rule as § 201.57(c)(7)) to clarify the scope of information for this section of labeling. See comments 71 through 75.

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

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

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

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

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

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

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

FDA also removed the requirement that significantly more severe reactions be listed before other reactions regardless of frequency. In most cases, frequency information is paramount, but in other cases, severity information may be more important or a combination of the two may be the best approach. The categorization scheme selected for the "Adverse Reactions" section should be appropriate to the drug's safety database and reflect the relative public health importance of the information.

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

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

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

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

of exposures to the drug compared to the number of suspected reactions reported are unknown, making estimation of incidence calculations difficult.

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

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

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

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

Thus, the agency has revised proposed § 201.57(c)(9) (designated in this final rule as § 201.57(c)(7)) to require manufacturers to include details about the relationship of adverse reactions to drug dose where sufficient data are available and necessary to prescribe the drug safely and effectively. The agency

does not believe, however, that it needs to require that separate presentations of adverse reactions always be included for different doses. If there are important differences in adverse reaction rates for different doses, the section can include a single table that directly compares the adverse reactions rates for different doses. Presenting rates for different doses side by side in a table, for example, is an effective way to make a dose-response relationship apparent.

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

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

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

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

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

The approximate frequency of each adverse reaction must be expressed in rough estimates or orders of magnitude essentially as follows:

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

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

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

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

The agency agrees that clarification is needed regarding presentation of incidence information for adverse reactions. The language in the proposed rule is not sufficiently precise to accurately reflect current practices in characterizing the incidence of adverse reactions associated with the use of

a drug product. The preamble to the 1975 proposed rule indicates that precise percent figures would be appropriate if there is scientific evidence from well-controlled trials substantiating such figures and when inclusion of percent figures does not falsely imply a greater degree of accuracy than actually exists (40 FR 15392 at 15393, April 7, 1975). The science of clinical trials has progressed so substantially over time that ascertaining such rates is typically part of virtually all drug development programs.

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

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

if precise meanings were defined, would reinforce the misconception that frequency is synonymous with seriousness.

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

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

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

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

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

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

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

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

Under the final rule, elimination half-life of drugs and differences in the elimination half-life as a function of specific populations (including age-related populations) must be reported in the "Pharmacokinetics" subsection of the "Clinical Pharmacology" section of the labeling (§ 201.57(c)(13)(i)(C)). In

addition, if there are clinically significant differences in elimination half-lives among specific populations and those differences require special monitoring or alternate dosing regimens, such information must be included in other sections, such as "Use in Specific Populations," "Warnings and Precautions," and "Dosage and Administration." Information about drug metabolism, including metabolic pathways and the enzyme systems involved, is also required in the "Pharmacokinetics" subsection of the "Clinical Pharmacology" section.

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

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

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

One comment requested that in vitro data supporting the "Mechanism of action" subsection in the "Clinical Pharmacology" section be permitted to be included in the subsection because such information is helpful in understanding a drug's physiologic activity and in differentiating a drug from other therapeutic agents.

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

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

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

infective therapy. Several comments stated that the absence of in vitro data will make it difficult for practitioners to identify appropriate broad spectrum agents when broad coverage is needed. One comment requested that in the event the agency decides to go forward and exclude in vitro data related to effectiveness unless a waiver has been granted, the agency explain in detail the process by which a waiver could be granted.

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

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

The agency has reconsidered its proposal to exclude from the "Clinical Pharmacology" section in vitro data for anti-infectives that are not supported by clinical data. The agency is considering a broad range of issues concerning the development and labeling of anti-infective products, including the types of data that should be obtained to support indications, the way that indications and anti-infectives data should be presented in labeling, and ways to

meaningfully address resistance to anti-infective drugs. The agency believes a comprehensive and coordinated approach is needed to address these issues. Thus, FDA is deferring any action on the in vitro data proposals in the "Clinical Pharmacology" section of labeling at §§ 201.57(c)(13)(ii) and 201.80(b)(2) until the agency has developed a comprehensive plan. At that time, the agency may repropose changes to the way in which in vitro data are presented in labeling.

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

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

(Comment 83) Several comments recommended retaining in vitro data for anti-infective drugs in the "Clinical Pharmacology" section and strengthening

the current in vitro disclaimer statement that indicates that the clinical significance of the in vitro data is unknown.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Studies" section guidance contains FDA's recommendations on what studies are appropriate for inclusion in the "Clinical Studies" section (see section IV of this document).

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

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

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

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

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

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

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

FDA proposed to permit references to be included in labeling in place of a detailed discussion of a subject that is of limited interest, but nonetheless important (proposed § 201.57(c)(16)). The proposed provision stated that the reference must be based on an adequate and well-controlled clinical

investigation under § 314.126(b) or, for a biological product, upon substantial evidence of effectiveness.

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

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

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

As discussed in the response to the previous comment, in this final rule, the agency has clarified the conditions under which it is appropriate to include a reference in prescription drug labeling. The agency appreciates the comment's concern about inconsistent application of the criteria for inclusion

of references across different new drug review divisions. As part of its internal efforts to implement this final rule and related labeling initiatives, the agency intends to make considerable efforts to ensure consistent application of the requirements.

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

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

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

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

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

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

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

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

(Comment 93) Some comments supported the proposed requirement to reprint FDA-approved patient labeling at the end of the "Patient Counseling Information" section so that this information is readily accessible for healthcare practitioners. Other comments requested that the agency reconsider

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

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

However, the agency is persuaded that reprinting the FDA-approved patient labeling at the end of the labeling is not the only approach that would

successfully address the need to familiarize prescribers with this information. Therefore, the agency has revised the requirements at §§ 201.57(c)(18) and 201.80(f)(2) to require that FDA-approved patient labeling either accompany the prescription drug labeling or be reprinted at the end of such labeling (i.e., immediately following the "Patient Counseling Information" section of the FPI for products subject to § 201.57(c)(18) or after the last section of labeling for products subject to § 201.80(f)(2)).

The agency acknowledges that, in cases for which FDA-approved patient labeling is included with prescription drug labeling, additional costs will be incurred by the manufacturer. To help minimize the added cost, FDA has revised proposed § 201.57(c)(18) to specify that the same type size requirements that apply to prescription drug labeling (§ 201.57(d)(6)) also apply to FDA-approved patient labeling that is printed at the end of the labeling or accompanies labeling, unless a Medication Guide is to be distributed to patients in compliance with § 208.24 (see table 7 of this document). In most cases, this will be a minimum type size of 8 points. For trade labeling, this will be a minimum type size of 6 points (see response to comment 102 for discussion of 6-point minimum type size for trade labeling for products subject to § 201.57). For Medication Guides to be distributed to patients, the type size requirements set forth at § 208.20 apply. With regard to the labeling for products subject to § 201.80, the agency clarifies at § 201.80(f)(2) that the font size requirement for Medication Guides in § 208.20 does not apply to a Medication Guide that is printed in prescription drug labeling unless it is intended to comply with § 208.24 (i.e., the requirement to distribute Medication Guides to patients). Thus, for these products, there

is no minimum font size requirement for FDA-approved patient labeling that is included with labeling but not for distribution to patients (see table 7).

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

Labeling	Type Size Requirements for Labeling	FDA-Approved Patient Labeling Included with Labeling	Type Size Requirements for FDA-Approved Patient Labeling
New Format (§ 201.57)			
Trade Labeling (i.e., labeling on or within the package from which the drug is to be dispensed)	Minimum 6-point type	FDA-approved patient labeling that is not for distribution to patients	Minimum 6-point type
		Any FDA-approved patient labeling except a Medication Guide that is for distribution to patients	Minimum 6-point type
		Medication Guide that is for distribution to patients	Minimum 10-point type
Other Labeling (e.g., labeling accompanying promotional materials)	Minimum 8-point type	FDA-approved patient labeling that is not for distribution to patients	Minimum 8-point type
		Any FDA-approved patient labeling except a Medication Guide that is for distribution to patients	Minimum 8-point type
		Medication Guide that is for distribution to patients	Minimum 10-point type
Old Format (§ 201 80)			
Trade Labeling and Other Labeling	No minimum requirement	FDA-approved patient labeling that is not for distribution to patients	No minimum requirement
		Any FDA-approved patient labeling except a Medication Guide that is for distribution to patients	No minimum requirement
		Medication Guide that is for distribution to patients	Minimum 10-point type

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

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

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

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

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

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

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

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

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

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

If a product that does not have an "Information for patients" subsection becomes subject to the new content and format requirements at § 201.57, the product's manufacturer would be required to develop a "Patient Counseling Information" section for the product's prescription drug labeling unless a "Patient Counseling Information" section would be clearly inapplicable (see § 201.56(d)(4)) and thus not required. The agency anticipates that few products

would qualify for such an exception. The agency believes that the vast majority of products that will be required to have a "Patient Counseling Information" section will already have an "Information for patients" subsection in their existing labeling on which to base the "Patient Counseling Information" section. Thus, this new requirement is anticipated to impose minimal burdens on manufacturers.

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

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

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

The agency agrees that use of the required format in conjunction with an electronic medium may have benefits over paper labeling. As discussed in section V of this document, the agency believes that, in the future, the Internet and other electronic sources for labeling will most likely be the primary means for delivering drug information to practitioners. At the present time, however,

some practitioners may not have the requisite computer equipment or skills to access prescription drug labeling in an electronic format. The agency anticipates that it will be several years before the phase-out of paper labeling as the major source of prescribing information can begin. Therefore, the agency believes that it is important to establish minimum format requirements for paper labeling.

(Comment 99) One comment recommended the use of more blank space among sections of Highlights. The comment expressed concern that, because Highlights contains a significant amount of information in a constrained space and uses a variety of formatting techniques, the overall effect would be confusing. One comment stated that the placement of the "Patient Counseling Information Statement" above the "Highlights Limitation Statement" in Highlights is not ideal because it appears that the "Patient Counseling Information Statement" is the title of the limitation statement. The comment also requested that the FPI be required to be in a two-column format because such a format enables users to stay better aware of the overall information structure, as well as read individual sections more easily.

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

from manufacturers about the costs associated with adding to the length of labeling.

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

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

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

- *Bolding (Proposed § 201.57(d)(5))*

In the proposal, the agency specifically sought comment on whether the requirement in proposed § 201.57(d)(5) to bold the information required by proposed § 201.57(a)(1) through (a)(4), (a)(11), and (a)(15) (i.e., the following information in Highlights: Drug names, dosage form, route of administration, and controlled substance symbol; the inverted black triangle symbol; the prescription drug symbol; boxed warnings or contraindications; adverse

reaction reporting contacts; and Highlights limitation statement) would ensure the visual prominence of the bolded information or whether different highlighting methods would be more effective.

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

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

(Comment 101) One comment requested that the agency revise the format of Contents to make it easier to read and use. The comment stated that the information in Contents is not as accessible as it could be because it uses

straight columns, which make it hard to distinguish the major labeling sections (e.g., "Use in Specific Populations") from subsections (e.g., "Pregnancy"). The comment recommended use of contrasting font types and sizes for the section titles and subheadings in each section, underlining section titles, indenting subheadings under each section title, and providing more blank space between each section. Another comment also recommended indenting the subheadings under the major sections to more readily distinguish between the major sections and the subheadings within the sections.

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

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

One manufacturer stated that 6-point type was generally adequate for prescribing information, and another manufacturer stated that it typically uses 4- to 6-point type. Some manufacturers were concerned that a minimum 8-

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

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

In the preamble accompanying the proposed rule, FDA summarized studies that demonstrated the importance of type size in evaluating readability of written information and its effect on visibility and reading speed (see 65 FR 81082 at 81096 and Refs. 6 through 9). Type size combined with other

graphical elements (e.g., letter and line spacing, contrast, print and background color, and type style) also affect readability (Ref. 10).

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

The agency also agrees with the comments requesting that there be an exception for trade labeling. FDA believes that a minimum 6-point type size requirement is satisfactory for such labeling. FDA's telephone survey of office-

referred to by physicians substantially less frequently than other sources of prescribing information (Ref. 11, p. 30). Because manufacturers could incur substantial costs in converting trade labeling to 8-point type and the public

health benefits of such conversion may not justify these costs, the agency believes it is reasonable to allow a 6-point minimum type size for trade labeling (see comment 124). Thus, proposed § 201.57(d)(6) was revised to permit a 6-point minimum type size for trade labeling.

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

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

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

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

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

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

The agency believes that a one-half page Highlights is adequate for the vast majority of products. As discussed previously, Highlights provides introductory information to the more detailed FPI. The agency does not agree

that multiple disclaimers or qualifying statements would be useful or appropriate.

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

The agency strongly believes that limiting the length of Highlights is critical to preserving its usefulness. In the physician surveys relied on by the agency in developing and refining the new labeling format, 80 percent of physicians indicated that a summary or highlights section should be no more than one-half page. The surveys found that the perceived usefulness of Highlights declined considerably with increasing length. Accordingly, the labeling format was designed to accommodate, on a single page, a one-half page Highlights and a one-half page Contents. To test the feasibility of limiting Highlights to one-half of a page, the agency did numerous mockups of Highlights for a wide range of products and found that the one-half page limit provided adequate space in each case. Thus, the agency anticipates that the length restriction will be feasible in the vast majority of cases.

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

Some comments agreed that it was highly desirable to call attention to new information in the FPI and that the vertical line is adequate to identify the new information. Other comments stated that it was desirable to call

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

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

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

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

The agency believes that it would not be adequate to identify labeling changes only in a section of the labeling devoted to changes. The agency believes it is important to also identify the specific text that has been changed

so that practitioners will be able to locate changes and access the complete text.

J. Comments on Revisions to Container Labels

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

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

(Comment 106) Several comments opposed the proposal to eliminate the requirement that the label of a prescription drug product for other than oral

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

Several comments also opposed the proposal to eliminate the requirement that the label of a prescription drug product bear a statement directed to the pharmacist specifying the type of container to be used in dispensing the product to maintain its identity, strength, quality, and purity. The comments maintained that eliminating dispensing information from the container label, and placing it in prescription drug labeling, would make the information less accessible to pharmacists and would thus be inefficient and frustrating for pharmacists. The comments were concerned that making information on storage and handling less accessible could lead to inappropriate storage and handling. Some comments urged that the label at least be required to state any special or unusual conditions for storage. One comment recommended mandatory use of a symbol that signifies when a product requires special handling. Two comments supported removal of information on storage and

handling from product labels, agreeing that less information on the container label could make other information on the label more accessible and legible.

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

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

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

(Comment 107) One comment requested that the proposed requirement to specify in the "How Supplied/Storage and Handling" section the type of

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

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

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

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

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

In rulemaking (initiated under section 126 of the Food and Drug Administration Modernization Act of 1997), the agency amended its regulation

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

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

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

K. Miscellaneous Comments

(Comment 111) One comment requested that the agency clarify how the content and format of the brief summary required to accompany prescription drug advertising under § 202.1 would be affected by the proposed revisions

to prescription drug labeling. Another comment suggested that the agency entertain the idea that Highlights could serve as an alternative to the brief summary because the agency has noted that Highlights contains the most important information about drug-related risks.

The proposed regulations were not designed to affect either the content or the format of the brief summary of prescribing information required to accompany prescription drug advertisements under § 202.1 (21 U.S.C. 352(n)). As discussed in the proposed rule (65 FR 81082 at 81087), statements made in promotional labeling and advertisements must be consistent with all information included in labeling under proposed § 201.57(c) to comply with current §§ 201.100(d)(1) and 202.1(e).[9] The agency does believe, however, that Highlights communicates important information about a drug. The agency therefore will explore further, in conjunction with other prescription drug advertising initiatives, the concept that Highlights could serve as a brief summary (see also FDA's response to comment 112 about the brief summary for consumer directed advertisements).

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

The purpose of prescription drug labeling is to provide health care practitioners information necessary for safe and effective use. The agency believes that use of medical and scientific terminology is necessary to effectively communicate to practitioners information about a product's risks

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

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

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

L. Comments on the Proposed Implementation Plan

For new and more recently approved drugs, FDA proposed a staggered implementation schedule for the labeling requirements, with revised labeling

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

In the proposal, the agency specifically sought comment on whether the revised content and format requirements should be applied, as proposed, to drug products with an NDA, BLA, or efficacy supplement that is pending at the effective date of the final rule, that was submitted on or after the effective date of the final rule, or that has been approved from 0 up to and including 5 years prior to the effective date of the final rule, or whether alternative application criteria should be used.

(Comment 113) Several comments agreed with the categories of prescription drugs that would be subject to the new labeling content and format requirements in the agency's proposed implementation plan. Other comments expressed concern that the proposed implementation plan is too

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

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

Some comments from manufacturers maintained that it would be most practical to apply the new format requirements only to products whose applications are submitted on or after the effective date of the final rule. They stated that broader implementation would place a substantial burden on FDA

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

The agency believes the implementation plan as proposed for new and more recently approved drug products is the best option for implementing the new format requirements. The agency agrees that it is desirable for all prescription drugs to be subject to the same labeling rules. However, the agency has carefully considered the costs and benefits of implementing the revised labeling format and determined that requiring broader implementation (e.g., to all prescription drugs) of the new format requirements would be an excessive regulatory burden.

This initiative will require substantial resource allocation by the agency and industry for a period of several years. The agency's proposed implementation plan, which is being finalized in this rule as proposed, is intended to make the best use of these resources. As discussed in the preamble to the proposed rule (65 FR 81082 at 81098), the plan targets newer products because practitioners are more likely to refer to the labeling for newer products. In FDA's survey of physicians, newness of the product was a reason rated by 87 percent of physicians as very likely to trigger a labeling referral for a drug (Ref. 11, p. 35). In addition, the labeling for newer products is typically longer and more complex and, thus, more likely to benefit from a new format that

makes the information more accessible. The implementation plan will also capture many older products that would not otherwise be covered by the plan when manufacturers seek new indications for their products (i.e., submit an efficacy supplement). For these reasons, the agency believes the implementation as proposed is the most reasonable approach to maximizing the public health benefit and best utilizing available resources in requiring the new content and format for labeling. In addition, manufacturers of older products not covered by the implementation plan may voluntarily revise, and submit for review, labeling for their products in the new format at any time.

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

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

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

electronic format will permit access to labeling information in both the old and new labeling formats.

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

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

would compromise the drug approval process. One comment requested that the agency clarify what types of statements would have to be removed.

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

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

While the agency will not require a systematic evaluation of all existing labeling to identify unsubstantiated claims within 1 year of the effective date

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

(Comment 115) One comment recommended an implementation period of 3 years, rather than 1 year as proposed, to append any FDA-approved patient labeling to the end of the labeling for trade packages. The comment maintained that additional time was needed for reconfiguration and replacement of packaging equipment.

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

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

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

described at § 314.127(a)(7), approval of an ANDA when the reference listed drug has protected labeling.

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

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

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

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

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

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

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

M. Comments on Environmental Impact

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

As stated in section IX of the proposed rule (65 FR 81082 at 81103), the agency determined that it is not required to do an environmental assessment or an environmental impact statement. This is an action excluded under § 25.30(h) and (k) (21 CFR 25.30(h) and (k)) (i.e., does not individually or

cumulatively have a significant effect on the human environment). The changes made to the proposal in this final rule do not change this conclusion. Therefore, neither an environmental assessment nor environmental impact statement is required.

VII. Legal Authority

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

A. Statutory Authority

FDA's revisions to the content and format requirements for prescription drug labeling are authorized by the act and by the Public Health Service Act (the PHS Act). Section 502(a) of the act deems a drug to be misbranded if its labeling is false or misleading "in any particular." Under section 201(n) of the act, labeling is misleading if it fails to reveal facts that are material with respect to consequences which may result from the use of the drug under the conditions of use prescribed in the labeling or under customary or usual conditions of use. Section 502(f) of the act deems a drug to be misbranded if its labeling lacks adequate directions for use and adequate warnings against use in those pathological conditions where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users. Section 502(j) of the act deems a drug to be misbranded if it is dangerous to health when used in the dosage or manner, or with the frequency or duration, prescribed, recommended, or suggested in its labeling.

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

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

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

B. First Amendment

FDA's requirements for the content and format of prescription drug labeling are constitutionally permissible because they are reasonably related

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

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

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

asserted, and [fourth,] whether it is not more extensive than is necessary to serve that interest.

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

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

Finally, under the fourth part of the *Central Hudson* test, there are not numerous and obvious alternatives (in fact, there are no reasonable alternatives) (*Cincinnati* v. *Discovery Network*, 507 U.S. 410, 418 n.13 (1993))

to the content and format requirements of this final rule that directly advance the government's interest but are less burdensome to speech. Health care practitioners are accustomed to looking to the prescription drug labeling as their primary source of information about a product, and patients rely for their drug information primarily on practitioners. Neither a public education campaign, nor encouraging sponsors to provide information on the risks and benefits of drugs but not requiring such information, would ensure that practitioners have the information they need about the conditions in which prescription drugs can be used safely and effectively. Requiring disclosures meets the fourth part of the test.

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

VIII. Paperwork Reduction Act of 1995

The final rule contains information collection provisions that are subject to review by the OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description and respondent description of the information collection provisions are shown below with an estimate of the reporting burdens. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information. The OMB and FDA received no comments concerning the information collection provisions of the proposed rule.

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

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

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

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

Section 201.56 requires that prescription drug labeling contain certain information in the format specified in either § 201.57 or § 201.80, depending on when the drug was approved for marketing. Section 201.56(a) sets forth general labeling requirements applicable to all prescription drugs. Section 201.56(b) specifies the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in §§ 201.56(d) and 201.57. Section 201.56(c) sets forth the schedule for implementing these revised content and format requirements. Section 201.56(e) specifies the sections and subsections, required and optional, for the labeling

of older prescription drugs not subject to the revised format and content requirements.

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

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

B. Estimates of Reporting Burden

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

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

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

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

Based on information received from the pharmaceutical industry, FDA estimated that it took applicants approximately 3,200 hours to design, test, and submit prescription drug labeling to FDA as part of an NDA or BLA under former labeling requirements (see row 1 of table 8a). FDA estimates that it will

take an additional 149 hours to generate Highlights and Contents and otherwise comply with the additional requirements of the final rule (see row 2 of table 8a). Therefore, it will take a total of approximately 3,349 hours to design, test, and submit new labeling. Approximately 85 applicants would submit approximately 107 new applications (NDAs and BLAs) to FDA per year, totaling 358,343 hours (see Total of table 8a).

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

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

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

Efficacy supplemental applications for older drugs submitted on or after the effective date of the final rule are subject to the content and format requirements at §§ 201.56(d) and 201.57. To meet these requirements,

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

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

The reporting burden for generic products subject to the requirements of the final rule has only been estimated for those products requiring revisions to their existing labeling. Reporting burdens for generating newly approved labeling for generic products (§ 314.94(8)) is already approved under OMB control number 0910–0001. According to the data in the economic analysis, beginning in year 3 and continuing throughout the 10-year period analyzed, approximately 42 generic applications per year must submit labeling supplements to comply with the final rule (see section XI.D.2.a of this document). For purposes of this analysis, approximately 336 already approved generic drug applications must submit labeling supplements over the 10-year

period after the effective date of the rule (see section XI.D.2.a of this document). The time required to revise and submit this labeling to FDA would be approximately 27 hours per application, totaling 9,072 hours (see row 3 of table 8b). In addition to this burden, a minimal reporting burden associated with a very small number of generic applications referencing older drugs may continue indefinitely.

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

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

C. Capital Costs

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

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

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

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

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

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

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

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

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

IX. Environmental Impact

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

X. Executive Order 13132: Federalism

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

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

An NDA must include the "proposed text of the labeling," together with "annotations to the information in the summary and technical sections of the

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

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

The FDA review process for an NDA is thorough and scientifically rigorous. An NDA must contain proposed labeling and all information about the drug (whether favorable or unfavorable) that is pertinent to evaluating the application and that is received or otherwise obtained by the applicant from any source (21 CFR 314.50 and 601.2(a)). FDA scientists evaluate this information, and may request additional information as necessary to provide a complete and accurate picture of the product. FDA may supplement the expertise of its in-house scientific personnel with advice from scientific advisory committees of outside experts (21 CFR 14.171).

Under the act and FDA regulations, the agency determines that a drug is approvable based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's benefits

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

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

The part of a prescription drug product's approved labeling directed to health care practitioners * * * is the primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals. This part of approved labeling is a compilation of information based on a thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant * * * . [T]he primary purpose of prescription drug labeling is to provide practitioners with the essential information they need to prescribe the drug safely and effectively for the care of patients.

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

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

The act and FDA regulations prescribe several procedures to ensure that FDA receives information about risks that become apparent after approval. Because clinical trials involve time-limited administration of the investigational product to a relatively small and homogeneous population of study subjects, adverse events that were not observed during clinical trials may be recognized or identified following approval. The act provides that a manufacturer must establish and maintain such records, and make such reports, as FDA may require by regulation (section 505(k) of the act). To implement this provision, FDA has issued regulations requiring prompt reports of serious, unexpected drug experiences and periodic reports of all information

relating to the safety and effectiveness of the drug (21 CFR 314.80 and 314.81). Manufacturers may also commit to conduct additional safety and effectiveness studies following approval and submit data from these studies to the agency. (See section 506B of the act (21 U.S.C. 356b).)

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

The agency carefully reviews all the information submitted by a sponsor in a marketing application to make its statutorily required judgment as to whether the product is safe and effective and otherwise in compliance with the act. It also reviews adverse event information submitted after marketing approval and determines what action, if any, should be taken. In rare cases, FDA finds that the information supports a determination to withdraw the product from the market (section 505(e) of the act; 21 CFR 601.5(b)(1)). In other

instances, FDA uses other risk management techniques. One such technique is incorporating additional risk information into, or otherwise modifying, the prescription drug labeling (§ 201.57(e)). In many cases, review of the submitted reports does not lead to any change, e.g., because FDA determines that the event reported is not causally related to the product.

Changes to prescription drug labeling typically are initiated by the sponsor, subject to FDA review, but are sometimes initiated by FDA. Under FDA regulations, to change prescription drug labeling (except for editorial and other minor revisions), the sponsor must submit a supplemental application fully explaining the basis for the change (§§ 314.70 and 601.12(f)). FDA permits two kinds of labeling supplements: (1) Prior approval supplements, which require FDA approval before a change is made (§§ 314.70(b) and 601.12(f)(1)), and (2) CBE supplements, which may be implemented before FDA approval, but after FDA notification (§§ 314.70(c) and 601.12(f)(2)). Labeling changes to the FPI to add or strengthen a warning, precaution, contraindication, or adverse reaction statement are within the category of changes for which CBE supplements are required by FDA regulations (§§ 314.70(c)(6)(iii) and 601.12(f)(2)(i)) (see comment 5). While a sponsor is permitted to add risk information to the FPI without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading under section 502(a) of the act. To mitigate this risk, manufacturers often consult with FDA before adding risk information to labeling. As noted in response to comment 5, however, a sponsor may not use a CBE supplement to make most changes to Highlights.

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

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

Section 4(c) of Executive Order 13132 instructs us to restrict any Federal preemption of State law to the "minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated." This final rule meets the preceding requirement because, as discussed in more detail above, it preempts state law only to the extent required to preserve Federal interests. Section 4(d) of Executive Order 13132 states that when an

agency foresees the possibility of a conflict between State law and federally protected interests within the agency's area of regulatory responsibility, the agency "shall consult, to the extent practicable, with appropriate State and local officials in an effort to avoid such a conflict." Section 4(e) of Executive Order 13132 adds that, when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency "shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings."

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

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

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

XI. Analysis of Economic Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory

alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, unless the agency certifies that the rule is not expected to have significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize any significant impact of the rule on small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation).

The agency believes that this rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. The final rule would amend current requirements for the format and content of human prescription drug product labeling. Although the effectiveness of the revised labeling in achieving time savings and reductions in adverse reactions is uncertain, based on the following analysis as summarized in table 9, FDA projects that the present value of the quantifiable benefits of the final rule over 10 years range from $330 million to $380 million and from $420 million to $480 million at a 7 and 3 percent discount rate, respectively. Direct costs of the final rule are projected to range from approximately $7 million to $17 million in any one year, for a total present value of approximately $90 million and $120 million over 10 years at a 7 and 3 percent discount rate, respectively. The agency thus concludes that the benefits of this final rule outweigh the costs. Furthermore, the agency has

determined that the final rule is not an economically significant rule as described in the Executive order, because annual impacts on the economy are substantially below $100 million. Because the rule does not impose any mandates on State, local or tribal governments, or the private sector that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act. The current inflation-adjusted statutory threshold is about $115 million.

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

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

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

[1] Numbers may not sum due to rounding.

A. Purpose of the Final Rule

The purpose of the final rule is to make it easier for health care practitioners to find and read information important for the safe and effective use of prescription drugs. As described elsewhere in this preamble, the agency

has found that the current format of prescription drug labeling can be improved to more optimally communicate important drug information (see section I of this document). Enhanced communication of drug information to physicians should make them better informed prescribers. The final rule is designed to achieve these objectives by amending the current content and format of the labeling for certain human prescription drug products to, among other things, highlight frequently accessed and new information, include a table of contents for the detailed information in labeling, and reorder this detailed information.

B. Comments on the Economic Impact Analysis

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

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

Although our analysis did not separate administrative costs from other labeling design costs, the agency anticipated that manufacturers would require some "detailed discussions and drug-specific decisions" during the design phase of labeling (e.g., regarding exactly which adverse reactions should be listed in Highlights) (65 FR 81082 at 81106). Currently, manufacturers submitting new applications (i.e., NDAs and BLAs) and efficacy supplements

have to negotiate the content of labeling as part of the review process. Because any information in Highlights is also in the FPI, the agency does not agree that negotiating the content of Highlights will impose significant administrative costs beyond what is currently incurred by these manufacturers. As noted, to facilitate this process, the agency is making available guidance to assist manufacturers in selecting information for inclusion in Highlights (section IV of this document).

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

(Comment 122) The agency sought specific comment on whether the potential impact of the proposed rule on small entities has been accurately estimated by the agency, and whether small business concerns have been adequately addressed. One comment stated that because the proposal has the potential to substantially affect larger companies (could double the length of labeling and require extensive re-engineering and re-design of packaging lines and ancillary equipment), its impact would be even greater on smaller companies.

Although the agency had requested input from small companies that might be affected by the rule, all comments on this question came from large companies. FDA believes it is difficult to predict the effect of the rule on small

firms. While small firms may have lower sales volume over which to spread the fixed costs of compliance, some industry consultants have found that small pharmaceutical firms have less organizational layers and incur lower costs for the same activity than large pharmaceutical firms (Ref. 12). Table 22 in section XI.E.2 of this document illustrates the potential impact that the final rule might have on small firms.

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

The agency acknowledges that there is not direct empirical support for the estimate of 15 seconds time savings, but is persuaded based on consultation with physicians that the labeling changes would save time. The agency consulted physicians in a national survey, focus groups, and a public meeting to design labeling that provides easier and faster access to the most important and commonly referenced prescribing information (65 FR 81082 at 81083 through 81085; see also Ref. 11). Using a standard format with frequently accessed sections at the beginning of labeling will help physicians find important information quickly and retain that information. Inclusion of Contents and references in Highlights to the full prescribing information that is cited or concisely summarized will speed access to detailed information in the FPI. In the absence of quantitative evidence suggesting a different estimate of time savings, the agency is retaining 15 seconds as a conservative estimate

of the amount of time health care practitioners can save when seeking drug product information in labeling.

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

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

To reduce the burden on industry, the final rule requires that trade labeling be printed in at least 6-point type size (see comment 102), similar to the size of the baseline case used in the original analysis and a size generally

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

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

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

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

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

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

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

More space will be needed to print longer trade labeling and labeling distributed with promotional materials for new and recently approved

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

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

The agency believes that health care practitioners have varied access to company information via the Internet and other sources, thus including the phone number is unlikely to overly burden a company's ability to handle incoming calls. The agency believes that changes in corporate phone numbers are an ordinary business expense.

C. Benefits of Regulation

The expected economic benefits of this final rule are the sum of the present values of: (1) The reduced time needed by health care practitioners to seek desired information in prescription drug labeling; (2) the increased

effectiveness of drug treatment; and (3) the avoided costs of treating drug-related errors due to misunderstood or incorrectly applied drug information.

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

1. Decreased Health Care Practitioner Time

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

A 1994 FDA survey of physicians found that 42 percent referred to prescription drug labeling at least once a day, 33 percent less often than once a day but more often than once a week, and 25 percent once a week or less (Ref. 11, pp. 30–31). These findings suggest that a physician seeks drug

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

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

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

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

the new format with Highlights would lengthen the time practitioners spend looking for information.

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

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

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

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

The final rule only applies to new and recently approved products. Moreover, implementation for recently approved products is phased in over several years. Thus, the final rule will initially apply only to a small percentage of prescription drug labeling. The rule's focus on newer products includes the prescription drug labeling that health care practitioners consult most frequently. In FDA's survey of physicians, newness of the product was the factor most often rated by physicians as "very likely" to trigger referral to

prescription drug labeling (Ref. 11, p. 35). Similarly, the pharmacy association's survey found that pharmacists were most likely to consult labeling if the drug was recently approved (48 percent).

Although the average practitioner regularly prescribes from 40 to 100 pharmaceutical products (Ref. 24), the proportion of these that are new drugs is unknown. Because the agency received no comments and has no other information on the percentage of reformatted labeling that practitioners will consult, the initial assumptions remain unchanged (65 FR 81082 at 81104). This analysis, therefore, assumes that the rule will begin affecting the length of time needed for prescription drug labeling consultations in the second year of implementation, only affecting 5 percent of all consultations in that year. The percentage of reformatted prescription drug labeling consulted by physicians is assumed to increase to 10, 15, and 25 percent in years 3, 4, and 5 respectively. Thereafter, it is assumed to increase an additional 5 percent each year, reaching 50 percent in year 10. Thus, in year 10, the time savings for physicians and pharmacists is projected to equal about 276,000 and 113,900 hours, respectively. FDA has not attempted to project impacts beyond 10 years, due to the uncertainty of the longer term technological changes that would affect these estimates (see section V of this document).

To estimate the monetary value of the time saved, an hourly loaded wage for physicians is calculated using data from the American Medical Association (AMA) on the average net annual income of all non-Federal physicians (excluding residents), the average weekly workload, average number of weeks worked per year and benefits adjusted by the proportion of self-employed physicians (Refs. 22 and 23). The loaded wage for pharmacists is calculated from Bureau of Labor Statistics data (Ref. 18). At $88.16 per hour for physicians

([$194,400 x (1 + 0.2)] / [47 weeks x 56.3 hours / week]) and $46.75 per hour for pharmacists ($33.39 / hour x (1 + 0.4)), table 10 shows the annual monetary value of time saved and indicates that the present value over 10 years equals approximately $90 million or $120 million using a 7 or 3 percent discount rate, respectively.

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

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

[1] Numbers may not sum due to rounding.

2. Improved Effectiveness of Treatment

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

the final rule is intended, therefore, to present the complex drug information contained in labeling in a way that will improve the ability of practitioners to select and prescribe drugs to their patients safely and effectively.

The initial U.S. approval date will alert practitioners to newer products that should be used with greater vigilance. There are over 100 NDAs, including about 30 new molecular entities, approved every year in the United States. Initial approval is based on data from clinical trials conducted to determine the safety and effectiveness of a product. These trials typically include only enough subjects to detect 1 adverse reaction in every 300 to 500 patients (Ref. 25). It is not uncommon for drugs to have significant adverse effects that occur at lower frequencies than can be detected in premarketing clinical trials. Adding contact information where practitioners can report suspected adverse reactions will facilitate the collection of drug safety information and make it easier for the agency and manufacturers to identify significant safety concerns that can emerge after a drug is marketed and a much larger population is exposed to the product. Moreover, by identifying those sections of the labeling in which there have been important recent changes, the new format will also alert practitioners to significant new safety concerns and other significant changes to labeling once a product has been approved.

In addition, any FDA-approved patient labeling must be printed at the end of the labeling, or accompany the labeling, regardless of when the product was approved. Including patient information enhances the likelihood that physicians will communicate important information to patients, improving patient understanding and adherence to treatment recommendations. FDA is unable to quantify the magnitude of these expected improvements in treatment

effectiveness and health outcomes, but the agency believes they could be significant.

3. Decrease in Costs to Treat Avoidable Adverse Reactions

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

No national study on the incidence or associated costs of adverse reactions has been conducted. Furthermore, it is difficult to compare published studies because they are either too limited in scope or differ in methodology. Nevertheless, studies of hospitalized patients suggest that the rate of preventable adverse events that occur during hospitalization is approximately 1.2 to 1.8 adverse events per 100 patients admitted (Refs. 27 through 29). Moreover, 1 of these studies conducted in the early 1990s in the northeastern United States found that a majority of preventable adverse events (about 1 adverse event per 100 hospital admissions) were related to errors or miscalculations in physician ordering, the stage most likely to be affected by improved prescription drug labeling information (Ref. 28). A more recent study conducted in the southwestern United States reported 4.2 adverse events per

100 patients, of which only 15 percent where deemed preventable (Ref. 29). Given the approximately 36 million annual hospitalizations in the United States (Ref. 30), these data suggest that between 229,000 and 364,000 adverse reactions among hospitalized patients are potentially preventable each year.

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

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

FDA lacks data to estimate the actual proportion of the adverse reaction costs that would be prevented under the final rule. Combining the projected

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

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

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

[1] Numbers may not sum due to rounding.

[2] Assumes the rule will avoid 1 percent of the preventable hospitalization costs from in-hospital and outpatient adverse drug events.

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

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

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

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

When compared with other published studies, the agency's estimate of the cost of adverse reactions is likely less than the total social cost of such events. In particular, FDA's estimates include only hospital costs, and exclude the willingness to pay of patients to reduce these risks. Because these risks include fatality risks, the willingness to pay may be quite large. Using a restrictive definition of adverse events and including direct and indirect costs, a large study of hospital discharge records conducted by Thomas and others in Utah and Colorado was published in 1999 and estimated that preventable adverse events cost society at least $17 billion (in 1996 dollars) each year (Ref. 33). In contrast, a 2001 revision of the 1995 Johnson and Bootman cost-of-illness model used current costs whenever possible and predicted that drug-related illness occurring in ambulatory care settings cost about $177.4 billion each year, or more than 40 times the estimate of avoided costs that was used in the rest of this analysis (Refs. 34 and 35). While we acknowledge that we have

no direct evidence about how the rule would reduce preventable adverse reactions, if the final rule avoided at least one-tenth of a percent of the costs predicted by the Thomas study, annual benefits of the rule would approximately equal annual costs.

D. Costs of Regulation

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

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

Second, the proposed rule would have revised the content and established format requirements for labeling of new and recently approved applications. Although the agency modified some specific content and format requirements, the staggered implementation schedule and most provisions were retained for the final rule. Therefore, direct costs incurred to change prescription drug labeling include the costs of: (1) Designing or revising prescription drug labeling and submitting the new labeling to FDA, (2) producing longer trade labeling including any equipment adjustments, (3) layout and artwork for

labeling not accompanying drug products, (4) producing longer labeling for labeling not accompanying drug products, and (5) printing longer labeling in the PDR.

1. Labeling Changes for All Approved Prescription Drug Products

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

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

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

d. *Physicians' Desk Reference (PDR) Costs.* The agency estimates that 75 percent of prescription drug products have labeling already printed in the PDR. In 2002, an additional page in the PDR costs manufacturers $9,750.[14] Thus, the per product annual cost to print two additional pages is about $19,500 ($9,750 x 2). For the estimated 60 affected products (80 products x 0.75), the

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