	3.9
Total	43.1	4.5	47.6	39.1	30.5

[1] Numbers may not sum due to rounding.
[2] Printed in 6.5-point type size at an average per page cost of $9,755.

Table 21 summarizes the estimated compliance costs for the three major cost categories over a 10-year period.

TABLE 21.—COMPLIANCE COSTS OVER 10-YEAR PERIOD[1]

Year	Cost Category ($ million)			Total Costs ($ million)
	Design and Producing Trade Labeling; Modify Packaging Equipment	Reformat and Producing Labeling Not Accompanying Drug Products	Printing PDR	
1	3.1	1.7	2.4	7.3
2	3.1	2.8	3.1	9.0
3	4.9	4.2	4.1	13.2
4	4.6	4.4	4.9	13.9
5	4.6	4.6	5.8	15.0
6	4.8	4.4	6.6	15.8
7	5.0	4.3	7.4	16.6
8	3.8	3.6	7.9	15.3
9	4.0	3.1	8.3	15.5
10	4.0	2.7	8.8	15.5
Total Current Value	42.0	35.9	59.3	137.2
Total Present Value Discounted at 3 Percent	35.7	30.5	49.0	115.3
Total Present Value Discounted at 7 Percent	29.2	24.9	38.8	92.9

[1] Numbers may not sum due to rounding.

E. Impacts on Small Entities

1. The Need for and the Objective of the Rule

Developments in recent years have contributed to an increase in the length and complexity of prescription drug labeling, making it more difficult for health care practitioners to quickly find specific information about a drug. Therefore, practitioners expend time that could be spent with patients and may miss critical information about the safe and effective use of prescription drug products. The objective of the requirements is to improve prescription drug labeling by making it easier for health care practitioners to access, read, and use labeling information about prescription drug products. The agency believes that having better access to critical information will improve the use of prescription drugs and lead to a decrease in the number of preventable adverse reactions that occur in the United States each year.

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

This final rule would affect all small entities required to design their prescription drug labeling to comply with this rule. The Small Business Administration (SBA) considers Pharmaceutical Preparation Manufacturing firms (NAICS 325412) and Biological Product Manufacturing firms (NAICS 325414) with fewer than 750 and 500 employees, respectively, to be small. U.S. Census reports in 1999 there were 265 biological product manufacturing firms (Ref. 37) and 749 pharmaceutical preparation manufacturing firms (Ref. 38). However, employment size classes for pharmaceutical preparation manufacturing do not correspond to SBA size categories. Nevertheless, 1999 Census data suggest that approximately 94 percent of biological product manufacturing firms and at least 87 percent of the pharmaceutical preparation manufacturing firms could be considered small. Despite the large number of small manufacturers, large companies manufacture most prescription drug products. Although the agency cannot predict the number of new approvals granted to small entities, the following estimates are based on 5 years of recent submissions (65 FR 81082 at 81110, updated for 1997–2001). On average, 17 small entities will receive product approvals each year. In addition, about 64 small entities will be affected during years 3 to 7 of the rule, when applicants with products approved 5 years prior to the effective date of the final rule must submit reformatted prescription drug labeling for approval. Only six firms will have more than two existing products affected by the rule. Of these six, four firms will have two products affected in the same year and one firm will have three products affected in a single year.

The compliance requirements for small entities under this final rule are the same as those described above for other affected entities. Compliance primarily involves: (1) designing prescription drug labeling that conforms to the content and format requirements, and (2) once the labeling is approved by FDA, ensuring that all future printed prescription drug labeling is in the new format with the required minimum type size. Because manufacturers already submit labeling with NDAs, BLAs and efficacy supplements to FDA, no additional skills will be required to comply with the final rule.

The group of small entities likely to bear the highest total costs under this final rule are those firms that have: (1) Existing products with prescription drug 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 prescription drug 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 costs of compliance, but the incremental cost per unit sold would be higher.

Although the agency solicited comment on the initial regulatory flexibility analysis from small entities, the only comments submitted specifically about the impact on small entities were from large firms (see comment 122). The following examples illustrate possible impacts on small entities with different production volumes. Prescription drug labeling costs are estimated 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 22 outlines the projected per-unit and total costs to the firm with 3 different levels of production: 1,000, 10,000, and 100,000 units produced per year.

In addition to the costs identified in table 22, 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 believes that the final rule would not have a significant impact on most small entities in this industry, but it is possible that a few small firms may be significantly affected by the final rule.

TABLE 22.—ESTIMATED COSTS FOR HYPOTHETICAL SMALL FIRM WITH A SINGLE PRODUCT, UNDER THREE ALTERNATIVE LEVELS OF PRODUCTION[1]

Cost Category	Number of Units Produced and Sold Each Year		
	100,000	10,000	1,000
Example 1—Revise labeling of product approved less than 1 year prior to effective date:			
Prescription drug labeling redesign/application	$8,700	$8,700	$8,700
Printing trade labeling[2]	$200	$20	$2
Printing prescription drug labeling not accompanying drug products[3]	$1,050	$105	$10
Total	$9,950	$8,825	$8,712
Additional cost per unit sold	$0.10	$0.88	$8.71
Example 2—Add printed patient information to existing labeling for a product:			
Prescription drug labeling redesign	$2,850	$2,850	$2,850
Printing trade labeling[4]	$750	$75	$8
Printing longer PDR[5]	$19,500	$19,500	N/A
Total	$23,100	$22,425	$2,858
Additional cost per unit sold	$0.23	$2.24	$2.86

[1] Numbers may not sum due to rounding.

[2] Number of pieces of trade labeling printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $0.001791 per labeling.

[3] To calculate the cost for printing labeling not accompanying drug products, the number of units is adjusted by the ratio of the average number of pieces printed for mailings to the average number printed as trade labeling (i.e., 1.126), and multiplied by the incremental printing cost of $0.0085 per piece.

[4] Number of pieces of trade labeling printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $0.006837 per labeling.

[5] Assume that prescription drug labeling is already being printed in the PDR. Most low-volume products (i.e., less than 10,000 units per year) will not have labeling in the PDR.

F. Alternatives Considered

1. Do Nothing

The agency considered and rejected this option. The current prescription drug labeling is complex, requiring health care practitioners to spend unnecessary time seeking information they need for the safe and effective use of drug products by their patients. Preventable adverse reactions have many causes and are a serious public health issue. Changing prescription drug labeling to meet the needs of health care practitioners that use it is one of many public health initiatives aimed at reducing these adverse reactions and improving health care.

2. Formatting Alternatives

FDA has considered numerous alternative formats, including a longer Highlights. Highlights is limited to one-half page in 8 points to respond to health care practitioners' concerns about length as well as to reduce the incremental printing costs to manufacturers.

The agency also considered requiring larger minimum type sizes. A 10-point minimum size requirement would increase the amount of paper needed to print the average reformatted labeling by about 200-square inches at an incremental cost of $18,000 per million pieces. Over 10 years, the total present value of producing longer trade labeling in 10 points compared to 6 points would equal $95 million or $120 million with a 7- or 3-percent discount rate, respectively. In addition to higher incremental printing costs, requiring 10-point minimum type size would make labeling so large that many manufacturers would be forced to modify or replace packaging equipment. The agency therefore rejected this option because the potential benefits of the larger type size did not outweigh the costs.

The agency also considered and rejected a 10-point minimum size requirement for labeling not accompanying drug products. Compared to the minimum requirement of 8 points in the final rule, this larger type size would have taken about 100-square inches more paper at an incremental cost of $9,000 per million pieces.

Finally, the agency proposed a minimum size requirement of 8 points for trade labeling instead of the 6-point requirement in the final rule. At 6 points, the average revised labeling will increase by about 20-square inches. Requiring the larger minimum size would take another 70-square inches of paper and cost industry about $6,000 per million pieces of trade labeling. Because this requirement would be burdensome on industry, the agency rejected the 8-point minimum type size.

3. Alternative Categories of Affected Products

Three alternative categories of products to be covered by the rule were considered: (1) All drugs, (2) a 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 reactions. The agency believes including only labeling of new and more recently approved drug products is the best option for implementing the new format requirements (see comment 113). Even this limited set of products will require substantial resources from both industry and the agency for a period of several years. The agency's proposed implementation plan, which is being finalized in this rule as proposed, is intended to make the best use of these resources. Because there is a lack of standardized data on prescription volume and volumes can fluctuate considerably over time, the agency does not believe that categories based on volume would be prudent or feasible. As discussed in the preamble to the proposed rule (65 FR 81082 at 81098), the plan targets newer products because practitioners are more likely to refer to the labeling for newer products. Internal agency analysis finds that fully 40 percent of adverse reaction reports submitted to the FDA are for drugs approved within the last 3 years. Therefore, the agency rejected these three alternative categories in order to focus efforts on recently approved drug products whose labeling is more likely to be consulted by physicians.

4. Alternative Implementation Schedule

FDA considered a shorter implementation schedule of 3 years after the effective date for all applications and efficacy supplements approved 5 years prior to the effective date. The agency selected the more gradual implementation schedule of up to 7 years to reduce the cost impact of the rule, especially on small entities.

XII. Civil Justice Reform

This rule has been reviewed under Executive Order 12988, Civil Justice Reform. This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988.

XIII. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procdure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR 601

Adminstrative practice and procedure, Biologics, Confidential business information.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 201, 314, and 601 are 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.

■ 2. Section 201.56 is revised to read as follows:

§ 201.56 Requirements on content and format of labeling for human prescription drug and biological products.

(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. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

(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 must 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), biologics license application (BLA), or efficacy supplement was approved by the Food and Drug Administration (FDA) between June 30, 2001 and June 30, 2006;

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after June 30, 2006.

(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 June 30, 2006, proposed conforming labeling must be submitted as part of the application.

(2) For products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006, or that has been approved any time from June 30, 2005, up to and including June 30, 2006, a supplement with proposed conforming labeling must be submitted no later than June 30, 2009.

(3) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2004, up to and including June 29, 2005, a supplement with proposed conforming labeling must be submitted no later than June 30, 2010.

(4) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2003, up to and including June 29, 2004, a supplement with proposed conforming labeling must be submitted no later than June 30, 2011.

(5) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2002, up to and including June 29, 2003, a supplement with proposed conforming labeling must be submitted no later than June 30, 2012.

(6) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2001, up to and including June 29, 2002, a supplement with proposed conforming labeling must be submitted no later than June 30, 2013.

(d) *Labeling requirements for new 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 headings and subheadings and in the following order:

Highlights of Prescribing Information
- Product Names, Other Required Information

- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations

Full Prescribing Information: Contents

Full Prescribing Information
- Boxed Warning
- 1 Indications and Usage
- 2 Dosage and Administration
- 3 Dosage Forms and Strengths
- 4 Contraindications
- 5 Warnings and Precautions
- 6 Adverse Reactions
- 7 Drug Interactions
- 8 Use in Specific Populations
  - 8.1 Pregnancy
  - 8.2 Labor and delivery
  - 8.3 Nursing mothers
  - 8.4 Pediatric use
  - 8.5 Geriatric use
- 9 Drug Abuse and Dependence
  - 9.1 Controlled substance
  - 9.2 Abuse
  - 9.3 Dependence
- 10 Overdosage
- 11 Description
- 12 Clinical Pharmacology
  - 12.1 Mechanism of action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 Nonclinical Toxicology
  - 13.1 Carcinogenesis, mutagenesis, impairment of fertility
  - 13.2 Animal toxicology and/or pharmacology
- 14 Clinical Studies
- 15 References
- 16 How Supplied/Storage and Handling
- 17 Patient Counseling Information

(2) Additional nonstandard subheadings that are used to enhance labeling organization, presentation, or ease of use (e.g., for individual warnings or precautions, or for each drug interaction) must be assigned a decimal number that corresponds to their placement in labeling. The decimal numbers must be consistent with the standardized identifying numbers listed in paragraph (d)(1) of this section (e.g., subheadings added to the ''Warnings and Precautions'' section must be numbered 5.1, 5.2, and so on).

(3) Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the full prescribing information.

(4) Omit clearly inapplicable sections, subsections, or specific information. If sections or subsections required under paragraph (d)(1) of this section are omitted from the full prescribing information, the heading ''Full Prescribing Information: Contents'' must be followed by an asterisk and the following statement must appear at the end of Contents: ''* Sections or subsections omitted from the full prescribing information are not listed.''

(5) Any risk information that is required under § 201.57(c)(9)(iv) is considered ''appropriate pediatric contraindications, warnings, or precautions'' within the meaning of section 505A(l)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355A(l)(2)), whether such information appears in the ''Contraindications,'' ''Warnings and Precautions,'' or ''Use in Specific Populations'' section of labeling.

(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) Omit clearly inapplicable sections, subsections, or specific information.

(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) must 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 immediately after the last section of the labeling.

(6) The requirement in § 201.80(f)(2) to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling must be implemented no later than June 30, 2007.

■ 3. 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 drug and biological 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 requirement in paragraph (c)(18) of this section to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) *Highlights of prescribing information.* The following information must appear in all prescription drug labeling:

(1) *Highlights limitation statement.* The verbatim statement ''These highlights do not include all the information needed to use (*insert name of drug product*) safely and effectively. See full prescribing information for (insert name of drug product).''

(2) *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 must be included as required by § 1302.04 of this chapter.

(3) *Initial U.S. approval.* The verbatim statement ''Initial U.S. Approval'' followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the line immediately beneath the established name or, for biological products, proper name of the product.

(4) *Boxed warning.* A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word ''WARNING'' and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: ''See full prescribing information for complete boxed warning.''

(5) *Recent major changes.* A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), 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 identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(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., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: ''(Drug) is a (name of class) indicated for (indication(s)).''

(7) *Dosage and administration.* A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

(8) *Dosage forms and strengths.* A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets) and whether the product is scored.

(9) *Contraindications.* A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) *Warnings and precautions.* A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) *Adverse reactions.* (i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement ''To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA at (*insert current FDA phone number and Web address for voluntary reporting of adverse reactions*).''

(iii) For vaccines, the verbatim statement ''To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions*).''

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) *Drug interactions.* A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(13) *Use in specific populations*. A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) *Patient counseling information statement*. The verbatim statement ''See 17 for Patient Counseling Information'' or, if the product has FDA-approved patient labeling, the verbatim statement ''See 17 for Patient Counseling Information and (insert either FDA-approved patient labeling or Medication Guide).''

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

(b) *Full prescribing information: Contents*. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) *Full prescribing information*. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) *Boxed warning*. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word ''WARNING'' and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the ''Contraindications'' or ''Warnings and Precautions'' section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) *1 Indications and usage*. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the ''Clinical Studies'' section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the ''Dosage and Administration'' section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) 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), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) 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 this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness 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.

(iv) For drug products other than biological products, all indications listed in this section 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 the labeling if not included in this section.

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

(3) *2 Dosage and administration*. (i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant.

Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section 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 reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim 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 Dosage forms and strengths*. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(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 in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) *4 Contraindications*. This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include 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 the drug and for whom no potential benefit makes the risk acceptable. 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 must state ''None.''

(6) *5 Warnings and precautions*. (i) *General*. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association 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 may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) *Other special care precautions*. This section must 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).

(iii) *Monitoring: Laboratory tests*. This section must identify any laboratory tests 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*. This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., ''Drug Interactions'' section).

(7) *6 Adverse reactions*. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) *Listing of adverse reactions*. This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) *Categorization of adverse reactions*. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) *Clinical trials experience*. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and

severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) *Postmarketing experience.* This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) *Comparisons of adverse reactions between drugs.* For drug products other than biological products, 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.

(8) *7 Drug interactions.* (i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the ''Contraindications'' or ''Warnings and Precautions'' sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the ''Clinical Pharmacology'' section that are pertinent to clinical use of the drug must not be repeated in this section.

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

(9) *8 Use in specific populations.* This section must contain the following subsections:

(i) *8.1 Pregnancy.* This subsection 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 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 and Precautions' section.'' Under the ''Warnings and 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 used during pregnancy, or if the patient becomes

pregnant while taking this drug, 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 used during pregnancy, or if the patient becomes pregnant while taking this drug, 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) *8.2 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 and Usage section, this subsection 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 is unknown, it must state that the information is unknown.

(iii) *8.3 Nursing mothers*. (A) If a drug is absorbed systemically, this subsection 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 must contain one of the following statements, as appropriate. If the drug is associated with serious 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 nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious 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 nursing woman.''

(C) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection must contain one of the following statements, as appropriate. If the drug is associated with serious 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 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 nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious 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 nursing woman.''

(iv) *8.4 Pediatric use*. (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(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 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, and appropriate pediatric dosage information must be given under the ''Dosage and Administration'' section. The ''Pediatric use'' subsection 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 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 and Precautions'' section(s).

(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 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. 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 and Precautions'' section(s).

(D)(*1*) 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*).

(*2*) Data summarized in the preceding prescribed statement in this subsection must be discussed in more detail, if appropriate, under the ''Clinical

Pharmacology'' or the ''Clinical Studies'' section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose response information should be described in the ''Clinical Pharmacology'' section. Pediatric dosing instructions must be included in the ''Dosage and Administration'' section. 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 and, as appropriate, in the ''Contraindications,'' ''Warnings and 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 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, or, if appropriate, the hazard must be stated in the ''Contraindications'' or ''Warnings and Precautions'' section 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 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, or, if appropriate, the hazard must be stated in the ''Contraindications'' or ''Warnings and Precautions'' section and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are 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 and Precautions'' section.

(v) *8.5 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, and appropriate geriatric dosage must be stated under the ''Dosage and Administration'' section. The ''Geriatric use'' subsection 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 must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection must be discussed in more detail, if appropriate, under ''Clinical Pharmacology'' or the ''Clinical Studies'' section. As appropriate, this information must also be contained in the ''Warnings and Precautions'' and/or ''Contraindications'' section(s).

(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 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 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 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 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 and Precautions,'' ''Dosage and Administration,'' or other sections.

(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 and in detail under the ''Clinical Pharmacology'' section. The ''Clinical Pharmacology'' and ''Drug Interactions'' sections 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 must include the statement:

This drug is known to be substantially excreted by the kidney, and the risk of adverse 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, or, if appropriate, the hazard must be stated in the ''Contraindications'' or ''Warnings and Precautions'' section, and the ''Geriatric use'' subsection must refer to those sections.

(E) Labeling under paragraphs (c)(9)(v)(A) through (c)(9)(v)(C) of this section may include statements, if they are necessary for safe and effective use of the drug, and 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)(9)(v)(A) through (c)(9)(v)(E) of this section are 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*. Additional subsections 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).

(10) *9 Drug abuse and dependence*. This section must contain the following information, as appropriate:

(i) *9.1 Controlled substance*. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

(ii) *9.2 Abuse*. This subsection must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used.

(iii) *9.3 Dependence*. This subsection 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 and the principles of treating the effects of abrupt withdrawal must be described.

(11) *10 Overdosage*. This section must be based on human data. If human data are unavailable, appropriate animal and in vitro data may be used. The following specific information must be provided:

(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 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 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 (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be based on data available for the specific drug or experience with pharmacologically related drugs. Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated.

(12) *11 Description*. (i) This section 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 biological products, 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 biological product labels;

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

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

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

(G) 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) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

(A) *12.1 Mechanism of action*. This subsection 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). If the mechanism of action is not known, this subsection must contain a statement about the lack of information.

(B) *12.2 Pharmacodynamics*. This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity. Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack

of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., ''Warnings and Precautions'' or ''Dosage and Administration'') must not be repeated in this subsection, but the location of such recommendations must be referenced.

(C) *12.3 Pharmacokinetics*. This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), pertinent half-lives ($t_{1/2}$), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (V_d) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., ''Warnings and Precautions,'' ''Dosage and Administration'' or ''Use in Specific Populations'') must not be repeated in this subsection, but the location of such recommendations must be referenced.

(ii) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section only under the following circumstances:

(A) 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.''

(B) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled studies, as defined in § 314.126(b) of this chapter, to be necessary for the safe and effective use may be included in this section only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

(14) *13 Nonclinical toxicology*. This section must contain the following subsections as appropriate:

(i) *13.1 Carcinogenesis, mutagenesis, impairment of fertility*. This subsection must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the ''Warnings and Precautions'' section, must not be included in this subsection of the labeling.

(ii) *13.2 Animal toxicology and/or pharmacology*. Significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling must be included in this section (e.g., specifics about studies used to support approval under § 314.600 or § 601.90 of this chapter, the absence of chronic animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

(15) *14 Clinical studies*. This section must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required under §§ 201.56 and 201.57 because the study is essential to an understandable presentation of the information in that section of the labeling, any detailed discussion of the study must appear in this section.

(i) For drug products other than biological products, any clinical study that is discussed in prescription drug labeling 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. For biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute 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.

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

(16) *15 References*. When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(17) *16 How supplied/storage and handling*. This section 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 include, as appropriate:

(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 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, imprinting, and National Drug Code number; and

(iv) Special handling and storage conditions.

(18) *17 Patient counseling information*. This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling. Any FDA-approved patient labeling printed immediately following this section or

accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be detached and distributed to patients in compliance with § 208.24 of this chapter. Medication Guides for distribution to patients are subject to the type size requirements set forth in § 208.20 of this chapter.

(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 required by paragraphs (a) and (c) of this section 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)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (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)(ii) through (a)(11)(iv), and (a)(14) of this section 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, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) 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) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2-inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

■ 4. Section 201.58 is revised to read as follows:

§ 201.58 Waiver of labeling requirements.

An applicant may ask the Food and Drug Administration to waive any requirement under §§ 201.56, 201.57, and 201.80. A waiver request must be submitted in writing to the Director (or the Director's designee), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or, if applicable, the Director (or the Director's designee), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200 North, Rockville, MD 20852–1448. The waiver must be granted or denied in writing by the Director or the Director's designee.

§ 201.59 [Removed]

■ 5. Section 201.59 is removed.

■ 6. Newly redesignated § 201.80 is amended by:

a. Revising the section heading;

b. Amending paragraphs (b)(2)(ii), (c)(3)(i), (c)(3)(v), and (g)(4) by removing the phrase ''§ 314.126(b)'' the second time it appears and by adding in its place the phrase ''§ 314.126(c)'';

c. Removing the phrase ''induced emesis,'' in paragraph (i)(6);

d. Revising paragraphs (c)(2), (f)(2), and (m)(1); and

e. Adding a new sentence after the first sentence of paragraph (j).

The additions and revisions read as follows:

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

* * * * *

(c) * * *

(2)(i) For drug products other than biological products, all indications listed in this section 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.

(ii) For biological products, all indications listed in this section 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.

* * * * *

(f) * * *

(2) *Information for patients.* This subsection must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling. The type size requirement for the Medication Guide set forth in § 208.20 of this chapter does not apply to the Medication Guide that is reprinted in or accompanying the prescription drug labeling unless such Medication Guide is to be detached and distributed to patients in compliance with § 208.24 of this chapter.

* * * * *

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

* * * * *

(m) * * *

(1)(i) If the clinical study is cited in the labeling in place of a detailed discussion of data and information concerning an indication for use of the drug, 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.

(ii) When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

* * * * *

■ 7. Section 201.100 is amended by revising paragraph (d)(3) to read as follows:

§ 201.100 Prescription drugs for human use.

* * * * *

(d) * * *

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

* * * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 8. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

■ 9. Section 314.70 is amended by:

a. Removing from paragraph (b)(2)(v)(B) the phrase ''(b)(8)(iv) of this chapter.'' and adding in its place the phrase ''(b)(8)(iv) of this chapter; and'';

b. Adding paragraph (b)(2)(v)(C);

c. Revising the introductory text of paragraph (c)(6)(iii); and

d. Revising paragraph (d)(2)(x).

The additions and revisions read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(b) * * *

(2) * * *

(v) * * *

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(*1*) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(*2*) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

* * * * *

(c) * * *

(6) * * *

(iii) Changes in the labeling, except for changes to the information required in § 201.57(a) of this chapter (which must be made pursuant to paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

* * * * *

(d) * * *

(2) * * *

(x) An editorial or similar minor change in labeling, including a change to the information allowed by paragraphs (b)(2)(v)(C)(*1*) and (*2*) of this section.

* * * * *

PART 601—LICENSING

■ 10. The authority cite for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

■ 11. Section 601.12 is amended by:

a. Adding two sentences after the second sentence and before the third sentence in paragraph (f)(1);

b. Revising the introductory text of paragraph (f)(2)(i);

c. Removing from paragraph (f)(3)(i)(B) the word ''and'';

d. Removing from paragraph (f)(3)(i)(C) the phrase ''Medication Guide.'' and adding in its place the phrase ''Medication Guide; and''; and

e. Adding paragraph (f)(3)(i)(D).

The additions and revisions read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * *

(1) * * * An applicant cannot use paragraph (f)(2) of this section to make any change to the information required in § 201.57(a) of this chapter. An applicant may report the minor changes to the information specified in paragraph (f)(3)(i)(D) of this section in an annual report. * * *

(2) * * *

(i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label, except for changes to the package insert required in § 201.57(a) of this chapter (which must be made pursuant to paragraph (f)(1) of this section), to accomplish any of the following:

* * * * *

(f) * * *

(3) * * *

(i) * * *

(D) A change to the information required in § 201.57(a) of this chapter as follows:

(*1*) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(*2*) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

* * * * *

Dated: December 7, 2005.

Andrew C. von Eschenbach,

Acting Commissioner of Food and Drugs.

Dated: December 7, 2005.

Michael O. Leavitt,

Secretary of Health and Human Services.

[FR Doc. 06–545 Filed 1–18–06; 10:28 am]

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