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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

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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:

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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

[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.

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.

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.

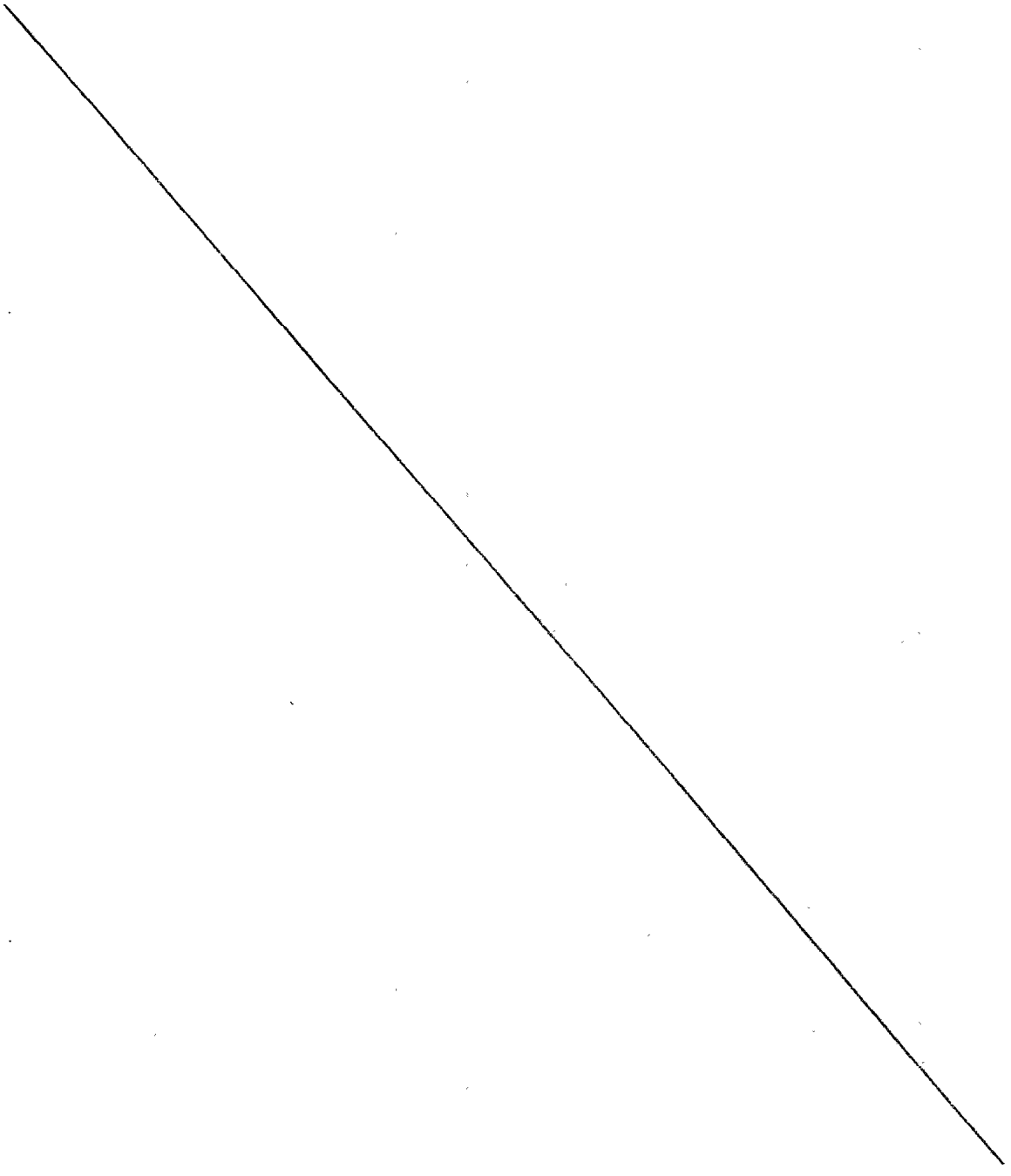

Table 1.--Prescription Drug Labeling Sections

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)
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 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

[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).

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

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[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.

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 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

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[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).

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. 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

[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-

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 claims would be preempted by its regulation of prescription drug labeling: (1) Claims that a drug sponsor

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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)).

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