DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 330, and 358

[Docket Nos. 96N–0420, 92N–454A, 90P–0201, and 95N–0259]

RIN 0910–AA79

Over-The-Counter Human Drugs; Proposed Labeling Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to establish a standardized format for the labeling of over-the-counter (OTC) drug products. FDA has determined that because the design and format of labeling information varies considerably among OTC drug products, consumers often have difficulty reading and understanding the information presented on OTC drug product labeling. The proposal is intended to enable consumers to better read and understand OTC drug product labeling and to apply this information to the safe and effective use of OTC drug products. This document supersedes the agency's proposed rule regarding the use of interchangeable terms, published in the Federal Register of March 4, 1996 (hereinafter referred to as the March 1996 proposal), and responds to the comments that were submitted to FDA as a result of that proposal (Docket No. 92N–454A). Accordingly, this document formally withdraws the March 1996 proposal. Finally, this proposal would preempt State and local rules that establish different or additional format or content requirements.

DATES: Submit written comments by June 27, 1997. Submit written comments on the information collection requirements by March 31, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Diana M. Hernandez, Center for Drug Evaluation and Research, Division of OTC Drug Products (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Introduction

Under the Federal Food, Drug, and Cosmetic Act (the act), OTC drug products must be safe and effective in order to be marketed. The agency is conducting a comprehensive review of these drug products, which are available to consumers without a prescription. As a result of this review, the agency has required specific language to be included in the labeling of many OTC drug products, describing the uses, directions, warnings, drug interaction precautions, active ingredients, and other information, so that consumers can use these products safely and effectively.

As a result of escalating health care costs and the increasing availability of OTC drug products, some of which were once available only by prescription, more consumers are engaging in self-medication. Thus, it is increasingly important that consumers read and understand the information on drug product labeling.

On January 6, 1993, the agency issued final regulations to help consumers read and understand the information on food product labeling (58 FR 2079). The new regulations, which provide for a standardized graphic presentation for food nutrients, were issued in response to the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Pub. L. 101–535, November 8, 1990). The 1990 amendments directed the Secretary of Health and Human Services to issue implementing regulations to:

> * * * require the required information to be conveyed to the public in a manner which enables the public to readily observe and comprehend such information and to understand its relative significance in the context of a total daily diet.

(Section 2(b)(1)(A) of the 1990 amendments)

This new, standardized format allows the consumer to judge the significance of the level of a particular nutrient in a particular food in the context of the total daily diet.

FDA believes it is equally important for consumers to be able to make reasoned decisions about the drugs they take. On August 24, 1995 (60 FR 44182), FDA proposed a comprehensive program to increase the distribution and quality of easy to read and easy to understand written information about prescription drugs to patients. Recently enacted legislation provides that various private entities will work to transform these goals into a satisfactory program. FDA is now proposing to improve the way that information on the labeling OTC drug products is communicated.

The design, format, and placement of required labeling information varies considerably among OTC drug products. As a result, consumers often have difficulty finding, reading, and understanding this labeling information. Modifying and simplifying the manner in which the information is presented can improve the legibility and understandability of OTC drug product labeling. FDA is, therefore, proposing to establish a standardized format for the labeling of all marketed OTC drug products. This action is intended to enable consumers to better read and understand OTC drug product labeling and to apply this information to the safe and effective use of OTC drug products.

The agency is proposing five types of labeling changes for OTC drug products. First, the proposal would require that OTC drug product labeling include standardized headings and subheadings presented in a standardized order, as well as standardized graphical features such as the Helvetica type style, minimum standards for type size, leading (i.e., space between two lines of text), kerning (spacing between lette upper and lower case letters, and graphical highlights.

Second, the proposal would permit manufacturers, packers, or distributors to delete specific terms, referred to for purposes of this rulemaking as "connecting terms," that are currently required in OTC drug product labeling. Holders of approved new drug applications (NDA's), antibiotic drug applications, and abbreviated new drug and antibiotic drug applications (referred to collectively in this document as "marketing applications") who wish to delete a "connecting term" in their labeling would also be permitted to delete the "connecting term" in accordance with 21 CFR 314.70. Typically, such terms are found within quotation marks in OTC drug monographs and in specific regulations. Deletion of these terms would only be permitted where deletion would not change the meaning of the information. Deletion of these terms would not be required but, rather, would be permitted as needed to simplify the presentation of labeling information (which is usually presented in a lengthy paragraph format), so that manufacturers, packers, distributors applicants can comply with the proposed, easier to read format.

Third, the proposal would expand the list of "interchangeable terms" found in the current regulations (§ 330.1(i) (21 CFR 330.1(i))), to facilitate the use of more concise, easier to understand

statements on the labeling of OTC drug products. Expanding the list of interchangeable terms would provide manufacturers, packers, distributors, or applicants with a broader choice of terms for a particular statement on the labeling. This proposed rule addresses the same interchangeable terms (as well as additional interchangeable terms) that were proposed on March 4, 1996 (61 FR 8450). Thus, this proposal formally withdraws the March 1996 proposal.

Fourth, the proposal would amend specific warning language required under current monographs and regulations (the pregnancy-nursing warning, the "keep out of reach of children" warning, and the overdose/accidental ingestion warning (§§ 201.63, 201.314(a) and (g)(1) (21 CFR 201.63, 201.314(a) and (g)(1)), and 330.1(g)) to make the warnings easier to understand and more concise.

Finally, in order to ensure that OTC drug product labeling is easier to read and understand, and to ensure the safe and effective use of OTC drug products, FDA is proposing to preempt State and local rules that establish different or additional format or content requirements than those in this proposed rule. The agency believes that such State and local requirements for OTC drug labeling would undermine the agency's objectives of ensuring the safe and effective use of OTC drug products through the use of a uniform easy-to-read format for all OTC drug product labeling.

II. Regulatory Scheme for OTC Drug Product Labeling

A. Current Statutory and Regulatory Requirements

The act and FDA's implementing regulations require specific information on the labeling of all OTC drug products. FDA regulations, including OTC drug monograph regulations, require information on the labeling of OTC drug products by product type (e.g., antacid, bronchodilator). Additionally, manufacturers, distributors, and packers may place the information required under OTC drug monographs in any format and order, as long as the information complies with the appropriate monograph and other applicable regulations. OTC drug products marketed under a marketing application must be labeled in accordance with the labeling approved in the application. As a result, the format of required labeling information varies considerably among OTC drug products.

Under section 502 of the act (21 U.S.C. 352), a drug is misbranded if the labeling does not contain: The name and place of business of the manufacturer, packer, or distributor and a statement of the quantity of contents in terms of weight, measure, or numerical count (section 502(b)); the established name, if any, of the drug, and the established name of each active ingredient if the drug is fabricated from two or more ingredients (section 502(e)); and adequate directions for use and adequate warnings against unsafe use (section 502(f)). In addition, a drug is misbranded if its labeling is false or misleading in any particular (section 502(a)), or if it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling (section 502(j)).

The act also addresses the prominence and conspicuousness of drug product labeling. Section 502 of the act states that:

> A drug * * * shall be deemed to be misbranded—
> * * * * * * *
> (c) If any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

FDA has implemented the general labeling requirements under section 502 of the act in part 201 of the regulations (21 CFR part 201). Section 201.1 sets forth requirements with respect to the name and place of business of the manufacturer, packer, or distributor. Section 201.5 defines adequate directions for use as "directions under which the layman can use a drug safely and for the purposes for which it is intended." Adequate directions include a statement of all the manufacturer's intended uses of the drug (frequently termed "Indications"), quantity of dose, route or method of administration, and the frequency, duration, and timing of administration (§ 201.5). Section 201.10 sets forth requirements for ingredient information required by section 502(e) of the act.

Section 201.17 sets forth requirements concerning the location of expiration dating, which is required under the current good manufacturing practice (CGMP) regulations (§ 211.137 (21 CFR 211.137)). Section 201.18 requires a lot number "capable of yielding the complete manufacturing history of the package." A related CGMP regulation (§ 211.132 (21 CFR 211.132)) that applies to most OTC drug products requires a labeling statement alerting consumers to certain tamper-resistant packaging features (§ 211.132(c)).

Sections 201.60 through 201.62 define and set forth requirements for the principal display panel of OTC drug product labeling. The principal display panel is defined as the part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale. The information required to be on the principal display panel includes a statement of identity of the drug and the net quantity of contents of a drug. The statement of identity must include the established name of the drug, as well as the pharmacological category or principal intended action of the drug. If the drug is a mixture and has no established name, its general pharmacological actions or its principal intended actions must be stated (§ 201.61(b)). Under § 330.1(c)(1) (21 CFR 330.1(c)(1)), the statement of identity of a drug covered by an OTC drug monograph shall be the term or phrase used in the applicable monograph.

Under section 502(e)(3) of the act, the established name of a drug is generally derived from its official title in an official compendium. When the established name for a single or a multiple ingredient drug product is stated in terms of the active ingredient(s), the active ingredient(s) will appear on the principal display panel. However, when a multiple ingredient product does not have an established name, the active ingredients are not required to be placed on the principal display panel (§ 201.61(b)), but may be prominently placed on the back or side panel in accordance with section 502(e) of the act and §§ 201.10 and 201.15. Under § 330.1(j), the agency recommends that the labeling of a product contain the quantitative amount of each active ingredient, expressed in terms of the dosage unit stated in the directions for use (e.g., tablet, teaspoonful).

Current regulations also address the format of OTC drug product labeling, but do not require a specific print size or print style. For example, implementing regulations in § 201.15 describe a number of situations in which the agency considers information on a drug product's label as lacking the prominence and conspicuousness required by section 502(c) of the act. For example, a statement may lack the prominence and conspicuousness required by section 502(c) of the act by reason of, among others, "[s]mallness or style of type in which such word,

statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter" (§ 201.15(a)(6)).

Section 201.61(c) requires that the statement of identity of an OTC drug product shall be in boldface type on the principal display panel, in a size reasonably related to the most prominent printed matter on such panel, and in lines generally parallel to the base on which the package rests as it is designed to be displayed. In some instances, the agency has required that warnings for certain OTC bronchodilator drug products shall appear in boldface type (§ 341.76(c)(6)(i) and (c)(6)(ii) (21 CFR 341.76(c)(6)(i) and (c)(6)(ii))).

In the Federal Register of March 13, 1995 (60 FR 13590), the agency issued final regulations (part 328 (21 CFR part 328)) that require the principal display panel of all alcohol-containing OTC drug products intended for oral ingestion to state the percentage of alcohol present in a product. Section 328.50(d) specifies that this information must appear in a size "reasonably related to the most prominent printed matter on the panel or label on which it appears * * *." This requirement is based on the agency's belief that consumers, especially those who wish to avoid or limit alcohol ingestion, need to be able to readily determine the alcohol content of OTC drug products at the time of purchase (60 FR 13590 at 13592).

Section 330.1(g) currently requires that the labeling of all OTC drugs contain the warning: "Keep this and all drugs out of the reach of children" and requires that drugs contain specific language outlining procedures to follow in case of accidental overdose for drugs administered orally, and in case of accidental ingestion for drugs administered topically or rectally. Sections 201.63 and 330.2 (21 CFR 330.2) require a warning for persons who are pregnant, or are breast feeding a baby, on the labeling of all OTC drugs intended for systemic absorption.

In addition to the warnings required under OTC drug monographs, the agency has specific warning requirements for certain ingredients in OTC drug products. Some examples are the Reye's syndrome warning for OTC aspirin and aspirin-containing drug products in § 201.314(h) and the warnings for water-soluble gums and related ingredients in § 201.319. These regulations mandate specifically worded warning statements for drugs containing sodium, mineral oil, wintergreen oil, ipecac syrup, acetophenetidin, salicylates, OTC drugs intended for minor sore throats, and guar gum, and address safety concerns associated with these ingredients and conditions. (See, e.g., §§ 201.64, 201.302, 201.303, 201.308, 201.309, 201.314, 201.315, and 201.319.) For example, § 201.315 requires in certain circumstances the following warning for OTC products intended for the temporary relief of minor sore throats:

"Warning—Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by physician."

The agency has issued other warnings and caution statements for certain ingredients in OTC drugs in part 369 (21 CFR part 369) as "interpretative statements." These warnings and cautions are "suggested," because manufacturers are not required to use the specific text of the warnings on their products. These warnings are based on safety considerations associated with the ingredients to which they apply. Products that do not contain a similar warning to those suggested in part 369 are deemed to be misbranded under section 502(f) of the act.

The important warning information, as well as the other required or recommended labeling information, does not appear in the same location, in the same sequence, or in the same print size in the labeling of OTC drug products. The agency has determined that consumers would be able to use OTC drug products more effectively if this information appeared with sufficient prominence (at or above a specified minimum print size) and in a uniform location in the labeling of all OTC drug products. Such labeling uniformity is a major goal of this proposal.

B. Requirements for Labeling of Drugs Covered by an OTC Monograph

In addition to being subject to the general and specific labeling requirements, OTC drugs marketed under a final OTC drug monograph are subject to specific labeling requirements contained in the monograph. The general criteria for establishing adequate labeling for OTC drugs under a monograph are set forth in § 330.10(a)(4)(v) (21 CFR 330.10(a)(4)(v)). Under these criteria, labeling of OTC drugs must be clear and truthful, not misleading, and must state the intended uses, warnings, side effects, and adverse reactions associated with a product in "such terms as to render them likely to be read and understood by the ordinary individual, including individuals of a low reading comprehension level, under customary conditions of purchase and use."

The labeling requirements established in OTC drug monographs cover various categories of drug information, including the statement of identity, indications, directions, warnings, and drug interaction precautions. However, the specific information required to appear under these categories varies according to the therapeutic class, active ingredients covered by the monograph, and safety concerns. In addition, the labeling information is not required to appear in the same location, in the same sequence, or in the same print size. Thus, the format varies among drug products covered by the same OTC drug monographs. This proposal is intended to provide a uniform format so that consumers will be able to use OTC drug products more safely and effectively.

In the Federal Register of May 1, 1986 (51 FR 16258), FDA amended its policy (known as the exclusivity policy) for the labeling of OTC drug products (§ 330.1(c)) to allow the use of alternate, industry provided terminology in the "indications" section of OTC drug product labeling. The rule establishes three alternatives for stating the indications for use in OTC drug product labeling. The label and labeling of OTC drug products are required to contain, in a prominent and conspicuous location, either: (1) The specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES;" (2) other wording describing such indications for use that is truthful and not misleading, which shall neither appear within a boxed area nor be designated "APPROVED USES;" or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is truthful and not misleading, which shall appear elsewhere in the labeling. The rule states that all required OTC drug labeling other than indications for use (e.g., statement of identity, and warnings) must appear in the specific wording established under an OTC drug monograph where exact language has been established and identified by quotation marks in an applicable monograph or by regulatio (§ 330.1(c)(vi)).

C. Requirements for Labeling of Drugs Not Marketed Under an OTC Drug Monograph or a Marketing Application

Some OTC drug products are not currently marketed under an approved

marketing application or a final OTC drug monograph. Many of these OTC drug products will become the subject of final monographs and, as discussed in section VI. of this document, they will then be subject to the labeling and format requirements in this proposed rule. Other products in this category that are, or become, the subject of pending marketing applications, would be required to submit labeling with their application in compliance with this rule.

III. The Need for Improved Labeling Design for OTC Drug Products

The labeling requirements for OTC drug products set forth specific wording for the information presented (e.g., directions for use, warnings, etc.) to consumers to ensure the safe and effective use of OTC drug products. FDA has examined representative examples of currently marketed OTC drug product labeling and has found that the design and format of labeling information varies considerably among these products. The agency has determined that consumers would have less difficulty reading and understanding the information if the labeling included uniform headings and subheadings presented in a standardized order, utilizing a minimum type size and other graphical features, and if certain required information could be made more concise.

While some manufacturers of OTC drug products have taken significant steps to improve the presentation of information on OTC drug product labeling, many of these products still have labeling that is difficult to read. In addition, consumers often have difficulty comparing the labeling on different products and deciding which product to purchase, because the information is not presented in the same format.

The agency has determined that a standardized format for OTC drug product labeling would improve legibility and understandability and enable consumers to become more familiar with the type and location of specific important labeling information, thus increasing consumer knowledge about the safe and effective use of OTC drug products. A standardized format would also improve the ability of consumers to compare products, thereby helping consumers select the appropriate product to meet their needs.

In reaching this determination, the agency has considered the increased use of OTC drug products in the marketplace and the changing patterns of use of these products by consumers. The agency also has considered comments that it has received from consumers expressing their concerns with the legibility and understandability of OTC drug product labeling. Additionally, the agency has reviewed literature studies that confirm consumers' concerns with current OTC drug product labeling. These studies recommend ways to improve legibility and understandability, discuss the importance of adherence to the "directions for use" and "warnings" sections of the labeling, and report on preventable adverse drug reactions from OTC drug products.

In the August 16, 1995 (60 FR 42578), Federal Register notice the agency sought comment on to what extent OTC drug labeling influences consumer judgements and behavior. No data or comments were submitted in response to this request. The agency also conducted a review of the literature on this issue. Although there is voluminous literature on the effects of labels on a variety of consumer products, there is little information about the influence of label variations regarding OTC drug products. Because the agency believes that this information is important and relevant to this proposed rule, the agency again seeks comment or submission of data or research relating to OTC drug labeling and its influence on consumer behavior and comprehension of label information.

During the comment period the agency intends to conduct research on the revised format compared to existing labeling. This research will focus on consumer reading and comprehension of the information from the revised format, compared to existing labeling. It will also examine consumers' reading of OTC drug labels under a variety of conditions for a variety of consumers (e.g., at various literacy levels). It will also examine the impact of new OTC label designs on comprehension of the intended messages. The research will also explore consumer judgments about OTC drug products for the intended population. Additionally, the agency intends to collect data relevant to overall judgments of the relative value of revisions in the OTC drug labeling format. The agency intends to seek public comment on the results relevant to the development of standardized format and content requirements prior to finalizing these provisions. After this rule becomes final, the agency intends to examine the consumer behavioral effects and the public health impact of imposed OTC drug labeling.

A. Changing Patterns of OTC Drug Use

OTC drug products are readily available and may be used without medical supervision. In recent years, more potent drugs have been switched from prescription to OTC status (e.g., cimetidine, naproxen sodium, ketoprofen, nicotine polacrilex, nicotine transdermal system, and minoxidil topical) and new uses have been approved for certain OTC drugs (e.g., acid reducer claims for several drug products, and hair growth claims for topical minoxidil). This trend of switching from prescription to OTC status is expected to increase in the future as the safety profile of many drug products becomes more established. Additionally, consumers are becoming more actively involved in their own health care. As a result, consumers are more likely to practice self-diagnosis and self-medication with OTC drug products. Thus, it is increasingly important that OTC drug product labeling provide consumers with uniform and understandable information for the safe and effective use of these products.

One important factor contributing to the increased use of OTC drug products has been rising health care costs. Hospital charges, physician fees, and the costs of prescription medications and other health-related products and services are higher and have risen faster than the associated costs of self-medication with OTC drug products. Today, four times as many health problems are treated by consumers with OTC drug products instead of seeing a physician, and 60 to 95 percent of all illnesses are initially treated with some form of self-care, including self-medication with OTC drug products (Ref. 1). Although 60 percent of the medications purchased by consumers in the United States are OTC, these purchases account for less than 2 percent of the U.S. health-care dollar, making it likely that, as a low-cost alternative, OTC drug use will continue to grow (Ref. 1).

Another significant factor contributing to the increased use of all drugs, including OTC drug products, is the advancing age of many consumers. The elderly comprise 12 to 17 percent of the population but consume about 30 percent of all medications (Ref. 1). The elderly are projected to consume as much as 50 percent of all medications by the year 2000 (Ref. 1).

B. Difficulties With Current Labeling

Although significant strides have been made in improving the legibility and understandability of OTC drug product labeling, there are still many products with labeling that is difficult to read. The agency has received numerous reports from consumers, health

professionals, patient advocacy organizations, literacy experts, and others stating their concerns about current OTC drug product labeling. Reports in the literature document similar concerns (Refs. 2 and 3).

Type size, letter and line spacing, contrast, print and background color, and type style are all factors that contribute to poor legibility of information (Refs. 3, 4, and 5). A recent study examined the effects of type size (vertical letter height) and horizontal letter compression on the legibility of OTC drug product labeling in persons 60 years of age and older (Ref. 3). The subjects were tested using three marketed OTC analgesics. The researchers found that a significant number of the elderly population could not adequately see the print on certain OTC product labels due in part to the small type sizes and high degree of horizontal compression (Ref. 3). Another study evaluated the visual acuity needed to read 25 marketed OTC drug product labels (Ref. 2) The authors found that the majority of labels required a visual acuity much greater than what is considered normal (Ref. 2). Another study found that 26.2 percent of the test subjects indicated difficulty reading print on product labels, even though over 90 percent of those tested reported always or sometimes reading the label (Ref. 6).

Visual acuity alone, however, is not the only consideration, because persons with normal vision report having trouble reading OTC drug product labeling (Ref. 3). Much of the informational text in OTC drug product labeling is specifically required by regulation and, on many products, the required text may be extensive. The information is often presented in a paragraph format that is unappealing to the eye and may cause the reader to lose interest.

In contrast, warnings in outline layout may have greater eye appeal, be easier to process, and be more effective than warnings in paragraph form (Ref. 7). An outline format may provide the reader with spatial cues as to the organization of the text and is likely to increase attention to the message (Ref. 7). Without the modifications presented in this proposed rule, it would be extremely difficult to organize labeling text to provide the spacial cues necessary to increase the appeal and visibility of the messages.

C. Problems With Adherence and Preventable Adverse Drug Reactions

OTC drug products are safe and effective when used as directed in the labeling. However, because of the changing patterns of OTC drug use, the potential for adverse drug reactions and misuse of OTC drug products is increasing. Although much of the data on the incidence of adverse drug reactions, including hospital or physician visits due to these reactions, does not distinguish between prescription and OTC drugs, inappropriate use of drug therapy generally is a major concern (Refs. 6, 8, and 9). Studies indicate that the elderly sometimes take OTC drug products for the wrong reasons (Ref. 10). This misuse has been attributed to the lack of information or misinformation from various sources (Refs. 3 and 11).

Additionally, the possibility of adverse drug interactions has increased because more new medications (as a result of prescription-to-OTC switches) are now available OTC and there are new OTC combination drug products for multiple symptoms. Consumers may not be aware that a particular prescription drug product that they are taking is in the same drug class as an OTC drug product that they are also taking. For example, a number of nonsteroidal anti-inflammatory drugs (NSAID) are marketed both as high-dose prescription anti-inflammatory arthritis treatments as well as lower dose OTC pain relievers/fever reducers. Patients who self-medicate with an OTC analgesic who are also taking a prescription NSAID place themselves at risk for NSAID-induced gastrointestinal problems (Ref. 12). Making OTC drug product labeling information easier to read and understand could ensure that patients become aware of this important information and avert potential problems.

D. FDA's Requests for Public Comment

During the past several years, many consumers have written to FDA to express concern about the legibility and understandability of OTC drug product labeling. Many individuals, especially the elderly, are concerned with small print size, print style, and lack of color contrast. Consumers stated that poor labeling legibility may cause them to select an improper dose, and, thus, may result in unsafe or ineffective use of the product. Consumers have also submitted comments to FDA about the print size of OTC drug product labeling in response to various OTC drug product rulemakings.

Additionally, the agency received a citizen petition requesting that FDA adopt regulatory standards for the size and style of print used for OTC drug product labeling. In response to consumer comments and the citizen petition, the agency published two requests for public comments in the Federal Register that related to the legibility and understandability of OTC drug product labeling. In addition, in an effort to solicit more information and views on specific aspects of OTC drug product labeling design that would improve communication to consumers, FDA held a public hearing on September 29, 1995. A discussion of the citizen petition, requests for comment, and the public hearing follows.

1. Citizen Petition and March 6, 1991, Request for Comments

Pharmacists Planning Service, Inc., petitioned FDA (Docket No. 90P–0201) to adopt regulatory standards for optimum size and style of print used for OTC drug product labeling. The petition stated that regulatory standards are needed to maximize readability of the print for persons with deteriorating vision, and because most people (especially the elderly) are unable to read the small print that currently appears on some OTC drug product labeling.

The petition requested that FDA adopt regulatory standards for the following reasons: (1) Medication misuse and abuse are serious and cost problems to patients, health providers, health care insurance plans, and Federal, State, and local governments; (2) prescription drugs continue to be switched to OTC status along with their attendant side effects and cautions on use; (3) OTC drugs are marketed in containers of all shapes and sizes, and the labeling bears instructions, cautions, and side effects associated with their use; and (4) most people, particularly the elderly, are unable to read the small print, which often includes vital information.

The petition also stated that:

> more than 240,000 older adults were hospitalized due to adverse drug reactions, mixing OTC drugs, which are available through sources other than a qualified health professional, and through lack of medical/pharmaceutical information on the proper method of administration of these medications.

The petition asserted that FDA regulatory standards could result in a $10 billion savings in hospital costs.

In response to this petition, and in an effort to determine what further steps needed to be taken, FDA published a notice to seek public comments on the feasibility of regulatory standards for tl print size and style of OTC drug product labeling (hereinafter referred to as the March 1991 notice) (56 FR 9363, March 6, 1991). FDA also requested comments on whether any new labeling requirements would have a substantial economic impact on manufacturers.

FDA requested specific comments on the following issues:

(1) Are current print, sizes, types, colors, contrasts, and backgrounds of OTC drug product labeling adequate in providing readable information for individuals with normal eyesight and for those with poor or deteriorating eyesight?

(2) Should there be a mandatory minimum print size or other readability standard and, if so, what should it be? If the answer is yes, should this be established through a regulation or a guideline?

(3) Should a package insert or larger carton be mandatory if a minimum print size standard is implemented and, because of package size, the manufacturer is unable to meet the specifications?

(4) What impact would a Federal legibility/readability regulation have on State laws that relate to "slack-fill?"

(5) What relevant data are available and what studies have been performed to determine optimum print size, background, and contrast for package products?

(6) What adverse effects have been documented that are associated with the inability or failure to read labels on OTC drug products?

(7) Will the Nonprescription Drug Manufacturers Association's (NDMA's) guidelines be effective and have a positive impact on labeling and, if so, are these guidelines adequate so that a Federal regulation or guideline is not needed?

FDA received 57 comments on the March 1991 notice (see Docket No. 90P–0201). About half of these comments were from consumers and favored larger or more readable print. Congressional representatives, professional organizations, manufacturers, health professionals, health departments, universities, a nursing home, a hospital, and a trade association expressed strong support for new FDA regulations. In contrast, a professional organization, a trade association, and several OTC drug product manufacturers preferred limited regulation or guidelines.

Some comments attached studies or documents on readability. One document discussed the loss of visual acuity with increased age, and concluded that size, color, and background of OTC product labeling are important. One study involving 36 students and 29 elderly subjects concluded that the results showed that labeling of small bottles need not be restricted to bottle surface area, but can be incorporated on wings and tags attached to the label.

One comment, which favored voluntary guidelines, included a number of suggestions concerning inserts, slack-fill laws, and larger packages. The comment submitted a publication that analyzed print size and style used in publications and listed 30 suggested guidelines for print, including type selection, size, line leading, proportional spacing, line width, columns, paragraphing, etc. The comment also submitted parts of a text that discussed legibility, color, surface, spatial arrangement, and position of printing.

NDMA, a trade group representing manufacturers of OTC drug products, agreed that efforts should be made to enhance labeling legibility, and submitted several references dealing with print size and style. NDMA stated that it had established a Special Task Force on Label Readability and had distributed guidelines to its membership as part of industry's voluntary program to enhance readability of OTC drug product labeling. NDMA also stated that it had held a briefing session for the entire industry, which was open to the public, to explain and help implement the guidelines.

NDMA stated that its guidelines provide for enhanced readability of OTC drug product labeling by addressing improvements in print size, type, style, colors, contrasts, and backgrounds. NDMA's guidelines, in 1991, recommended a minimum of 4.5 point type, where package size and copy requirements prohibit larger print. (These guidelines were revised in 1995, however, to recommended 6 point type, with 4.5 type as an absolute minimum in very small packages where space does not allow 6 point type.) NDMA claimed, however, that it is unreasonable to assume that all labeling can be made easily readable to all persons with poor or deteriorating eyesight.

NDMA also stated that there is a need for national uniformity in slack-fill laws because multiple State laws could be inconsistent or contradictory with each other and with Federal requirements for print size.

One comment submitted an investigative survey of consumers' ability to read OTC drug product labeling printed with the minimum type sizes recommended by NDMA's guidelines. According to the comment, the survey demonstrates that a significant proportion of the adult population over 20 years of age is not able to read OTC drug product labeling with 4.5 point minimum type size, and that only 48 percent of the public who currently purchase OTC medications are able to read labels with the 4.5 point minimum type size. People over 51 years of age have the most trouble reading labels with the 4.5 point type size—only 32 percent were able to read it—and only 63 percent of people under age 51 were able to read the labels.

The comment asserted that although 80 percent of all those surveyed were able to read 6 point reverse type size (which was NDMA's suggested minimum type size for white print on colored background), only 68 percent of the people over 51 were able to read the 6 point reverse type size. Thus, the comment recommended that FDA not accept NDMA's guidelines on minimum type size until further research and testing of consumers' ability to read labels are completed.

2. Public Hearing and August 16, 1995, Request for Comments

In an effort to solicit more information and views on specific aspects of OTC drug product labeling design that would improve the communication of labeling information to consumers, FDA published a notice in the Federal Register (August 16, 1995 (60 FR 42578)), announcing a public hearing on OTC drug product labeling issues. The notice stated that the hearing would address consumer use, legibility and consumer comprehension of OTC drug product labeling, OTC drug product labeling design features, and behavioral issues. The notice requested comments from the public about whether FDA should set standards for type size, color, contrast, type style, spacing, white space, uppercase and lowercase letters, and boldface letters.

FDA stated in the notice that a standardized format would help consumers know what information to look for and where to find it. The agency requested comments on the communication benefits that a uniform, standardized OTC drug product labeling format would provide to consumers. The agency also requested comments about what features should be made consistent on a standardized labeling format (e.g., order of information, major headings or subheadings for information, the use of lines or boxes around information, and certain labeling statements).

Recognizing that proposing a standardized format could necessitate revisions to many of the existing monographs, FDA published a subsequent notice in the Federal Register of September 14, 1995 (60 FR 47752), requesting comments on the process that should be followed by FDA to ensure that any revisions would be

completed in an efficient and expedient manner.

The public hearing was held on September 29, 1995, and included presentations from 22 panelists including representatives from government agencies, universities, industry associations, consumer associations, and corporations. The agency accepted written comments on the notice and the docket until October 30, 1995. Following the public hearing, the agency's Nonprescription Drugs Advisory Committee held a public meeting to further discuss OTC drug labeling issues. (Transcripts of the Advisory Committee meeting are available from the Freedom of Information Staff (HFI–35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.) A summary of the presentations made at the public hearing and the comments submitted in response to the notice follows:

a. *NDMA's comments.* NDMA supported FDA's initiative to improve OTC drug product labeling, and stated that:

> [b]y establishing mandatory standard headings and subheadings and a mandatory standard order for these headings, simplifying warnings, reducing duplicative and complex wording, and assuring a label that will be uniform throughout the United States, FDA can help to reduce label clutter and promote greater consumer use of label information.

NDMA recommended that FDA adopt uniform headings and subheadings for "mandatory information" pertaining to active ingredients, actions, uses, directions, and warnings, and that FDA adopt a standardized order for these headings and subheadings. NDMA also recommended that FDA combine contraindications, warnings, precautions, adverse reactions, and other similar information under one general heading titled "Warnings." In addition, NDMA recommended that the following subheadings be included under the "Warning" heading: Complete contraindications; warnings that depend upon a doctor's advice based on the physical condition of the consumer; warnings that relate to pregnancy and nursing, concurrently taking other drugs, or dietary restrictions; in-use precautions; warnings for topical products; and warnings concerning the use of the terms "doctor" or "health professional."

NDMA recommended a 6 point or greater type size, or 4.5 point as an "absolute minimum." NDMA also recommended the use of bullet points, but did not support mandatory pictograms. NDMA endorsed FDA's current practice of not requiring symbols or pictograms but rather permitting their voluntary use in addition to required warning language. In addition, NDMA recommended that FDA make available an expanded list of alternative words and phrases for OTC labeling terminology.

NDMA also recommended that FDA mandate a uniform national system because multiple State laws could be inconsistent or contradictory with each other and with Federal requirements. NDMA stated that dual, national and State labeling regulations, could confuse the public, undermine the credibility and effectiveness of FDA, create costly and burdensome barriers to interstate commerce, and expose companies to potential product liability suits. NDMA stated that "[n]ational uniformity is consistent with principles of federalism and will prevent the prospect of fifty 'mini-FDA's' applying a plethora of differing and inconsistent standards that would hinder implementation of FDA's own regulatory scheme."

Finally, NDMA urged FDA not to amend any monographs for OTC drug ingredients as part of this rulemaking because "to do so would lengthen the regulatory process and possibly undermine support for a prompt and efficient relabeling process."

b. *Other comments.* Other comments from individuals, drug companies, and professional associations generally supported FDA's efforts to improve the legibility and understandability of OTC drug product labeling, and most comments supported FDA's recommendation for a standardized format. Many comments endorsed NDMA's recommendations. Most comments did not support a monograph-by-monograph review of OTC drug products to determine what labeling revisions should be made.

Several comments supported the use of color, boxed warnings, pictorials, high contrast, and symbols. Some comments stated that specifying font size is not enough, and that FDA should specify stroke width, color, letter-line spacing, types of fonts, line height, and compression. Other comments recommended that FDA propose standards for the frequency of words, sentence length, and word length. One comment recommended that ornate typefaces, italics, and capitalization of entire words should be prohibited, and that FDA should establish clear standards for leading, contrast, and substrate (i.e., material and finish of the label).

Several comments provided suggestions on how to address the readability and legibility concerns of the elderly population. One comment requested that a bold black box containing the drug's expiration date, lot number, and other important information, such as major drug interactions or warnings, be prominently displayed in the labeling of OTC drug products. One comment stated that, although larger type is preferable, the legibility of text in small copy can be enhanced by using highlighted words, delineation, and paragraphing, without actually increasing text size. The comment stated that the stronger the contrast between the color of the text and the color of the background, the easier it is for the elderly to read the text.

One comment recommended 12 point type as the smallest type size for elderly people. Because the comment recognized that 12 point type is not possible for many OTC drug product labels, the comment urged FDA to consider a sliding scale of typeface sizes based on the size of the product package. One comment stated that 48 percent of adults are not able to read the 4.5 point type, and recommended that the type be at least 6 point.

Several comments asserted that OTC drug product labeling needs to be simplified, so that adults with a low reading comprehension will be able to understand the information. One comment stated that FDA should require a consumer mailing address on all OTC drug product labels so that consumers can write to the company with questions. The comment stated that FDA should not require a toll free phone number because it would be an unreasonable cost burden for small companies.

A comment submitted on behalf of the Uniform Code Council, administrator of the Universal Product Code (U.P.C.), stated that if FDA were to mandate a smaller U.P.C. symbol, it would make product scanning more difficult and would require product manufacturers to relabel at an enormous cost.

A comment from the Cosmetic, Toiletry, and Fragrance Association (and endorsed by NDMA) stated that cosmetic drugs that do not bear dosage limitations should not be required to list active ingredients before the inactive ingredients. The comment contended that the names of most of the active ingredients contained in such produ do not have any meaning to most consumers, except in specific situati where those consumers have been advised by a doctor to avoid a specific ingredient or want to do so for other reasons. The comment stated, however, that even in those situations, such consumers are accustomed to examining

the list of ingredients to look for that ingredient.

IV. Efforts to Improve the Design of OTC Drug Product Labeling

A. FDA Efforts

On August 17, 1995, FDA met with NDMA, at NDMA's request, to discuss proposed labeling changes for OTC drug products. At this meeting, NDMA representatives presented a proposal for text simplification (i.e., the use of words understood by persons of low comprehension, and a reduction in the number of words through text consolidation) of the pregnancy-breast feeding warning and the drug interaction precaution statement for OTC drug monograph ingredients.

In February 1996, FDA conducted a focus group study to investigate participant's perceptions of risks and benefits of prescription and OTC drugs (Ref. 13). The study looked specifically at how the participants react to different wording, claims, and statements contained in prescription and OTC drug product labeling. In addition, the study looked at the format and order of the information contained in the labeling. Participants confirmed that it would be beneficial to emphasize side effects and warnings, either by using bullets, bold type, block lettering, or larger type. Although there was no consensus about the best placement order for the information, the participants agreed that "simple" directions would be beneficial. In addition, participants stated that they wanted labeling information to be in "plain English" so they could better understand what the ingredients were, and how the drug works. Participants stated that this increased knowledge would help to alleviate their concerns of any health risk from taking the drug.

B. States' Efforts

In addition to FDA's efforts, the State of California has taken steps to improve the readability of OTC drug product labeling. On September 12, 1990, the Governor of the State of California signed a bill (AB 2713) to amend the Health and Safety Code regarding the labeling of OTC drug products. Section 1 of the bill states that printed materials on labels and notices packaged with OTC drug products may be difficult to read, presenting a potential danger to the health and safety of customers.

Section 2 of the bill adds the following to the State's Health and Safety Code: (1) Manufacturers of nonprescription drugs that are sold in the State of California shall evaluate and may modify the labeling of nonprescription drugs to maximize the readability and clarity of label information, in both the cognitive and visual sense; (2) NDMA shall report on a quarterly basis to, and seek advice periodically from, the California State Department of Health Services, consumer groups, health professionals, and drug manufacturers regarding the progress made by the nonprescription drug industry with respect to the readability and clarity of labeling information; and (3) the Director of the California State Department of Health Services shall report to the legislature regarding the progress made by the nonprescription drug industry with respect to the readability and clarity of labeling information. The effective period of the bill has now lapsed.

C. Industry Efforts

NDMA has taken steps to improve OTC drug product labeling. NDMA endorsed the California legislation and, recognizing the difficulty in reading OTC drug product labeling, appointed a task force on labeling to: (1) Explore the issues associated with label readability, and (2) evaluate the need and opportunity to make labels more easily read and understood by the public. The task force made recommendations on options to achieve such labeling, including type-size, print, style, color, contrast, package inserts, and special larger size packages.

NDMA has also worked with FDA in an effort to improve the legibility of OTC drug product labeling. NDMA issued "Label Readability Guidelines" that identify specific technical factors that can be addressed to improve the readability of OTC drug product labels. These guidelines cover major elements of readability pertaining to layout and design (e.g., information placement, hyphenation, uppercase/lowercase letters, paragraphs) and typography and printing (e.g., type size and style, contrast, printing process, color). The guidelines state that no single factor can determine readability by itself because the total effect of all factors must be considered. Because OTC drug product labeling is still difficult to read and understand, despite the voluntary guidelines, NDMA has urged FDA to adopt new regulations.

FDA has also worked individually with a number of companies in their efforts to improve labeling readability and understandability.

V. Description of the Proposed Rule

The proposed rule would establish a standardized labeling format for all OTC drug products and require manufacturers to revise the format and content of current OTC drug product labeling. The proposed rule would not, however, apply to the format or content of the principal display panel. The proposed rule would establish Federal preemption of State and local laws, rules, regulations, or other requirements for OTC drug product labeling content or format that are different from or in addition to those required by FDA. As proposed, this preemption would not include statutory or common law causes of action in tort, based on the format or content of OTC drug product labeling. The agency is, however, specifically requesting comment on several aspects of the scope of the preemptive effect of this regulation.

A. Scope

The proposed format and general content requirements would apply to OTC drug products that are the subject of a pending marketing application, OTC drug products marketed under an existing final OTC drug monograph, and OTC drug products marketed under an approved marketing application. The proposed requirements would also apply to marketed products pending under the monograph review process when the applicable monograph is finalized.

The proposed rule would not apply to any drug labeled as being homeopathic and which is also listed in the Homeopathic Pharmacopeia of the United States (H.P.U.S.). The labeling of such products is addressed in FDA's Compliance Policy Guide 7132.15, "Conditions Under Which Homeopathic Drugs May Be Marketed."

As discussed in section II. of this document, OTC drug products marketed under a final OTC drug monograph are subject to the specific labeling requirements contained in the monograph (21 CFR part 330). The agency is proposing that where an OTC drug product is the subject of an applicable final monograph or regulation that contains content and format requirements that conflict with proposed § 201.66, then the format and content requirements in § 201.66 must be followed. For example, where a final monograph states that the indications for use must be listed under the heading "Indications," such a monograph provision would be superseded by proposed § 201.66(c)(3) requiring that indications for use must be listed under the heading "Uses."

In the January 15, 1997, Federal Register (62 FR 2218), the agency issued a final rule requiring a specific warning statement in the labeling of drug products in solid dosage form that contain iron or iron salts as an active

ingredient. Although the agency currently is not aware of any marketed OTC drug products that would require such a statement, the agency recognizes that there may be conflicts with the provisions set forth in this proposed rule and the iron final rule. Conforming amendments regarding iron-containing drug products would be proposed and finalized prior to the implementation of the provisions set forth in this proposed rule.

B. Definitions

Proposed § 201.66(b) would define "active ingredient" as:

> any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

This definition is consistent with the definition of active ingredient in § 210.3(b)(7) for the CGMP regulations.

As set forth in section 502(e)(3) of the act, proposed § 201.66(b) would define "established name" of a drug or active ingredient as the applicable official name designated under section 508 of the act (21 U.S.C. 358), or, if there is no designated official name and the drug or active ingredient is recognized in an official compendium, the official title of the drug or active ingredient in such compendium, or if there is no designated official name and the drug or active ingredient is not recognized in an official compendium, the common or usual name of the drug or active ingredient.

Proposed § 201.66(b) would define "ingredient" as any substance in the drug product, whether added to the formulation as a single substance or in admixture with other substances. This definition is consistent with the definition of ingredient in § 201.10(b).

C. Content Requirements

As discussed in sections II.A. and II.B. of this document, the act and implementing regulations require that certain information (such as the established name of the active ingredients, the statement of identity, adequate directions for use, and adequate warnings against unsafe use) appear in OTC drug product labeling. OTC drug monographs require that specific information be included in the labeling of OTC drug products, depending on the therapeutic class and active ingredients covered by the monograph. The agency has also issued regulations that require specific OTC drug products to bear certain warnings. Drugs marketed under an approved marketing application must the labeled in accordance with the labeling approved in that application.

Because the content and format of OTC drug product labeling varies depending on the drug product, consumers often have difficulty finding, reading, and understanding the information. As discussed in section III. of this document, the agency has solicited comments from industry in order to develop a standardized format that would facilitate the readability and understandability of the information presented in OTC drug product labeling. Based on these comments and other information currently available to the agency, the agency is proposing, in § 201.66(c)(1) through (c)(7), that the outside container or wrapper of the retail package (or the immediate container label if there is no outside container or wrapper) of OTC drug products contain the labeling information required in final OTC drug monographs or in approved marketing applications in the order listed in paragraphs (c)(1) through (c)(7), with the appropriate headings and subheadings listed below. The agency is also proposing that the interchangeable terms and the connecting terms listed in proposed § 330.1(i) and (k) shall apply both to the OTC drug monographs set forth in part 331 *et seq.*, and to the OTC drug product labeling requirements provided in part 201. In the case of OTC drugs marketed under a new drug or antibiotic drug application, the use of the these terms to change approved labeling, and the use of the proposed format to change approved labeling, would have to be accomplished in accordance with § 314.70.

Proposed § 201.66(c)(1) would require the section heading "Active Ingredient (In Each [insert type of dosage unit]):" or "Active Ingredients (In Each [insert type of dosage unit]):", followed immediately by the established name of each active ingredient. For example, the heading would read, "Active Ingredient (In Each Tablet):". Other dosage units could include capsule, suppository, or per 5 milliliter (mL) dose or per teaspoon. For other products marketed without discrete dosage units (e.g., most topicals), the section heading would read "Active Ingredient" or "Active Ingredients". The quantity, proportion, or concentration of each ingredient per dosage unit, if contained in or if required to appear in the labeling, would appear after the established name of each active ingredient. The agency believes that specifying the amount or concentration of active ingredient per dosage unit would provide consumers with information they need to understand how much active ingredient is contained within each unit in the package. This information would allow consumers to make better product comparisons and to have greater information regarding proper dosing, thereby ensuring safe and effective use.

Section 502(e) of the act requires that drug product labeling contain the established name of each active ingredient for drugs fabricated from two or more ingredients. OTC products that are fabricated from two or more ingredients are not currently required to contain a statement of the quantity of each active ingredient unless the product contains one of the ingredients specifically listed in section 502(e)(1) of the act. Current regulations recommend that the labeling of OTC drug products contain the quantitative amount of each active ingredient per dosage unit in the "Directions for Use" section of the labeling (§ 330.1(j)). Given the customary conditions under which most consumers of OTC drugs must make a product selection decision, the agency believes that the quantity of each active ingredient within a dosage unit should appear prominently on the labeling. In order for consumers to distinguish among products within a pharmacological category, and select the appropriate product to meet their needs, such information is essential and therefore may be required under sections 201, 502, 505, 507, and 701 of the act (21 U.S.C. 321, 352, 355, 357, and 371). The agency specifically invites comments from the public on this point.

Proposed § 201.66(c)(2) would require that all OTC drug product labeling include the heading "Purpose:" or "Purposes:", followed by an accurate statement of the general pharmacological category(ies) or the principal intended action(s) of the drug, or, where the drug consists of more than one ingredient, the general pharmacological categor(ies) or the principal intended action(s) of each active ingredient. The information contained after the "Active Ingredient(s)" and "Purpose" heading would be required to be consistent with the information provided in the applicable OTC drug monographs.

For products that contain more tha one active ingredient, the information would be required to be presented in such a way as to make it obvious to the reader which active ingredients are associated with each purpose listed. The proposed rule would require that the "Active Ingredient" heading and

information be presented immediately adjacent and to the left of the "Purpose" heading and information (proposed § 201.66(d)(5)). The agency is also proposing that where there is more than one active ingredient, the active ingredients be listed in alphabetical order (proposed § 201.66(d)(5)).

An example of how labeling requirements proposed in § 201.66(c)(1) and (c)(2) would appear follows:

Active Ingredients (In Each Tablet):	Purpose:
Chlorpheniramine Maleate 2 mg	Antihistamine
Dextromethorphan 15 mg	Cough suppressant
Pseudoephedrine HCl 30 mg	Nasal decongestant

In the example, there are three active ingredients, listed in alphabetical order, followed by the amount of each ingredient per dosage unit, and the purpose for each active ingredient. The purpose is presented in such a way as to make it obvious to the reader which active ingredients are associated with each purpose listed.

Section 201.64 (to become effective on April 22, 1997) will require that OTC drug products intended for oral ingestion that contain 5 milligrams or more of sodium per single recommended dose, state the sodium content per dosage unit on the labeling. Section 201.64(b) will require that the sodium content per dosage unit be listed on a separate line after the heading "Sodium Content" as the last statement in the ingredients section. In the Federal Register of April 22, 1996 (61 FR 17807), the agency proposed similar provisions for the labeling of products containing more than specified amounts of calcium, magnesium, and potassium, per single dose.

The agency requests comment on the presentation of this information within the proposed labeling format. For example, information regarding the quantity of sodium, calcium, magnesium, and potassium, could be listed under the heading entitled "Dietary Information." Alternatively, this information could be listed under the heading "Other Information," discussed below. The agency recognizes that the placement of this information within the proposed labeling format may require a conforming amendment to § 201.64. FDA intends to include dietary information on the various formats that will be tested during the comment period.

Proposed § 201.66(c)(3) would require that all OTC drug product labeling include the section heading "Use:" or "Uses:", followed by the indication(s) for the drug product. An example of how this would appear on the labeling is as follows: "Use: Aids in the prevention of dental cavities" (§ 355.50(b)). Another example would be:

Uses: For the temporary relief of these cold symptoms	
* sneezing	* nasal congestion, stuffiness
* runny nose	* cough

Proposed § 201.66(c)(4) would require that all OTC drug product labeling include the heading "Warning:" or "Warnings:", followed by one or more of the specific warning subheadings (proposed § 201.66(c)(4)(i) through (c)(4)(viii)), if applicable.

Proposed § 201.66(c)(4)(i) would require, where appropriate, the subheading "Warning:" or "Warnings:", followed by any specific warnings that are required for certain products. Such warnings are currently required to appear as the first warning(s) under the heading "Warnings", such as the Reye's syndrome warning for aspirin and aspirin-containing drug products that reads "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness reported to be associated with aspirin" (§ 201.314(h)(1) and (h)(2)). This section would also require that, where appropriate, the subject of the warning be specified in the subheading before the word "Warning", for example, "Allergy Warning:" and "Alcohol Warning:" for certain OTC analgesics.

Proposed § 201.66(c)(4)(ii) would require, where appropriate, the words "Do Not Use:", followed by any contraindications for the use of the product. These contraindications are "absolute" and are intended specifically for situations where consumers are urged not to use the product unless a prior diagnosis has been established by a physician or for situations in which consumers are urged not to use the product under any circumstances regardless of whether a doctor or health professional is consulted. "Absolute" contraindications under this subheading would include the need for a diagnosis of asthma prior to the use of an OTC bronchodilator drug product, monoamine oxidase inhibitor interactions, or allergies to active or inactive ingredients when there is no specific allergy warning heading. For example, this subheading would contain the following for OTC bronchodilator drug products (§ 341.76(c)(1)): "Do Not Use: this product unless a diagnosis of asthma has been made by a doctor." And this subheading would contain the following statement for a nasal decongestant drug product: "Do Not Use: this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. * * * " (§ 341.80(c)(1)(D)). Another example, for eyewash drug products, would be, "Do Not Use:" followed by the warning "Obtain immediate medical treatment for all open wounds in or near the eyes" (§ 349.78(c)(2)).

Proposed § 201.66(c)(4)(iii) would require, where appropriate, the words "Ask a Doctor Before Use" immediately followed by one or more specific warning subheadings (proposed § 201.66(c)(4)(iii)(A) through (c)(4)(iii)(C)), as appropriate. These specific warnings are intended for situations where consumers should not use the product until a doctor is consulted. Warnings under this heading

include those that contain phrases such as "unless directed by a doctor," "without first consulting your doctor," and "except under the advice and supervision of a doctor."

Proposed § 201.66(c)(4)(iii)(A) would require, where appropriate, the words "If You Have:", followed by any warnings for persons with certain preexisting conditions (excluding pregnancy, which is discussed under proposed § 201.66(c)(4)(vi) and warnings for use in persons experiencing certain symptoms). Examples of preexisting conditions that would be included are disease states or conditions, such as "If You Have: hea. disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland" (§ 341.80(c)(1)(i)(C)). This example, when presented under the proposed format, would appear as follows:

Ask a Doctor Before Use:
If You Have:
* Heart disease
* High blood pressure
* Thyroid disease
* Diabetes
* Difficulty in urination due to enlargement of the prostate gland

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Proposed § 201.66(c)(4)(iii)(B) would require, where appropriate, the words "If You Are:", followed by any drug/drug interaction warnings and drug/food interaction warnings. An example of when this warning would be used is:

Ask a Doctor Before Use:
If You Are:
* Taking sedatives or tranquilizers
* On a sodium restricted diet

Proposed § 201.66(c)(4)(iii)(C) would require, as an alternative, and where appropriate, the words "If You:", followed by a combination of the warnings in paragraphs (c)(4)(iii)(A) and (c)(4)(iii)(B) of this section. For example, this heading would be appropriate if there is only one disease state or condition and one drug/drug interactio.. or drug/food interaction. An example is:

Ask a Doctor Before Use:
If You:
* Have kidney disease
* Are taking other drugs

Proposed § 201.66(c)(4)(iv) would require, where appropriate, the words "When Using This Product:", followed by the side effects that the consumer may experience, and the substances or activities to avoid while using the product (for example, alcohol, operating machinery, or driving a car). An example is:

When Using This Product:
* Use caution when driving a motor vehicle or operating machinery

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Proposed § 201.66(c)(4)(v) would require, where appropriate, the words "Stop Using This Product If:" followed by any signs of toxicity and other serious reactions that would necessitate the immediate discontinuation of use of the product, followed by the words "Ask a doctor. These may be signs of a serious condition." An example is:

Stop Using This Product If:
* Nervousness, dizziness, or sleeplessness occurs.
Ask a doctor. These may be signs of a serious condition.

The last two sentences would be required to be highlighted by bold type and indented under the "Stop Using This Product If:" heading. Alternatively, if there is only one sign of toxicity or serious reaction, this statement would read:

Stop Using This Product If: * * *

Ask a doctor. This may be a sign of a serious condition.

Proposed § 201.66(c)(4)(vi) would provide that any required warnings that do not fit within one of the categories of warnings listed in proposed 201.66(c)(4)(i) through (c)(4)(v), (c)(4)(vii), and (c)(4)(viii) must appear as a separate subsection, without a heading or subheading, after the information appearing under proposed § 201.66(c)(4)(v). For example, a "For external use only" warning would appear after the information in the "Stop Using This Product If:" section.

Proposed § 201.66(c)(4)(vii) would require, where appropriate, the warning statement for women who are pregnant or breast-feeding a baby, as set forth in § 201.63 and as amended in this proposal. The agency is proposing to amend the pregnancy-nursing section heading and warning statement in response to comments submitted by NDMA (see Docket No. 95N–0259) and to make the warning more concise and understandable. The revised warning statement in § 201.63 would state "If pregnant or breast-feeding, ask a health professional before use." The revised section heading would state "Pregnancy-breast feeding warning."

Proposed § 201.66(c)(4)(viii) would require, where appropriate, the "keep out of reach of children" warning and the accidental overdose or ingestion warning, as set forth in §§ 201.314(a) and (g)(1), 330.1(g), and as amended in this proposal. The agency is proposing to amend the "keep out of reach of children" and the accidental overdose or ingestion warning statements to make them more concise and understandable.

Furthermore, the agency is proposing to delete the recommendation to contact a poison control center because poison control centers do not exist in every State, and thus are not always accessible to all consumers. Instead, the revised recommendation reflects the idea that consumers generally may receive advice on overdose situations by contacting other medical professionals who may be more readily available to the consumer.

The revised overdose warning statements in § 330.1(g) would state: "The labeling of drugs used by oral administration shall also state: 'In case of overdose, get medical help right away.'" If required, the labeling for all drugs used topically, rectally or vaginally, and not intended for oral ingestion, shall state: "If swallowed, get medical help right away." However, for the specific category of topical drugs that are intended for oral use, the agency recognizes that the statement "If swallowed, get medical help right away," may be confusing to consumers who might think that any swallowing of the product during normal use may be dangerous. Therefore, to clarify to consumers that excessive amounts of the product should not be swallowed, labeling of topical drugs which are intended for oral use shall state, "If more than used for * * * is accidentally swallowed, get medical help right away" (see final rule for OTC anticaries drug products, 61 FR 52285 at 52286, October 7, 1996). The agency is also proposing to amend § 201.314(a) and (g)(1) to conform to this new, more concise, overdose warning.

The revised "keep out of reach of children" warning statements in §§ 201.314(a) and (g)(1), and 330.1(g) would state: "Keep out of reach of children." The agency is proposing to require this statement to be in bold print.

The agency also intends to revise §§ 369.20 and 369.21 to conform to these revised warning statements at or before the time that this proposed rule is finalized.

Proposed § 201.66(c)(5) would require that all OTC drug product labeling include the word "Directions:", followed by the appropriate directions for use. The proposal would require that the directions conform with the appropriate final OTC drug monograph or the approved application.

Proposed § 201.66(c)(6) would require, where appropriate, that OTC drug product labeling include the heading "Other Information:" followed by additional information that is not included under proposed § 201.66(c)(1) through (c)(5), but is required by or is optional under an applicable OTC drug monograph or is required under an approved marketing application. If included, this information would be required to immediately follow the "Directions" for use section on the label. An example of such required labeling, for pediculicide drug products, is the statement required by § 358.650(e) that describes different types of lice. Another example of such optional labeling is in the monograph for anticaries fluoride treatment rinses (§ 355.50(f)(1)), which permits, but does not require, the statement:

Other Information:
* The combined daily use of a fluoride preventative treatment rinse and a fluoride toothpaste can help reduce the incidence of dental cavities.

Proposed § 201.66(c)(7) would require that the labeling for all OTC drug products that are also cosmetics (as defined by section 201(i) of the act) include the words "Other Ingredients:" or "Inactive Ingredients:", followed by the cosmetic and/or inactive ingredients that are required to be stated on the label under § 701.3 (21 CFR 701.3). Current § 701.3(d) provides that "[w]here a cosmetic product is also a drug, the declaration shall first declare the active drug ingredients as required under section 502(e) of the act, and shall then declare the cosmetic ingredients." The new standardized format would list the active ingredients before the "Other Ingredients" or "Inactive Ingredients," but separated by the other required labeling information (i.e., "Purpose(s)," "Use(s)," "Warning(s)," and "Direction(s)").

Although many manufacturers, packers, and distributors voluntarily include a list of inactive ingredients on the labeling of OTC drug products, OTC drug products (that are not also cosmetics) are not currently required to list inactive ingredients on their labeling. In order to standardize the location of this information (if included), FDA is proposing that for OTC drug products that are not also cosmetics, the labeling must include the words "Inactive Ingredients:", followed by the inactive ingredients.

FDA has also received a citizen petition (96P–0318, CP1) requesting that existing regulations be changed to require placement of expiration dating on the immediate container of OTC drug products in a visible location so that the

date is legible throughout the use of the product and to adequately adapt the expiration dating to the way consumers use the products, particularly for drug products distributed in tubes. FDA is seeking public comment on whether current regulations should be revised to require expiration dating to appear in a specific location with specific legibility requirements on both the outer and immediate container packaging, especially for products marketed in tubes.

D. Format Requirements

The act and current regulations do not establish a standardized format for OTC drug product labeling. In addition, the agency has determined that some OTC drug product labeling may be difficult to read and understand. The agency understands the need for a flexible application of graphical techniques to achieve an acceptable level of readability for OTC drug product labeling. However, in order to ensure that labeling information is conveyed in a manner that enables the public to readily notice and comprehend such information, the agency is proposing to set minimal standards and requirements for certain key graphic elements of the format of OTC drug product labeling (except for the labeling on the principal display panel). Type size, letter and line spacing, contrast, print and background color, and type style are all factors that may contribute to poor readability and low comprehension of information (Refs. 3, 4, and 5). To provide further assistance to industry, the agency may, in the future, issue a guidance document to provide additional useful guidance on labeling format. The agency is proposing to revise the labeling format as follows:

Proposed § 201.66(d)(1) would require that all headings and subheadings must be in upper and lower case letters, and must be highlighted by bold type that prominently distinguishes the headings and subheadings from other information. FDA is also proposing to permit the use of shading or other color contrast to highlight headings and subheadings. FDA is proposing to require upper and lower case letters because the agency has tentatively determined that words in all upper case letters are harder to read. Consequently, the agency is also proposing to amend other regulations that explicitly require the use of all upper case letters (see §§ 201.63(e), 201.319(b), and 358.650(d)(1)). At the time of publication of the final rule, the agency intends to revise other labeling information that is required to appear in all capital letters to conform with the proposed requirement for the use of upper and lower case letters. FDA would not permit the use of "reverse type" (i.e., white or neutral color type on a darker color background) as a form of highlighting because this type of graphic technique is known to have poorer readability than regular type.

The agency is proposing to require that a horizontal line separate each section of information under the major headings listed in § 201.66(c)(1) through (c)(7). For example, a thin hairline would follow the active ingredient/ purpose, warnings, directions, other information, etc. The agency believes that horizontal lines will distinctively separate each section of important information to make it more conspicuous and easier to read.

Proposed § 201.66(d)(2) would require that the letter height or type size for headings and subheadings in proposed § 201.66(c)(1) through (c)(7) shall be no smaller than 6 point type. The agency is also proposing that the letter height or type size for all other OTC drug product labeling information (including, but not limited to, information on the outside container or wrapper, the immediate container label (if different), and the package insert (if any)) also shall be no smaller than 6 point type. The proposed minimum 6 point type requirement would not apply to the manufacturer's name and address or the labeling on the principal display panel. The format and content requirements for the principal display panel are set forth under §§ 201.60 and 201.62. The agency requests comments on whether FDA should establish minimum type size requirements for the principal display panel.

Based on the data and comments discussed in section III. of this document, FDA believes that the minimum type size requirements would benefit a substantial number of consumers who have difficulty reading the labeling on OTC drug products. The agency is, however, specifically requesting comment on whether to require that a package insert, or similar accompanying material, printed in a larger point size (such as 10 point type), be included with every OTC drug product. This requirement would help ensure the safe and effective use of OTC drug products by segments of the population (such as the elderly) who may be unable to read 6 point type.

In addition, the agency does not believe that the proposed minimum type size would require applicants, manufacturers, packers, or distributors to increase the size of OTC drug product containers.

The agency is proposing to allow manufacturers, packers, or distributors to delete specific "connecting terms" (that do not change the meaning of the information) that are currently required in OTC drug product labeling. Holders of approved marketing applications who wish to delete a "connecting term" in their labeling may do so in accordance with § 314.70. The ability to delete these terms would permit applicants, manufacturers, packers, and distributors to format their labeling to fit more legible information into the proposed bulleted format. Thus, FDA believes that the deletion of "connecting terms" would in a number of instances compensate for the increased demands on label space that may result from the increased minimum type size.

FDA recognizes that there may be some containers and packages that may not be able to accommodate 6 point type, even with the new proposed format. The agency believes, however, that the available surface area of the labeling on a number of these products could be increased without changing the size of the current container or package. For example, the labels affixed to some bottled drug products may be lengthened and widened to increase th surface area of the label without changing the size of the container. Also, the agency believes that the information presented on boxed drug products can, in some instances, be rotated 90 degrees in order to accommodate the proposed minimum type size without changing the dimensions of the package. The agency expects manufacturers, packers, distributors, and applicants to take all possible steps to increase the available surface area of the labeling, without changing the size of the container or package, in order to accommodate the proposed type size. In addition, the agency is specifically inviting comment on whether it should require manufacturers, packers, distributors, and applicants to use alternative packaging designs, such as extending a single side panel of a package, to increase available labeling space.

The agency also requests comment on whether to require a performance standard for the labeling on containers and packages that may be too small to accommodate 6 point type, and on the important elements such a performance standard should contain. A performanc standard would use performance-basec measuring techniques, rather than precise minimum requirements on the size, appearance, and format of a product's labeling, to ensure that the labeling is readable and understandable. For example, a performance standard could involve measuring a label's

readability based on a validated test of visual acuity (e.g., whether x number of persons with y visual acuity can read the labeling when it is z inches from the eye under specified or controlled lighting conditions).

Proposed § 201.66(d)(3) would require that all headings, subheadings, and information set forth in proposed § 201.66(c)(1) through (c)(7) shall be legible and clearly presented. The proposal would permit the use of shading or color contrast in order to increase the prominence and conspicuousness of the text. Shading or color contrast, however, would not be permitted to highlight or emphasize specific text or portions of text unless otherwise provided in an approved marketing application, final monograph, or an applicable regulation (e.g., current requirements for bold print in §§ 341.76 and 341.80, and requirement for box and red letters in § 201.318(c)(1)).

The proposal would require that the headings, subheadings, and information be presented in the Helvetica type style, which is an easy-to-read type style, and would require at least 1 point leading for the headings, subheadings, and information set forth in proposed § 201.66(c)(1) through (c)(7). The proposal also specifies, as a minimal kerning requirement, that letters should not touch. FDA believes that setting minimal requirements for upper and lower case type styles, leading, and kerning would enhance the readability of the proposed 6 point type.

Proposed § 201.66(d)(4) would require the use of bullet points to distinguish each piece of information found under each heading and subheading. For example, if there is more than one "use" for an OTC drug product, then the information required under the section heading "Uses" would be set off by a bulleted point before each unique piece of information. If more than one bulleted phrase is placed on the same horizontal line, the end of one bulleted phrase would be required to be separated from the beginning of the next bulleted phrase by at least two square em's (i.e., two squares of the size of the letter "M"). The agency is not proposing to specify a graphical icon for bulleted points. The proposed rule would not require the inactive ingredients or other cosmetic ingredients (proposed § 201.66(c)(7)) to be set off by bullet points.

Proposed § 201.66(d)(6) would require that the general labeling information required under the heading "Warnings" shall be continuous and not separated in any way, in order to increase the readability of this important information. For example, where the required labeling information is presented on two panels, the warning section shall be contained as a whole on one panel and not divided such that some information is on one panel and the rest is on another panel.

The agency is maintaining its current policy regarding the voluntary use of symbols and pictograms (see pregnancy-nursing warning, at 47 FR 54750, December 3, 1982 (§ 201.63(a)). The agency currently permits the voluntary use of symbols and pictograms, but does not permit symbols or pictograms to be used as a substitute for a required warning; they may only be used in addition to it. The agency, however, would not permit the use of a symbol or pictogram that is confusing or misleading, e.g., one that directs attention away from required labeling information or one that is ambiguous or could easily be misunderstood by consumers.

Examples of prototype OTC drug product labeling are attached in Appendix A. Example 1 demonstrates the general format and style contemplated by the proposed rule, including the proposed headings and subheadings, in the order proposed, as well as the proposed type style, hairlines, and bolding. Example 2 depicts OTC drug labeling for chlorpheniramine maleate, based on the applicable monograph, using the format and content specifications set forth in the proposed rule. The headings are presented in 8 point type, which is larger than the minimum type size proposed by the agency. The information is presented using an ordinary package size for this type of product. Example 3 depicts OTC drug labeling for a combination cough/cold product, based on the applicable monographs, using the proposed format and content specifications. Example 4 demonstrates how the same information shown in Example 3 can be presented directly on the package label for an 8 ounce bottle of syrup.

Examples 5 and 6 depict OTC drug labeling for a topical acne product and for a stannous fluoride product, respectively, based on the applicable monographs and using the format and content specification set forth in this proposed rule. The information is presented using an ordinary package size for each of these products.

Example 7 demonstrates OTC drug labeling for a chlorpheniramine maleate product, based on the applicable monograph, using the proposed amendment to the "exclusivity policy" set forth in § 330.1(c)(2) and described in Section V.I. of this document. Note that the approved information from the monograph is surrounded by a hairline forming a box and that the boxed area is entitled "FDA Approved Information." The additional information in this example is optional.

Example 8 demonstrates OTC drug labeling for a combination cough/cold product, based on the applicable monographs, using the proposed content and format specifications, except that the "Directions" section is presented before the "Warnings" section, and the directions for use are highlighted. The agency specifically requests comment on the order of appearance of the "Directions" and "Warnings" sections, as well as whether to require highlighting of the information contained in the "Directions" section.

Example 9 demonstrates OTC drug labeling for a chlorpheniramine maleate product, based on applicable monographs, using the proposed content and format specifications, except that the order is different than that proposed. The agency specifically requests comments on this, and other alternative for the order of information.

Each of these examples also makes use of proposed § 330.10(i) and (k) by deleting certain "connecting terms" and by substituting certain "interchangeable terms" as would be permitted by this proposed rule.

Finally, the agency is proposing that the new format will not apply to the product's immediate container, unless the product is sold without an outer package or wrapper. The agency believes that were it to require the proposed labeling format, and the information that would be presented within that format, to appear on the immediate container of all marketed OTC drug products, many products as currently marketed could not conform with the proposed requirements. The agency does not intend to require applicants, manufacturers, packers, and distributors to increase the container size of their products in order to conform to the proposed new format.

The agency recognizes, however, that dual labeling of products that are sold with outer packages or wrappers is beneficial because consumers may discard the outer package. For that reason, the agency is proposing that the letter height or type size for all other OTC drug product labeling information (except for the principal display panel) be no smaller than 6 point type. Thus, important information that is required to appear on the immediate containers of OTC drug products will be more legible to the consumer. The agency invites specific comment on whether additional elements of the proposed

new format, such as certain required headings, presentation of information in a standardized order, or the use of a bullet point format, should also be required for the immediate container labels of all OTC drug products.

E. Location

Proposed § 201.66(e) provides that the labeling information required under § 201.66(c)(1) through (c)(7) must be the first information that appears on the back or side panel of the outside container or wrapper of the retail package (or the immediate container label if there is no outside container or wrapper) of all marketed OTC drug products. FDA is specifying the location of this important information in order to enable consumers to become knowledgeable about OTC drugs and familiar with the type and location of specific information on OTC drug product labeling. Increased knowledge and familiarity with important information would help to ensure the safe and effective use of OTC drug products.

The agency is requiring that this labeling information appear in a uniform location in order to facilitate consumer familiarity with OTC drug product labeling information. Although current regulations require that the "statement of identity" and "net quantity of contents" appear on the "principal display panel" (see §§ 201.60, 201.61, 201.62)), important warning information does not appear in a uniform location in the labeling of various OTC drug products (as discussed in section III. of this document).

F. Exemptions and Deferrals

Some requirements in proposed § 201.66 may be inapplicable or impracticable for certain products. For example, it may be impracticable for a product, because of its attributes, to meet all of the labeling format requirements. Under proposed § 201.66(f), manufacturers, packers, distributors, or applicants may submit written requests to FDA to be exempted from one or more specific requirements in proposed § 201.66(a) through (e). Requests for exemptions would be required to be submitted in the form of a citizen petition under 21 CFR 10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from § 201.66 (OTC Labeling Format)." The request for exemption would be required to include documentation that demonstrates why the requirements are inapplicable or impracticable for this product. Such requests would be required to include documentation that demonstrates that the manufacturer has used all other graphical techniques to enhance readability, and has complied with as many of the format requirements in proposed § 201.66 as practicable. The agency seeks comment on whether there are particular types of products or packages that should be granted a regulatory exemption or should be required to meet a performance standard.

In addition, FDA on its own initiative may, based on the particular circumstances presented, exempt or defer any or all of the requirements set forth in these sections.

G. Interchangeable Terms

At the public hearing held by FDA on September 29, 1995, several comments, including NDMA comments, recommended that FDA consider amending its regulations to permit the use of synonyms that would promote greater comprehension among people with low or moderate literacy skills (see Docket No. 95N–0259). In response to these requests, the agency is proposing to amend current § 330.1(i) to include additional terms that may be used interchangeably in any of the labeling established for OTC drug products (including the OTC drug product labeling regulations in part 201, and parts 331 through 358), provided such use does not alter the meaning of the labeling that has been established and identified in an applicable monograph or by regulation. The proposal would not permit the titles of the headings and subheadings specified by the agency in proposed § 201.66(c)(1) through (c)(7) to be changed through the use of interchangeable terms, through the deletion of connecting terms, or in any other manner.

These interchangeable terms would be cross-referenced in proposed § 201.66(g). Expanding the current list of interchangeable terms would permit the formulation of easier to understand and more concise messages on the labeling of OTC drug products.

Because the part of speech (i.e., adjectives, nouns, adverbs, verbs, etc.) is not always the same for words that can be used in different ways, the contextual message conveyed by using certain substituted words may dramatically change the overall meaning of the labeling statement. Consequently, when using any interchangeable word, the meaning must not be changed.

Although these additional terms are based primarily on NDMA's recommendations, the agency is proposing some additional terms that were not included on NDMA's list of recommended terms. In addition, FDA is not proposing all of NDMA's suggestions in this proposal. One example of an NDMA recommendation that FDA is not proposing is NDMA's recommendation that the word "call" should be proposed as an interchangeable term with the current word "contact." The agency, however, is proposing "ask" instead of "call" because FDA does not want to limit other forms of "contact" (i.e., visit, or see).

Another example of an NDMA recommendation that FDA is not including in this proposal is the recommended phrase "use only on skin" as an interchangeable term with the current phrase "for external use only." The agency is not proposing this phrase because it is not interchangeable for topical ophthalmic or vaginal products. In addition, the phrase could be confusing for products intended to be used on cuts or abrasions.

In the March 1996 proposal, FDA proposed to amend § 330.1(i) to provide for interchangeable terms for the phrases "unless directed by a doctor" or "except under the advice and supervision of a physician." Labeling information about not using an OTC drug product under these circumstance appears in different OTC drug monographs in different language, but conveys the same message (see, for example, §§ 341.76(c)(2), 331.30(c)(1) and (c)(4) through (c)(7), 349.75(c)(2), 341.72(c)(3) and (c)(4), 346.50(c)(7)(ii), 341.72(c)(6)(i) through (c)(6)(iii), 358.750(c)(2)(ii), (c)(3), and (c)(4)). In addition, the phrase "unless directed by a doctor" has been used more recently and most frequently. The agency determined that all of these phrases could be interpreted in the same way (e.g., "* * * unless a doctor tells you") and that this simpler phrase may be better understood by consumers than some of the other phrases. Thus, the agency proposed to amend § 330.1(i) to include the phrase "unless a doctor tells you" as an alternative for these other phrases where they appear in the labeling of OTC drug products.

The proposal also stated that, in a few instances, the words "or your child's doctor" would be permitted as part of this phrase. The agency requested comments on whether it would be preferable to say "your" child's doctor or "the" child's doctor, or whether it does not make any difference which wording is used.

FDA received three comments supporting the proposal. NDMA recommended that FDA reconsider its proposal to adopt "unless a doctor tells you" because NDMA stated that the

phrase was "colloquial, awkward and incomplete in its instructional intent." (See Docket No. 92N–454A.) Another comment also urged FDA not to adopt the phrase "unless a doctor tells you," because the phrase could lead to ambiguity and confusion. The comments alternatively recommended that FDA adopt the phrases "unless told to do so by a doctor," "unless you first ask a doctor," "without checking with a doctor," or "without asking a doctor."

NDMA also recommended that FDA not adopt the phrase "your doctor" or "your child's" doctor because "it is limiting and should be dropped in favor of 'a doctor' or 'the child's doctor'." NDMA recommended that FDA adopt this broader language because a designated caretaker may administer an OTC drug product in the absence of a parent. Finally, NDMA recommended that FDA permit interchangeable terms defined in the OTC drug review to also be interchangeable with the same terms found in marketing applications.

Another comment recommended that for OTC drug products intended for use in conditions involving the feet (e.g., athletes foot, corns, calluses, etc.) the term "podiatrist" be added as an allowable interchangeable alternative to "doctor" or "physician" because many consumers consult their podiatrist rather than their usual doctor or physician for foot related conditions.

Because this proposed rule addresses the same interchangeable terms (as well as additional interchangeable terms), this proposed rule responds to the comments submitted to Docket No. 92N–454A. Therefore, the agency is, with this notice, formally withdrawing the March 1996 proposal.

FDA has carefully considered the comments and is proposing that the current terms, "unless directed by a doctor" and "except under the advice and supervision of a physician" be interchangeable with "unless told to do so by a doctor." In addition, the agency is proposing that the phrases "before a doctor is consulted," "without first consulting your doctor," or "consult your doctor before * * *" may be interchanged with "unless first told to do so by [the child's doctor] a doctor." The agency agrees with NDMA's comment that "a doctor" or "the child's doctor" is preferable to "your doctor" or "your child's doctor."

The agency disagrees with the comment that recommended that the term "podiatrist" be interchangeable with "doctor" or "physician" for OTC drug products intended for use in conditions involving feet (e.g., athlete's foot, corns, callouses, etc.). The agency does not believe that "podiatrist" would be an appropriate substitution for "physician" for all OTC drug products intended for use involving feet. Because the agency has determined that there may be specific limited instances where the term "or podiatrist" may be appropriate, however, current regulations do provide that "or podiatrist" may be used in addition to the word "doctor" when a wart remover product is labeled with the specific indication found in § 358.150(b)(2).

FDA agrees with NDMA's recommendation that FDA permit interchangeable terms defined in the OTC Drug Review to be interchangeable with the same terms found in approved marketing applications for OTC drug products. Applicants or holders of approved marketing applications for OTC drug products who wish to include an interchangeable term in their labeling would be required, however, to include the interchangeable term in the marketing application or supplemental application in accordance with § 314.70.

The agency recognizes that a large percentage of OTC drug products are purchased at retail stores where a pharmacist is present. FDA also recognizes that pharmacists are knowledgeable about OTC drug products and are trained to counsel and give advice about these products. Although the agency is not proposing the terms "doctor" and "pharmacist" as interchangeable terms, the agency believes the phrase "doctor or pharmacist," as in "Ask your doctor or pharmacist," may be appropriate guidance on OTC drug product labeling for certain products. The agency seeks comment on whether the phrase "or pharmacist" should be included on OTC drug labeling and, if so, on what section of the labeling, and for which products.

H. Connecting Terms

OTC drug product regulations currently contain statements or clauses that are in quotation marks. Information that is presented in a monograph in quotation marks is required to appear in the labeling exactly as it appears in the monograph (except to the extent an interchangeable term may apply). In order for these statements or clauses to fit into the new format, including the required minimum type size, certain words within the quotation marks may have to be deleted. Therefore, proposed § 330.1(k) includes a list of connecting terms that may be deleted from the labeling of OTC drug products required under OTC drug product regulations, including monograph regulations, when labeling is revised to comply with § 201.66, and when such deletion does not alter the meaning of the OTC drug product labeling requirements.

The agency is proposing to permit manufacturers, packers, or distributors to delete these connecting terms because these terms generally do not affect the meaning of the labeling, but are required in current regulations to ensure that sentences are grammatically correct. Holders of approved marketing applications who wish to delete a "connecting term" from their labeling may delete the "connecting term" in accordance with § 314.70. The agency is proposing this approach to simplify language and to enhance readability for consumers. In addition, the deletion of such connecting words would enable the currently required OTC drug product labeling language to fit into the new format without revising all of the current regulations. These connecting terms would be cross-referenced in proposed § 201.66(g). Manufacturers who choose to delete these connecting terms in the manner described would still be deemed to be using the exact monograph language where monograph language is specified in quotation marks. The agency recognizes that the proposed list does not include all connecting words that could be deleted and invites comment on additional terms.

I. "FDA Approved Information" Designation

The agency is also proposing to amend § 330.1(c)(2) regarding the use of the designation "APPROVED USES" or other similar designation when a manufacturer, packer, or distributor utilizes the exact language as it appears in an applicable monograph or regulation to state the indications for use. Section 330.1(c), in its present form, allows manufacturers some flexibility in describing the indications for use that are established in applicable monographs or regulations (§ 330.1(c)(2)(i) to (c)(2)(iii)). All other required OTC labeling, including required warnings, must be stated in the exact language established and identified (by quotation marks) in an applicable monograph or regulation (§ 330.1(c)(2)(vi)). Manufacturers, packers, or distributors who choose to delete connecting terms or use interchangeable terms in the manner described in this proposal would still be deemed to be using the exact monograph language where monograph language is specified in quotation marks. The agency is not proposing to change these elements of its "exclusivity policy" (see 51 FR 16258).

The agency is, however, proposing to amend § 330.1(c)(2) to make it

consistent with the labeling format proposed in this notice. Specifically, the agency would continue to invite manufacturers, packers, or distributors to use the exact language of a monograph or applicable regulation to describe the indications for use. Manufacturers, packers, or distributors who use such exact language to describe the indications for use would have the option of placing a box around all labeling information that has been established in an applicable final monograph or regulation, and to designate the boxed area, "FDA Approved Information." To be consistent with the standardized format being proposed, no other designation would be permitted, and the designation would appear in bold text with upper and lower cases letters (rather than in upper case letters). Manufacturers, packers, or distributors would not be permitted to use a boxed area around the "Uses" heading, but would be required to put a box around all of the information that is established in an applicable final monograph or regulation.

Manufacturers, packers, or distributors would also continue to have the option of using other truthful and nonmisleading statements to describe the indications for use, subject to the provisions of sections 301(d) (21 U.S.C. 331(d)), 502, and 505(a) of the act. As in the existing regulation, labeling that uses other truthful and nonmisleading statements to describe the indications for use could not be boxed and could not contain the "FDA Approved Information" designation (see § 330.1(c)(2)(ii)).

The agency recognizes that while it may be limiting the manner in which a manufacturer, packer, or distributor can make use of the boxed labeling technique, the agency is also proposing additional interchangeable terms and connecting terms. The agency believes that these proposed interchangeable terms and connecting terms would provide manufacturers, packers, and distributors more flexibility in using exact language (where exact language has been established or identified by quotation marks in an applicable monograph or regulation) to describe the indications for use. Therefore, manufacturers, packers, and distributors would have more opportunities to make use of the "FDA Approved Information" designation and box.

The agency is also considering whether it should instead take the step of deleting altogether the provisions for boxed labeling in § 330.1(c)(2). The agency seeks comment on this point.

J. Preemption

1. Need for Federal Regulation and Preemption

FDA has tentatively determined that to ensure that OTC drug product labeling conveys all material information to the consumer, and that the labeling conveys this information in a manner that is likely to be read and understood by the consumer, State and local rules that would establish different or additional format or content requirements than those in this proposed rule should be preempted.

The agency believes that a standardized format, and a single set of rules regarding the appearance and content of OTC drug labeling, will significantly improve the ability of consumers to read and understand OTC drug labeling. The agency expects that as consumers become familiar with the format, they will more readily recognize and focus on important information contained in the labeling regarding the use of the product. NDMA, the primary trade association representing nonprescription drug manufacturers, likewise has reached the conclusion that by establishing "a label that will be uniform throughout the United States, FDA can help to reduce label clutter and promote greater consumer use of label information."

With the number and variety of drug products available OTC, it is the norm that consumers face a range of choices when selecting an OTC drug product. However, all OTC products within the same pharmacological class or with the same principal intended drug action are not identical. Thus, uniformity will allow consumers to easily compare various OTC drug products, without having to take into account potentially confusing, and even misleading, differences in format or style. By helping consumers to easily and meaningfully distinguish among drug products, the agency believes it will increase the likelihood that consumers will select appropriate products for their needs.

A single format for all drug products, wherever sold, will minimize confusion while enhancing the readability and understandability of OTC drug labeling. Within a short period of time after implementation of the final rule, consumers will become familiar with the revised format and will be able to use it similarly to the way that they now use nutritional labeling on foods.

State and local requirements for OTC drug labeling format or content that differ from or add to those established by the proposed rule would interfere with FDA's proposed method and objectives. The proposed regulations are intended to allow consumers to glance at virtually any OTC drug product labeling anywhere in the country and find information in a format they recognize, presented in a manner that is easily read and understood. Consequently, the likelihood of safe and effective use of OTC drug products would be increased. A State or local requirement that differs from the proposed rule with respect to any of the standard format elements could frustrate the basis and purposes of the proposed regulations.

For example, changing the order in which required information must appear, or the size or graphic "look" of the area in which drug information will be contained, could confuse consumers and limit the intended effectiveness of the proposed format. Even if each State required only one small variation in the format, the resulting 50 different requirements throughout the country could undermine the goals the agency believes may be achieved through a uniform OTC drug labeling format.

In addition to the need for OTC label standardization and the adverse effect State and local requirements would have on it, State and local requirement could impose additional economic and distributional burdens on industry that ultimately would be borne by consumers. State requirements at variance with the Federal law would force manufacturers to develop unique sets of labeling or stop altogether the supply of OTC drug products to the residents of the jurisdiction involved. Moreover, were manufacturers required to tailor their products to different jurisdictions, they would likely face increased printing and distribution costs, leading to higher OTC drug prices for consumers and, therefore, more limited access for some consumers to safe and effective drugs.

The imposition of different or additional State or local labeling requirements could also make it difficult for some products to fit all of the FDA required labeling information within the proposed format, and may cause more products to have to seek an exemption from the new format.

Finally, the agency has tentatively determined that State or local interests in regulating OTC drug product labeling format or content would be modest when compared to the benefits of a national program. The agency to date has found little evidence to suggest that States or localities have a significant interest in controlling the format or content of OTC drug labeling. Moreover, the agency has tentatively determined that the benefits of clear, concise, and

consistent information that all consumers will receive as a result of this regulation would ordinarily outweigh the value of unique or unusual informational requirements for State or local consumers.

In sum, the agency has tentatively determined that for most consumers there are no inherent differences between States that would justify a need for different State regulation. Implementation of specialized rules could come at the expense of nationally uniform OTC drug labeling, and could ignore other national interests and priorities addressed by the proposed rule.

2. Scope of Proposed Preemption

The agency is proposing to preempt only those State and local requirements that would directly threaten the national uniformity sought to be achieved by the proposed rule, or otherwise directly interfere with the attainment of the agency's objectives outlined in this proposed rule. The agency has tentatively determined that State or local laws, regulations, or rules that establish or continue in effect additional or different requirements with respect to any of the elements of format or content addressed in the proposed rule could have a deleterious effect on the goals sought in this proposed rule. Thus, under the proposed preemption provision, a State or locality may not establish or continue in effect requirements different from or in addition to the agency's requirements with respect to the format (including headings, subheadings, order, boxing or title, lines and spacing, type size, color and contrast, and other format requirements in the proposed rule) or the content of OTC drug labeling. The agency also intends the preemption to apply to requirements that a State or locality may view as improving an agency requirement, such as requiring a larger minimum type size than 6 point and other minimum standards for graphical features. States or localities would similarly be prohibited from requiring more (or less) spacing between lines or letters, or requiring that the information appear in a different order or with different subheadings, or that additional information be included.

As proposed, the scope of this preemption would exclude statutory or common law causes of action in tort, based on the format or content of OTC drug product labeling. Because there may be situations in which information about potential harm from an OTC drug product may not be available to FDA until after an individual consumer may have been harmed, the agency does not want to preclude compensation through tort actions in all cases related to OTC drug product labeling. The agency specifically seeks comment on this exclusion.

The agency recognizes that in rare instances a State or local government may find a compelling need to issue a law, regulation, or ordinance relating to the format or content of OTC drug labeling. For example, there may be certain populations of patients in defined areas of the country who may be more sensitive to a particular aspect of an OTC drug product; and who would need to be warned of that aspect in order to ensure the safe and effective use of the product. Accordingly, the proposed rule contains a procedure for States and local governments to petition for an exemption from the preemption.

Finally, the agency specifically seeks comment on whether State or local warning statements that are different from, or that would be in addition to, those required by FDA should be preempted by this rule.

3. Legal Authority for Federal Preemption

The preemption doctrine is rooted in the Supremacy Clause of the United States Constitution (U.S. Const., Art. VI, Cl. 2). Under the Supremacy Clause of the Constitution, State law may be preempted by Federal law in a number of ways (U.S. Const., Art. VI, Cl. 2.). Congress may preempt State law by so stating in express terms (*Jones* v. *Rath Packing Co.*, 430 U.S. 519 (1977). Section 521 of the act (21 U.S.C. 360k), for example, contains an express preemption provision applicable to devices.

Federal preemption may also be based on any of several "implied preemption" principles. First, preemption may be found "where the scheme of federal regulation is sufficiently comprehensive to make reasonable the inference that Congress 'left no room' for supplementary state regulation" (*Hillsborough County* v. *Automated Medical Laboratories, Inc.*, 471 U.S. 707, 713 (1985), quoting *Rice* v. *Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)), or where "the federal interest is so dominant that the federal system will be assumed to preclude enforcement of state laws on the same subject" (*Rice*, 331 U.S. at 230; see *Hines* v. *Davidowitz*, 312 U.S. 52 (1941)).

Federal preemption may also be found where Federal law conflicts with State law. Such conflict may be demonstrated either where "compliance with both federal and state [law] is a physical impossibility" (*Florida Lime and Avocado Growers, Inc.* v. *Paul*, 373 U.S. 132, 142–143 (1963)), or where State law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" (*Hines*, 312 U.S. at 67).

State law is also preempted if it interferes with the methods by which a Federal law is designed to reach its goals. (See *Int'l Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987); *Michigan Canners & Freezers Ass'n* v. *Agricultural Marketing & Bargaining Bd.*, 467 U.S. 461, 477–478 (1984).)

A statutorily authorized regulation may preempt a State or local law under any of these implied preemption theories. (See *City of New York* v. *FCC*, 486 U.S. 57, 63–64 (1988); *Louisiana Public Service Comm'n* v. *FCC*, 476 U.S. 355, 368–369 (1986).) That is, "federal regulations have no less preemptive effect than federal statutes." (See *Fidelity Federal Savings & Loan Association* v. *de la Cuesta*, 458 U.S. 141, 153–154 (1982).) Thus, a federal agency, acting within the scope of its delegated authority, may preempt State or local laws that conflict with or frustrate the purposes of the agency's regulations. (See *City of New York*, 486 U.S. at 64.) In addition, an agency may, under certain circumstances, determine that its authority over an area of regulation is exclusive and expressly preempt State regulation in that area. *Id.* If the agency's choice to preempt "represents a reasonable accommodation of conflicting policies that were committed to the agency's care by statute [the regulation will stand unless] it appears from the statute or its legislative history that the accommodation is not one that Congress would have sanctioned." (See *United States* v. *Shimer*, 367 U.S. 374, 383 (1961).)

FDA's proposed regulations are within the scope of its delegated authority. (See section VII. of this document, "Legal Authority.") Furthermore, conflicts between State and local OTC labeling laws, with different or additional requirements than those of the Federal law, justify FDA's preemption of such laws. Although Congress did not expressly preempt State law in this area, the agency's action is appropriate because different or additional State and local laws would significantly interfere with both the goals of Federal law and the methods by which the Federal law is designed to achieve those goals.

Conflicting State and local laws for OTC drug labeling could undermine the agency's objectives to ensure greater legibility and comprehension of OTC drug labeling and to help ensure safe and effective use of OTC drug products.

Although States and localities may have an interest in developing their own requirements in the area of OTC drug product labeling, the agency has tentatively determined that the national standard set forth in this proposal is tailored to meet the agency's goal of ensuring safe and effective use of OTC drug products, and that the need for a national standard outweighs the interests of individual States and localities.

VI. Proposed Implementation Plan

The agency is proposing the following implementation plan for the proposed labeling format and content provisions. This proposed implementation plan is intended to minimize the economic impact on the regulated industry, while providing consumers with the benefit of more readable and understandable OTC drug product labeling at the earliest reasonable date. The proposed implementation plan provides implementation dates that vary according to the regulatory status of the particular OTC drug product. A product whose labeling does not comply with the proposed format and content provisions on or after the applicable implementation date would be liable to regulatory action.

The agency generally provides an implementation date of 1 year after the date of publication of the final monograph in the Federal Register for the use of labeling prescribed under a final OTC drug monograph (monograph labeling provisions). Accordingly, the agency is proposing that the implementation date for the new labeling format and content provisions for OTC final monographs, published on or after the effective date of the final rule based on this proposal, would be the implementation date for the applicable final OTC monograph. However, the agency encourages manufacturers, packers, and distributors of products pending under the monograph review process to voluntarily implement the new labeling format when they print new labels.

Because the labeling changes for information required under the final monograph and these new labeling format changes would be effective at the same time, manufacturers would only need to make one label printing to incorporate final monograph information into the new labeling format. In addition, implementation of the provisions of the final rule would be less burdensome because the agency and the industry will have gained information and experience from the planning, preparing, and printing of labeling in the new format for other products covered by either marketing applications or existing final monographs at the time of publication of the final rule. Accordingly, less time should be required for firms to bring OTC drug products pending under the monograph review process into compliance with the new labeling format requirements.

For an OTC combination product for which one component is pending under monograph review and another component is the subject of a final OTC drug monograph on or after the effective date of the final rule based on this proposal, the agency is proposing that the implementation date for the new labeling format and content provisions would be the earlier of 2 years after the effective date of the final rule based on this proposal or the effective date of the final OTC drug monograph applicable to the component under review. For an OTC combination drug product for which more than one component is pending under the OTC drug monograph review on or after the effective date of the final rule based on this proposal, the agency is proposing that the implementation date of the new format and content provisions would be the date on which any one of the components first becomes the subject of an effective OTC drug monograph.

For an OTC drug product that is the subject of a pending marketing application on or after the effective date of the final rule based on this proposal, the agency is proposing that the implementation date would be immediately (concurrent with initial product marketing) upon approval of the application. Manufacturers of such products would submit draft labeling in the proposed new format for review as part of the application.

For an OTC product with a low level of distribution (i.e., products with annual sales of less than $25,000), the agency is proposing that manufacturers comply with the new labeling format and content requirements within 3 years of the effective date of the final rule based on this proposal.

For all other OTC drug products, including those products marketed under a final OTC drug monograph, or an approved application, before the effective date of the final rule based on this proposal, the agency is proposing an implementation date of 2 years after the effective date of the final rule based on this proposal. By the applicable implementation date, applicants would be required to submit to FDA necessary changes in their product's labeling that would bring the product's labeling into compliance with the new standardized format requirements. The agency is proposing these dates to provide manufacturers with sufficient time to design and print new labeling and deplete existing stocks of products with old labeling.

Labeling changes to OTC drug products marketed pursuant to a marketing application would be made in accordance with § 314.70. Section 314.70(b) requires that FDA approve a supplement for a labeling change, prior to marketing any product with the labeling change, except for changes described in § 314.70(c)(2) or (d). Under § 314.70(c)(2), a supplement must be submitted at the time the change is made, and does not require agency preapproval if the change, among other things, is to add or strengthen a contraindication, warning, precaution, adverse reaction, or statement on overdose, or to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product, or to delete a false or misleading indication or claim. Under § 314.70(d) a supplement is not required for a change in labeling concerning, among others, the description of the drug product, how it is supplied, or for an editorial or similar minor change in the labeling. Instead, the change need only be described in the next annual report. Products that are marketed pursuant to an OTC drug monograph are not required to submit labeling to the agency.

The agency intends to work closely with sponsors of products that switch from prescription only status to OTC status prior to the implementation of the final rule on incorporating the new format and content requirements into the products' labeling. With respect to products currently marketed OTC pursuant to a marketing application, the agency is interested in receiving comment on whether changes made pursuant to the provisions set forth in this proposed rule should be made under § 314.70(b), (c), or (d).

The agency intends to make the final rule based on this proposal effective 30 days after the date of its publication in the Federal Register.

The proposed rule would not apply to any homeopathic drug products which are listed in the H.P.U.S. The labeling of such products is addressed in FDA's Compliance Policy Guide 7132.15 entitled "Conditions Under Which Homeopathic Drugs May Be Marketed.

VII. Legal Authority

FDA's legal authority to modify and simplify the manner in which certain information is presented in OTC drug product labeling derives from sections

201, 502, 505, 507, and 701 of the act. Regulating the order, appearance, and format of OTC drug product labeling is consistent with the agency's authority to ensure that drug labeling convey all material information to the consumer (21 U.S.C. 321(n) and 352(a)), and that the labeling communicate this information in a manner that is "likely to be read and understood by the ordinary individual under customary conditions of purchase and use" (21 U.S.C. 352(c)). Regulating the content of OTC drug product labeling is consistent with FDA's authority to ensure that the products are safe and effective for use (sections 201(n) and (p), 502, 505, and 507 of the act).

More specifically, the act authorizes FDA to regulate the marketing of drug products, including drugs composed wholly or partly of any antibiotic drug, to ensure that they are safe and effective for their intended uses (sections 201(p), 505(d), and 507 of the act). A major element of FDA's authority to ensure the safe and effective use of drug products is through FDA's review, approval, and monitoring of drug product labeling. Determinations about safety and effectiveness are to be made with respect to the conditions prescribed, recommended, or suggested in the labeling (sections 201(p) and 505(d) of the act).

Under section 505(d) and (e), FDA also must refuse to approve a new drug application, and may withdraw approval for a product, if the product's labeling is false or misleading in any particular. Moreover, under section 502(a) of the act, a drug product is deemed to be misbranded if its labeling is false or misleading in any particular. In determining whether the labeling of a drug is false or misleading, the agency must take into account not only the representations or suggestions made in the labeling, but also the extent to which the labeling fails to reveal material facts about the consequences that may result when the product is used according to its labeling or under the customary or usual conditions of use (section 201(n) of the act).

The act also provides that a drug product is misbranded, and liable to regulatory action, if:

> any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

(Section 502(c))

Implementing regulations in § 201.15 describe a number of situations in which the agency considers information on a drug product's label as lacking the prominence and conspicuousness required by section 502(c) of the act. For example, a labeling statement may lack the prominence and conspicuousness required by section 502(c) of the act by reason of, among others, "[s]mallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter" (§ 201.15(a)(6)).

The agency may also take regulatory action to ensure that OTC drug products contain "adequate directions for use" and "adequate warnings" against unsafe or dangerous uses (section 502(f) of the act).

Finally, section 701(a) of the act authorizes FDA to issue regulations for the efficient enforcement of the act (see *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973); see also *National Association of Pharmaceutical Mfrs.* v. *FDA*, 637 F.2d 877 (2d Cir. 1981); *National Confectioners Association* v. *Califano*, 569 F.2d 690 (D.C. Cir. 1978)).

The agency has tentatively concluded that a standardized format, with certain content requirements, for OTC drug products is necessary to fulfill the requirements of the act that information required to appear on the label or labeling of an OTC drug product be placed with such conspicuousness and prominence (as compared with other printed matter) as to render it likely to be read by the ordinary individual under customary conditions of use (section 502(c) of the act), and that the information be presented in a manner designed to communicate all material facts about the safe and effective use of the product to the consumer (section 502(a) of the act). The proposed regulations are also consistent with the agency's authority to ensure that OTC drug products are labeled with directions for use and warning statements that are adequate to guide the consumer in the safe and effective use of these products (section 502(f) of the act).

The currently available information, as summarized in section III. of this document, supports the conclusion that a standardized format and certain content requirements for all OTC drug products would help minimize the potential for consumers to be confused or misled when comparing products within the same pharmacologic class. As the number and variety of drug products available OTC continues to increase, consumers "under customary conditions of use" are frequently presented with a range of seemingly similar products. Given the complexity of the information contained on the label of an OTC drug, a standardized format and certain content requirements are necessary in order for the consumer to readily and meaningfully compare OTC drug products.

Finally, the agency believes that a standardized format and certain content requirements are essential to help ensure that consumers are able to recognize and understand important information about an OTC drug's proper use, its contraindications, and the adverse effects and safety hazards associated with its use. As discussed in greater detail in section III. of this document, many consumers have complained that OTC drug labels are difficult to understand and, among other things, that the print size on the labels is too small.

Thus, the agency's authority to ensure that material facts regarding the safe and effective use of an OTC drug product are adequately presented to the consumer derives directly from the agency's authority under sections 201, 502, 505, and 507 of the act. These provisions, combined with the agency's authority under section 701(a) of the act to issue regulations for the efficient enforcement of the act, authorize FDA to issue regulations to ensure that the information necessary to the safe and effective use of an OTC drug product is presented to consumers, and that this information is easily readable, readily understandable, and is not confusing or misleading.

VIII. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Therefore, in accordance with 44 U.S.C. 3506(c)(2)(B) and 5 CFR part 1320, FDA is providing below the title, description, and respondent description of the information collection contained in this proposal, along with an estimate of the resulting annual collection of information burden. This estimate includes the time needed for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's

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

Title: Over-the-Counter Human Drugs; Proposed Labeling Requirements.

Description: FDA's legal authority to modify and simplify the manner in which certain information is presented in OTC drug product labeling derives from sections 201, 502, 505, 507, and 701 of the act. Regulating the order, appearance, and format of OTC drug product labeling is consistent with FDA's authority to ensure that drug labeling convey all material information to the consumer (21 U.S.C. 321(n) and 352(a)), and that labeling communicate this information in a manner that is "likely to be read and understood by the ordinary individual under customary conditions of purchase and use" (21 U.S.C. 352(c)).

FDA is proposing to amend its regulations governing labeling requirements for human drug products to establish a standardized, more readable format for the labeling of all marketed OTC drug products. The proposed regulation merely standardizes the format for presenting information that is already required to be on the labeling.

The proposed format labeling changes present a one-time burden for manufacturers of OTC drug products marketed under new drug applications. Those manufacturers would have to submit a supplement detailing the labeling changes to be made by the manufacturer to comply with the format requirements. This burden is reflected in the chart below.

Other proposed labeling changes do not constitute collections of information because they provide for disclosure of information supplied by FDA. To enhance readability, proposed §§ 201.63, 201.314, 201.319, and 358.650 modify specific warnings or directions, proposed § 330.1(i) and (k) provide terms that may be used interchangeably in the labeling of OTC drug products and terms that may be deleted from the labeling, and proposed § 201.66(c) specifies words to be used in headings and subheadings on the labeling of the drug products. The proposed regulation specifies the wordings of the required disclosures. These labeling requirements provide for "public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public" and are, therefore, exempt from OMB review under 5 CFR 1320.3(c)(2).

Proposed § 201.66(d), which requires that the information be displayed in a certain format, is not included in the burden estimate because it is not a collection of information within the meaning of 5 CFR 1320.3.

To avoid double-counting, certain provisions in this proposal have not been included in the burden estimate because they merely cross-reference information collection requirements contained in other regulations. For example, proposed §§ 201.66(f) and (i) do not appear in the burden estimate table. Provisions that merely continue existing labeling requirements, such as proposed § 201.66(c), also have not been included in the burden estimate for this proposal.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.70	350	1	1,050	2	2,100
314.60(a)	350	1	30	2	60
314.97	20	1	102	2	204
314.96(a)	20	1	70	2	140
Total					2,504

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

The agency has submitted a copy of the proposed rule to OMB for its review and approval of this information collection. Interested persons are requested to send comments regarding this information collection to the Office of Information and Regulatory Affairs, OMB (address above).

IX. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) 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 12612: Federalism

FDA has examined the effects of this proposal on the relationship between the Federal Government and the States, as required by Executive Order 12612 on "Federalism." The agency concludes that preemption of State or local rules that establish requirements for OTC drug labeling format and content that would be in addition to, or would differ from, Federal law is consistent with this Executive Order.

Section 3(b) of Executive Order 12612 recognizes that Federal action limiting the discretion of State and local governments is appropriate "where constitutional authority for the action is clear and certain and the national activity is necessitated by the presence of a problem of national scope." The constitutional basis for FDA's authority to regulate the safety and effectiveness of OTC drugs is well established. Congress' decisions to vest in FDA the responsibility to establish a regulatory scheme over these products demonstrates Congress' view that the safety and effectiveness of these products is an issue of national scope.

Executive Order 12612 expressly contemplates preemption when there is a conflict between the exercise of State and Federal authority under Federal statute (section 4(a)). Moreover, sectio 4(b) of the Executive Order authorizes preemption of State law in the Federal rulemaking context when there is "firm and palpable evidence compelling the conclusion that the Congress intended to delegate to the * * * agency the authority to issue regulations preempting State law." State and local

laws and regulations that would impose different or additional requirements for OTC drug labeling format or content would undermine the agency's goal of ensuring that OTC drug labeling is easy to read and understand. The agency believes that a consistent format will enable consumers to find the information on OTC drug labeling and will ensure that it meets minimal standards to ensure legibility. Additionally, national consistency in OTC labeling information will ensure that labeling uses language that most consumers can understand, and will facilitate comparisons among like products. A fundamental purpose of the proposed rule is to help ensure the safe and effective use of OTC drug products. The agency believes that the readability and understandability of OTC drug labeling is directly related to the safe and effective use of these products.

Executive Order 12612 requires that Federal preemption be restricted to the minimum level necessary to achieve the objectives of the statute under which the regulations are issued (section 4(c)). The proposed regulation is narrowly drawn and focuses on OTC drug labeling format and content. The proposed regulations set forth a procedure for States and local governments to petition the agency for an exemption from preemption.

As required by the Executive Order, States and local governments will be given, through this notice and proposed rulemaking, an opportunity to participate in the proceedings to preempt State and local laws (section 4(e)). In addition, under the Order, the appropriate officials and organizations representing the States will be consulted before this proposed action is implemented (section 3(a)).

The agency concludes that the policy proposed in this document has been assessed in light of the principles, criteria, and requirements in Executive Order 12612; that this policy is not inconsistent with that Order; that this policy will not impose additional costs or burdens on the States; and that this policy will not affect the ability of States to discharge traditional State governmental functions.

XI. Analysis of Impacts

A. Background and Purpose

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (Pub. L. 104–4) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this proposed rule is to establish a standardized format for the labeling of all OTC drug products so that the labeling will be easier to read and understand, and will provide consistent information in like situations. The proposed rule is intended to help ensure the safe and effective use of OTC drug products.

B. Qualitative Description of Benefits

Variability and numerous weaknesses in the presentation of critical safety and effectiveness information in OTC drug product labeling make it difficult for consumers to select the most appropriate product and to use the product safely and effectively. For consumers to benefit from such information, this information must be easy to find, readable, readily understood, noted, and acted upon. Yet, despite the critical role of this information, OTC drug product labeling is often presented in small print using a crowded layout with minimal white space. The proposed rule sets forth a minimum standard for type size, leading, and kerning, and standards for type style, and other graphical features. The proposed rule also sets forth standardized headings and subheadings, and a standardized order for information.

At least two implicit benefits will flow from this proposed labeling format. First, an easy to read, standardized labeling format will help ensure that consumers select the right product to meet their needs. The lack of uniform presentation of information currently found on OTC drug product labeling makes product comparisons difficult. Consumers are faced with a number of choices for purchase decisions and can find it difficult to determine which product is right for them, based on their symptoms and their personal health situation. With this new format consumers can more readily and easily determine whether a product contains ingredients that they need or should take. Facilitating product comparisons will reduce market inefficiencies that can result from suboptimal purchases, inappropriate price-quality relationships, and competitive inefficiencies. It can also reduce consumer search and transaction costs and, concomitantly, increase the ability to select products consistent with individual needs.

Because health care costs are increasing and increasing numbers of products are switching from prescription to OTC products, more patients are relying on self-diagnosis and self-treatment. Consequently, the proposed rule will benefit consumers by allowing them to make more appropriate choices for self-treatment, and reduce the trial-and-error approach to self-medication. This can lead to decreased overall health care costs resulting from reduced visits to the doctor or hospital for treatment.

Second, the easy to read, standardized format will directly benefit consumers by helping ensure the safe and effective use of the product. Using the product as labeled can reduce the frequency of the adverse drug experiences associated with OTC drug products. Although the frequency of such events have not been quantified, it can be presumed that enabling consumers to make better choices and more easily understand the information will lead to fewer OTC adverse drug experiences.

The agency is not aware of any definitive studies that could be used to quantify such benefits. In the Federal Register of August 16, 1995 (60 FR 42578), the agency sought written comments addressing quantitative measures of benefits, to aid in the assessment of the costs and benefits of enhanced OTC drug product labeling. Little useful data was submitted in response to this request. The agency, again, requests submission of this data to help evaluate the overall benefits to the public health of having OTC drug labeling that is easy to read and easy to understand.

C. Nature of the Economic Impact

This rule will require the redesign of OTC drug labels in accordance with a predetermined schedule of effective dates. FDA acknowledges the substantial cost of preparing label revisions for thousands of products, as the procedures for each change involve

numerous levels of review and verification, in addition to needed technical production supplies and activities. This analysis, however, finds that, while substantial, a large part of these costs cannot be attributed to the proposed rule, because standard business procedures compel a periodic redesign of most OTC labels. The cost impact of the rule therefore is largely dictated by the agency's required implementation dates. For example, many firms already redesign labels within a 2-year period. These firms would incur little added cost from a rule that allowed a 2-year implementation period. Even if a firm typically redesigned its labeling only every 4 years, half of its labeling would, on average, be replaced within a 2-year period. Thus, this firm would need to accelerate redesign for only one-half of its products. Moreover, even those products whose redesign would have to be accelerated would, on average, lose only one-half of their expected lifetimes. Accordingly, to calculate the incremental cost of this rule, FDA counted only the value that would be lost due to the attenuation of the labeling's useful life, after accounting for those design changes that would have resulted from standard business practice. FDA calculated this cost as the product of the estimated number of products affected, the estimated number of years of lost labeling life, and the estimated lost value of a year of labeling life. Derivations for these variables are discussed below.

1. Number of Products Affected

Once the rule has become fully effective, a new OTC drug product labeling design would be required for each stock keeping unit (individual products, packages and sizes), commonly termed SKU's. Although the agency is unaware of any fully comprehensive data base that provides reliable counts of the number of SKU's that are regulated OTC drugs, A. C. Nielsen (Nielsen), a recognized provider of market research business information and analysis, maintains product data from a sample of 4,000 retail outlets selected to represent the geographical and retail characteristics of the U.S. OTC market. FDA used this data base as a primary source for estimating the size of the affected OTC drug market. According to this source, in 1995 OTC drug products accounted for $18.7 billion in sales in grocery stores, drug stores, and mass merchandise outlets. These sales figures exclude categories of OTC items not ordinarily regulated as OTC drug products such as vitamins, facial make-up, and nutritional supplements, but include product categories that may or may not be regulated as OTC drug products depending on the ingredients and/or product claims, such as some lotions, shampoos, and deodorants. To estimate and refine the count of items covered, FDA allocated the products in Nielsen's inventory into review categories based on their monograph review status. Because there are so few products subject to marketing applications relative to monograph review, it was believed this approach would not significantly bias the allocation. This categorization indicated that OTC drug products that are regulated under the monograph review process accounted for almost 30,000 brand name SKU's. The breakdown of these branded SKU's by monograph review status is as follows: 10,910 are under a final monograph, 8,241 are scheduled to become final within the next 2 years, and the remaining 8,488 after 3 years. (There is some uncertainty with the number "8,488" because the Neilsen coverage of products that have sunscreens is incomplete.)

FDA's estimate of the number of SKU's for private label store brands is much less certain, because the Nielsen data base did not provide adequate information for this purpose. Instead, FDA based its estimate on the number of private label store brands likely to be carried by individual retail outlets, multiplied by the number of such outlets in the United States. FDA assumed that only larger retail firms have the resources necessary to compete in the OTC drug product market with their own store label. As shown in Table 2, nearly 400 firms were found likely to market private label brands, including those that operate supermarkets, drug stores, and proprietary stores, with more than 9 establishments, and the very largest mass merchandising firms. According to the Nielsen data, firms that relabel generic OTC drug products carry from 55 to 280 different SKU's, with an average of 135 SKU's per firm. Since large retail stores would compete across more product categories than individual generic relabelers, FDA assumed that such retailers would carry from 100 to 400 SKU's, depending on their size, as displayed in the third column of Table 2. Multiplying the average number of private label store brand SKU's per firm type by the number of retailers adds 71,000 private label SKU's to the branded count. Assuming the same regulatory status distribution as for branded SKU's, FDA estimated that 40 percent of the 71,000 private label SKU's, or 28,400, are currently covered under final OTC drug monographs, 21,300 are scheduled to become final within the next 2 years, and the remainder after 3 years.

TABLE 2.—ESTIMATE OF PRIVATE LABEL SKU'S

Kind of Business	No. of Firms[1]	No. of SKU's[2]	Total SKU's	Average Sales/Firm ($Mil.)[1]
Supermarket				
10–24 establishments	148	100	14,800	133
25–49 establishments	45	150	6,750	380
50–99 establishments	35	200	7,000	750
100 establishments or more	37	350	12,950	4,187
Drug Store				
10–24 establishments	54	150	8,100	48
25–49 establishments	16	200	3,200	121
50–99 establishments	11	350	3,850	144

TABLE 2.—ESTIMATE OF PRIVATE LABEL SKU'S—Continued

Kind of Business	No. of Firms[1]	No. of SKU's[2]	Total SKU's	Average Sales/Firm ($Mil.)[1]
100 establishments or more	23	400	9,200	1,851
Proprietary Store				
10–24 establishments	5	100	500	12
25–49 establishments	4	150	600	(*)
50–99 establishments	1	200	200	(*)
100 establishments or more	1	350	350	(*)
Discount or Mass Merchandising				
10–24 establishments	8			122
25–49 establishments	3			299
50–99 establishments	5			2,160
100 establishments or more	10	350	3,500	8,661
Total affected	390		71,000	

[1] Source: U.S. Department of Commerce, 1992 Census of Retail Trade, Establishment and Firm Size, Table 3.
(*) Withheld to avoid disclosing data for individual companies.
[2] Estimate.

While the proposed rule would affect all OTC drug products covered under monographs, the implementation dates for labeling changes will vary according to regulatory status. Those products currently covered by a final drug monograph or marketing application, or about 39,400 SKU's, would be affected within 2 years of publication of this final rule. A second group of up to 29,550 SKU's could be affected by the final rule, depending on the timing of the publication of their final OTC drug monographs. Monographs for the remaining 29,788 SKU's are assumed to become final only after publication of this rule. Since products marketed under these OTC drug monographs would require labeling changes regardless of this rule, no costs were assigned to this latter group of products. Table 3 presents FDA's estimates of the number of SKU's for each respective regulatory status.

TABLE 3.—NUMBER OF ESTIMATED SKU'S BY REGULATORY STATUS

	Brand name	Private	Total
Final	10,910	28,400	39,310
Final by 1998	8,241	21,300	29,541
Remaining	8,488	21,300	29,788
Total	27,639	71,000	98,639

2. Cost of a Labeling Redesign

In the August 16, 1995, Federal Register notice announcing the September 29, 1995, public hearing, FDA requested economic data on the cost to design OTC drug product labeling, but received only one written comment with quantitative data. The agency obtained other estimates of labeling costs, but they vary widely and generally include the cost of redesigning the principal display panel (PDP) as well as the labeling affected by this proposal. Estimates of the average cost to redesign, including the cost of redesigning the PDP, ranged from $2,700 to $10,000 per SKU for branded products, and from $500 to $1,500 per SKU for private label products. (These costs included the drafting of language, art work, review, and implementation.) If the PDP accounts for 50 percent of the cost to redesign branded products, the average cost to redesign the labeling of the branded products affected by this proposal would be $1,350 to $5,000 per SKU. These high volume, nationally marketed, brand name OTC drug products, make up a small portion of the total number of OTC drug products, but the majority of the sales. For this analysis, FDA assumed that 20 percent of the SKU's affected by this proposal will be branded products, with incremental redesign costs of $1,350 to $5,000, and the remainder of the SKU's will have incremental costs ranging from $500 to $1,500 per SKU. Using the midpoints of the incremental redesign cost ranges, the average incremental cost to redesign OTC drug product labeling, weighted for type of product, is $1,500 per SKU.

Several industry comments indicated that most companies redesign OTC drug product labeling periodically, as part of standard business practice. Some companies redesign OTC drug product labeling more than once a year, while others redesign every 3 to 6 years. With the proposed 2-year implementation period, firms that normally redesign labeling every 2 years or less should incur no incremental costs as a result of this proposed rule.

3. Methodology

To calculate the economic impact on industry, FDA made the following assumptions:

Frequent labeling redesigns and the cost of printing labeling are part of the cost of doing business in the OTC drug product industry. As standard business practice, the labeling for 20 percent of the SKU's affected by the proposal are redesigned at least every 2 years; for the remainder of the SKU's, 50 percent are redesigned every 3 years and 50 percent are redesigned every 6 years.

In any given year, the number of OTC drug products requiring redesign are evenly distributed over the labeling life. For example, if the average life of a labeling design is 3 years, one-third of the products are redesigned in year one, one-third in year two, and one-third in year three. Moreover, in any given year, the expected return from the labeling design is constant (straight line depreciation of the labeling's value).

As a result, the economic impact of requiring OTC drug product labeling redesign can be measured as the lost value of the existing labeling designs. FDA estimated this loss as the amortized cost, using a discount rate of 7 percent, of the number of years of labeling use lost.

The above assumptions imply that 20 percent of the SKU's will incur no incremental costs, because their labeling would normally be redesigned within the proposed rule's 2-year implementation period. For the remaining SKU's, the loss will range from 1 to 4 years of the remaining usefulness of the design. The calculation of the economic impact (EI) was prepared in two steps and summed: First, for labeling designs with a 3-year expected life and second, for labeling designs with a 6-year expected life.

4. Total Incremental Cost

Table 4 presents estimates of the incremental costs of this rule under alternative implementation periods. The estimates are shown for products currently covered under a final OTC drug monograph and for OTC drug products expected to be covered under a final OTC drug monograph as of the time the final rule is published. The cost to industry would range from $1.4 million for a 5-year implementation period to $43.2 million for the 1-year period. The shorter implementation periods are associated with higher costs because firms lose a greater part of a label's useful life. With a 2-year implementation period, the cost to industry would be $11.3 million for final OTC drug monographs and $8.5 million for OTC drug monographs under review, for a total cost of $19.8 million. Actual costs for the set of OTC drug monographs under review will depend on the number of SKU's affected by each monograph and the timing of the respective publication dates.

TABLE 4.—TOTAL INCREMENTAL COSTS OF LABELING CHANGE FOR AFFECTED SKU'S ($ MILLION)

Years to Implement	Final Monographs	Monographs Under Review (final by 1998)	Total Cost
1	24.7	18.5	43.2
2	11.3	8.5	19.8
3	5.0	3.7	8.7
4	2.5	1.9	4.4
5	0.8	0.6	1.4

To reduce the economic impact on small entities, the proposed rule would allow an additional year for individual OTC drug products having sales of less than $25,000 per year. According to the Nielsen data, this extension applies to about 40 percent of the OTC drug products, but accounts for only about 1 percent of retail sales. (To calculate costs for the 40 percent, it was assumed that the labeling design for half of the SKU's had a 3-year expected life, and the other half, a 6-year life.) With this extension and a 2-year implementation period, the cost to industry would be about $14.2 million, almost a 30 percent reduction in the economic burden (Table 5).

TABLE 5.—SMALL BUSINESS ALTERNATIVES ($ MILLION)

Years to Implement	Small Business Extension		
	Total Costs	1 Year	2 Year
1	43.2	28.6	23.1
2	19.7	14.2	12.0
3	8.7	6.5	5.1
4	4.3	2.9	2.2
5	1.4	0.7	0.7

D. Small Business Impact

1. Need For, and Objectives of the Rule

Variability in the design, format, and placement of required labeling information may cause difficulties for consumers in both finding and reading information on OTC drug product labeling regarding safe and effective use. For consumers to benefit from having information, they must not only have ready access to the information, but it must also be readable and readily understandable. If information is not processed or is ignored because of factors affecting readability, such as small print size or crowded format, it cannot provide the expected benefits that would result from safe and effective use.

The purpose of this proposed rule is to establish a standardized format for the labeling of all OTC drug products so that the labeling will be easier to read, have uniform presentation of information, and consistent informatio in like situations. The proposed rule is intended to help ensure the safe and effective use of OTC drug products.

2. Types of Small Entities Affected

OTC drug product manufacturers and those entities that engage in the

relabeling of OTC drug products would be required to revise product labeling. Census data provide aggregate industry statistics on the number of manufacturers for Standardized Industrial Classification Code 2834 Pharmaceutical Preparations by establishment size, but do not distinguish between manufacturers of prescription and OTC products. According to the U.S. Small Business Administration (SBA) designations for this industry, however, over 92 percent of the roughly 700 establishments and over 87 percent of the 650 firms are small. (Because census size categories do not correspond to the SBA designation of 750 employees, these figures are based on 500 employees.)

IMS data on manufacturers of OTC drug products were also analyzed as an alternative method for estimating the number of small entities affected. Roughly 400 firms were identified as manufacturers of OTC products covered by IMS. Using the SBA size designation of 750 employees, 31 percent of the firms are large, 46 percent are small, and size data were not available for another 23 percent. Therefore, from 184 to 276 of the affected manufacturing firms would be considered small.

The agency is uncertain of the number of entities that relabel OTC products under private label store brands, but estimates that about 400 retail firms will need to relabel. (See Table 2.) These large retail stores offering private labels have average sales well above the SBA designations for small businesses.

3. Projected Reporting, Recordkeeping, and Other Compliance Requirements

This regulation would affect the information content and format associated with OTC drug product labeling. Firms that manufacture or relabel OTC drug products will need to change the information panel for each affected product. Since the agency has coordinated these requirements with labeling changes conducted in the normal course of business, many of these costs will be mitigated. Those OTC drug products that are marketed under a marketing application would need to submit revised labeling to the agency in accordance with § 314.70. This is a standard procedure that companies routinely follow for OTC drug product labeling changes. The proposed rule would not require new reporting and recordkeeping activities. Therefore, no additional professional skills are necessary.

4. Alternatives and Steps to Minimize the Impact on Small Entities

The proposed rule would require affected entities to change the information panel for affected OTC drug products. Among the steps the agency is taking to minimize the impact on small entities are: (1) To provide enough time for implementation to enable entities to use up existing labeling stock, (2) to provide sufficient time to coordinate a substantial proportion of the labeling changes with routine industry-initiated labeling changes, (3) to provide a mechanism for applying for an exemption or a deferral (when the requirements are judged inapplicable or impracticable), and (4) to provide an additional year to comply for individual OTC drug products having sales of less than $25,000 per year. Allowing 1 additional year for OTC drug products with sales of less than $25,000 per year reduces total industry costs by $5.5 million. While this last provision to extend the compliance time is targeted primarily at small entities, it provides flexibility for a substantial number of individual OTC drug products (about 40 percent), and the impact on overall retail sales would be negligible (less than 1 percent). The agency believes that the above actions provide substantial flexibility and reductions in cost for small entities.

The agency considered but rejected a voluntary labeling scheme, as previous industry efforts have been unsuccessful in achieving both a uniform format and an acceptable minimum print size for a majority of products in a timely manner. Further, a voluntary program would not provide relief to industry for conflicting labeling requirements at the State level.

The agency considered alternative implementation periods as options for all affected entities and for small entities. Industry costs for these implementation options are presented above in Tables 4 and 5, respectively. The agency selected a 2-year implementation period for all affected products. This reduces costs from $43 million (for a 1-year period) to $20 million. In order to further reduce the economic burden for small entities, the agency provided one additional year for low volume products. This alternative reduces total industry costs to $14 million. The agency believes that its approach provides significant reduction in cost while meeting the agency objective of achieving a standardized labeling format for a majority of products in a timely manner.

The agency considered but rejected revising all monographs on an individual basis because this approach would not achieve a standardized labeling format for a majority of products in a timely manner.

This analysis shows that this rule is not economically significant under Executive Order 12866 and that the agency has undertaken important steps to reduce the burden to small entities. Nevertheless, some small entities may incur significant impacts. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandate Reform Act does not apply to the proposed rule because it would not result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million.

XII. Request for Comments

Interested persons may, on or before June 27, 1997, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XIII. References

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

(1) Holt, G. A., and E. Hall, "The Self-Care Movement," *in* "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, 1990.

(2) Holt, G. A., et al., "OTC Labels: Can Consumers Read and Understand Them?" *American Pharmacy*, NS30:51–54, 1989.

(3) Watanabe, R. K., "The Ability of the Geriatric Population to Read Labels on Over-the-Counter Medication Containers," *Journal of the American Optometric Association*, 65:32–37, 1994.

(4) Wilkins, A. J., and M. I. Nimmo-Smith, "The Clarity and Comfort of Printed Text," *Ergonomics*, 30:1705–2020, 1987.

(5) Kalsher, M. J., et al., "Enhancing the Perceived Readability of Pharmaceutical Container Labels and Warnings: The Use of Alternative Designs and Pictorials," Proceedings of the Human Factors and Ergonomics Society 38th Annual Meeting, 1994.

(6) Landress, H. J., and M. A. Morck, "Prevalence and Risk of Medication

Mismanagement by the Elderly," *Journal of Florida Medical Association*, 71:261–266, 1984.

(7) Desaulniers, D. R., "Layout, Organization, and the Effectiveness of Consumer Product Warnings," *Human Factors Prospectives on Warnings*, Kenneth R. Laughery, Michael S. Wogalter, and Stephen L. Young (editors), the Human Factors and Ergonomics Society, pages 26–30, 1994.

(8) Manasse, H. R., "Medication Use in an Imperfect World," ASHP Research and Education Foundation, 1989.

(9) Caranasos, G. J., R. B. Stewart, and L. E. Cluff, "Drug-Induced Illness Leading to Hospitalization," *Journal of the American Medical Association*, 228:713–717, 1974. Quoted in J. E. Fincham, "Over-the-Counter Drug Use and Misuse by the Ambulatory Elderly: A Review of the Literature," *Journal of Geriatric Drug Therapy*, 1:3–21, 1987.

(10) Fincham, J. E., "Over-the-Counter Drug Use and Misuse by the Ambulatory Elderly: A Review of the Literature," *Journal of Geriatric Drug Therapy*, 1:3–21, 1987.

(11) Lumpkin, J. R., et al., "A Shopping Orientation Based Prescription for the Treatment of OTC Medication Misuse Among the Elderly," *Health Marketing Quarterly*, 8:95–118, 1990.

(12) Meckstroth, S., M. Scheartz, and N. Arawal, "NSAIDs—Safety Implications of Over-the-Counter Availability," *Drug Safety*, 7:221–244, 1992.

(13) Macro International Inc., "Women's Health Study Focus Groups Report," presented to the U.S. Food and Drug Administration on March 26, 1996.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 330

Over-the-counter drugs.

21 CFR Part 358

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, the proposed rule to amend 21 CFR 330.1 (61 FR 8450, March 4, 1996) is withdrawn, and it is proposed that 21 CFR parts 201, 330, and 358 be amended to read as follows:

PART 201—LABELING

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.63 is amended by revising the section heading, the first sentence in paragraph (a), and the warning statement in paragraph (e) to read as follows:

§ 201.63 Pregnancy breast-feeding warning.

(a) The labeling for all over-the-counter (OTC) drugs that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading "Warning" (or "Warnings" if it appears with additional warning statements) as follows: "If pregnant or breast-feeding, ask a health professional before use." * * *

* * * * *

(e) * * *

"IT IS ESPECIALLY IMPORTANT NOT TO USE" (SELECT "ASPIRIN" OR "CARBASPIRIN CALCIUM," AS APPROPRIATE) "DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY."

3. New § 201.66 is added to subpart C to read as follows:

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

(a) *Scope.* This section sets forth the format and content requirements for the labeling of OTC drug products. Where an OTC drug product is the subject of an applicable final monograph or regulation that contains content and format requirements that conflict with this section, then the content and format requirements in this section must be followed.

(b) *Definitions.* The following definitions of terms apply to this section:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act (secs. 201 *et seq.* (21 U.S.C. 321 *et seq.*)).

(2) *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

(3) *Established name of a drug or active ingredient* means the applicable official name designated under section 508 of the act, or, if there is no designated official name and the drug or active ingredient is recognized in an official compendium, the official title of the drug or active ingredient in such compendium, or, if there is no designated official name and the drug or active ingredient is not recognized in an official compendium, the common or usual name of the drug or active ingredient.

(4) *FDA* means the Food and Drug Administration.

(5) *Ingredient* means any substance in the drug product, whether added to the formulation as a single substance or in admixture with other substances.

(c) *Content requirements.* The outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper, of all marketed OTC drug products shall contain the labeling information required in the applicable final OTC drug monograph or in the labeling of an approved marketing application of an OTC drug product, in the order listed in paragraphs (c)(1) through (c)(7) of this section, under the appropriate headings and subheadings listed therein. The headings and subheadings shall be highlighted by bold type.

(1) "Active Ingredient (In Each [insert type of dosage unit]):" or "Active Ingredients (In Each [insert type of dosage unit]):", followed by the established name of the active ingredient(s) and, if contained in or if required to appear in the labeling, the quantity or proportion of each active ingredient per dosage unit. For products marketed without discrete dosage units (e.g., most topicals), the section heading shall read "Active Ingredient:" or "Active Ingredients:", followed by the established name of the active ingredient(s) and, if contained in or if required to appear in the labeling, the quantity or proportion of each active ingredient;

(2) "Purpose:" or "Purposes:", followed by an accurate statement of the general pharmacological category(ies) or the principal intended action(s) of the drug or, where the drug consists of more than one ingredient, the general pharmacological categor(ies) or the principal intended action(s) of each active ingredient;

(3) "Use:" or "Uses:", followed by the indication(s) for the specific drug product;

(4) "Warning:" or "Warnings:", followed by one or more of the following specific warning subheadings, if applicable:

(i) "Warning:", followed by any specific warnings that are required for certain products (such as Reye's syndrome for drug products containing

salicylates (§ 201.314(h)(1))). Where appropriate, the subject of the warning must be specified in the heading before the word "Warning" (such as "Allergy Warning:" or "Alcohol Warning:");

(ii) "Do Not Use:", followed by any contraindications for use with the product. These contraindications are "absolute" and are intended specifically for situations where consumers should not use the product unless a prior diagnosis has been established by a physician or where consumers should not use the product under any circumstances regardless of whether a doctor or health professional is consulted; or

(iii) "Ask a Doctor Before Use", immediately followed by one or more of the following specific warning subheadings, as appropriate. These specific warnings are intended only for situations where consumers should not use the product until a doctor is consulted:

(A) "If You Have:", followed by any warnings for persons with certain preexisting conditions (excluding pregnancy) and warnings for persons experiencing certain symptoms;

(B) "If You Are:", followed by any drug/drug interaction warnings and drug/food interaction warnings; or

(C) "If You:", followed by a combination of the warnings listed in paragraphs (c)(4)(iii)(A) and (c)(4)(iii)(B) of this section;

(iv) "When Using This Product:", followed by the side effects that the consumer may experience, and the substances or activities to avoid while using the product;

(v) "Stop Using This Product If:", followed by any signs of toxicity and other serious reactions that would necessitate immediately discontinuing use of the product, followed by the words: "Ask a doctor. These may be signs of a serious condition" (highlighted by bold type) or "Ask a doctor. This may be a sign of a serious condition." (highlighted by bold type));

(vi) Any required warnings that do not fit within one of the categories of warnings listed in paragraphs (c)(4)(i) through (c)(4)(v), (c)(4)(vii), and (c)(4)(viii) of this section;

(vii) The pregnancy-breast feeding warning set forth in § 201.63 of this part; or

(viii) The "Keep out of reach of children" warning and the overdose/accidental ingestion warning, as set forth in § 330.1(g) of this chapter;

(5) "Directions:", followed by the directions for use;

(6) "Other Information:", followed by additional information that is not included under paragraphs (c)(1) through (c)(5) of this section, but is required by or is optional under an applicable OTC drug monograph or is included in the labeling of an approved marketing application for an OTC drug product, where appropriate. If included, this information must immediately follow the "Directions" for use section;

(7) "Other Ingredients:" or "Inactive Ingredients:", followed by the cosmetic and/or inactive ingredients, as appropriate.

(d) *Format requirements.* All required labeling information for OTC drug products, except for the labeling on the principal display panel, shall be printed in accordance with the following specifications:

(1) All headings and subheadings set forth in paragraphs (c)(1) through (c)(7) of this section shall use only upper and lower case letters and shall be highlighted by bold type that prominently distinguishes the headings and subheadings from other information. In addition, shading or color contrast may be used to highlight headings and subheadings. Reverse type is not permitted as a form of highlighting. A horizontal line shall separate each section of information under the major headings listed in paragraphs (c)(1) through (c)(7) of this section;

(2) The letter height or type size for headings and subheadings set forth in paragraphs (c)(1) through (c)(7) of this section and all other required OTC drug product labeling shall be no smaller than 6 point type, except for the manufacturer's name and address;

(3) All headings, subheadings, and information set forth in or required under paragraphs (c)(1) through (c)(7) of this section shall be legible and clearly presented. The headings, subheadings, and information shall be presented only in the Helvetica type style. At least 1 point leading (i.e., space between two lines of text) shall be used for the headings, subheadings, and information set forth in or required under paragraphs (c)(1) through (c)(7) of this section, and letters shall not touch. Shading or color contrasts may be used to increase the prominence and conspicuousness of the text, but shall not be used to highlight or emphasize specific text or portions of text unless otherwise provided in an approved marketing application, final monograph, or an applicable regulation (e.g., current requirements for bold print in §§ 341.76, 341.80 of this chapter, and requirement for box and red letters in § 201.318(c)(1));

(4) Each unique labeling requirement for OTC drug product information listed under the headings and subheadings in paragraphs (c)(1) through (c)(6) of this section shall be preceded by a bullet point. If more than one bulleted phrase is placed on the same horizontal line, the end of one bulleted phrase shall be separated from the beginning of the next bulleted phrase by at least two square em's (i.e., two squares of the size of the letter "M");

(5) The heading and information required under paragraph (c)(1) of this section shall appear immediately adjacent and to the left of the heading and information required under paragraph (c)(2) of this section. Where there is more than one active ingredient, the active ingredients shall be listed in alphabetical order; and

(6) All information required under the general heading "Warnings" shall be presented in one continuous space and shall not be separated in any way on the labeling.

(e) *Location.* All information required under paragraphs (c)(1) through (c)(7) of this section shall be the first information that appears on the back or side panel of the outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper, of all marketed OTC drug products.

(f) *Exemptions and deferrals.* FDA on its own initiative or in response to a written request from any manufacturer, packer, distributor, or applicant, may exempt or defer, based on the particular circumstances presented, or on more specific requirements set forth in this section on the basis that the requirement is inapplicable or impracticable. Requests for exemptions shall be submitted in the form of a citizen petition under § 10.30 of this chapter, and should be clearly identified on the envelope as a "Request for Exemption from 21 CFR 201.66 (OTC Labeling Format)." Such requests shall include documentation which demonstrates why a requirement of this section is inapplicable to or impracticable for the labeling of the OTC drug product, and which demonstrates that the manufacturer, packer, distributor, or applicant has complied with as many of the format requirements in this section as practicable, including the use of all other graphical techniques to enhance readability.

(g) *Interchangeable terms and connecting terms.* The terms listed in § 330.1(i) of this chapter may be used interchangeably in the labeling of OTC drug products, provided such use does not alter the meaning of the labeling that has been established and identified in an applicable monograph or by regulation. The terms listed in § 330.1(k) of this chapter may be deleted from the labeling of OTC drug products when the

labeling is revised to comply with this section, provided such deletion does not alter the meaning of the labeling that has been established and identified in an applicable monograph or by regulation. The terms listed in § 330.1(i) and (k) of this chapter shall not be used to change in any way the specific headings and subheadings required under paragraph (c)(1) through (c)(7) of this section.

(h) *Preemption.* No State or local governing entity may establish or continue in effect any law, rule, regulation, or requirement for OTC drug product labeling format or content that is different from, or in addition to, that required by FDA. This paragraph is not intended to preempt statutory and common law causes of action in tort.

(i) *Requests for exemption from preemption.* A State or local governing entity may request an exemption from preemption upon petition under § 10.30 of this chapter. A petition for an exemption shall contain a detailed explanation of why an exemption should be granted, and include supporting documentation and data justifying the need for an exemption.

(j) An OTC drug product that fails to comply with the format and content requirements in this section is liable to regulatory action.

4. Section 201.314 is amended by revising the first two sentences in paragraph (a) and paragraph (g)(1) to read as follows:

§ 201.314 Labeling of drug preparations containing salicylates.

(a) The label of any oral drug preparation intended for sale without prescription and which contains any salicylate ingredient (including aspirin, salicylamide, other salicylates, and combinations) must bear a conspicuous warning statement in heavy block type on clearly contrasting background, such as: "Warning—Keep out of reach of children" (highlighted in bold type). "In case of overdose, get medical help right away." * * *

* * * * *

(g)(1) The label of any drug containing more than 5 percent methyl salicylate (wintergreen oil) should bear a conspicuous warning such as: "Warning: Do not use otherwise than as directed. 'Keep out of reach of children' (highlighted in bold type). The labeling of drugs shall also state as follows: For drugs used by oral administration, "In case of overdose, get medical help right away;" for drugs used topically and not inteded for oral ingestion, If swallowed, get medical help right away."

* * * * *

5. Section 201.319 is amended by revising paragraph (b) to read as follows:

§ 201.319 Water-soluble gums, hydrophilic gums, and hydrophilic mucilloids (including, but not limited to agar, alginic acid, calcium polycarbophil, carboxymethylcellulose sodium, carrageenan, chondrus, glucomannan ((B-1,4 linked) polymannose acetate), guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil tragacanth, and xanthan gum) as active ingredients; required warnings and directions.

* * * * *

(b) Any drug products for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient in an oral dosage form when marketed in a dry or incompletely hydrated form as described in paragraph (a) of this section are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following warnings and directions:

"'Warnings' (highlighted in bold type): Taking this product without adequate fluid may cause it to swell and block your throat or esophagus and may cause choking. Do not take this product if you have difficulty in swallowing. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention;" and

"'Directions' (highlighted in bold type):" (Select one of the following, as appropriate: "Take" or "Mix") "this product (child or adult dose) with at least 8 ounces (a full glass) of water or other fluid. Taking this product without enough liquid may cause choking. See warnings."

* * * * *

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

6. The authority citation for 21 CFR part 330 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

7. Section 330.1 is amended by revising paragraphs (c)(1), (c)(2)(i), and (c)(2)(ii), by removing the first three sentences in paragraph (g) and adding two sentences in their place, and by revising, paragraph (i), and by adding new paragraph (k) to read as follows:

§ 330.1 General conditions for general recognition as safe, effective, and not misbranded.

* * * * *

(c)(1) The product is labeled in compliance with chapter V of the Federal Food, Drug, and Cosmetic Act (the act) and subchapter C *et seq.* of this chapter, including the format and content requirements set forth in § 201.66 of this chapter. An OTC drug product that is not in compliance with chapter V and subchapter C, including § 201.66, is liable to regulatory action. For purposes of § 201.61(b) of this chapter, the statement of identity of the product shall be the term or phrase used in the applicable monograph established in this part.

(2)(i) The label and labeling of the product contain in a prominent and conspicuous location the labeling describing the product information that has been established in an applicable final monograph. At the option of the manufacturer, this labeling may be designated "FDA Approved Information." If the designation "FDA Approved Information" is used, the product labeling information that has been established in an applicable final monograph, or by regulation, shall appear within a boxed area and shall be stated in the exact language of the monograph or the regulation (i.e., stated in the exact language that has been established and identified by quotation marks in an applicable monograph or by regulation (e.g., § 201.63 of this chapter)).

(ii) At the option of the manufacturer, as an alternative to the requirements of paragraph (c)(2)(i) of this section, the label and labeling of the product may contain in the "Uses" section, other truthful and nonmisleading statements describing only those indications for use that have been established in an applicable monograph, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act. Such product labeling information shall not be boxed and shall not contain the statement provided in paragraph (c)(2)(i) of this section.

* * * * *

(g) The labeling for all drugs contai the general warning: "Keep out of reac of children (highlighted in bold type)." The labeling of drugs shall also state as follows: For drugs used by oral administration, "In case of overdose, get medical help right away;" for drugs used topically, rectally, or vaginally and

not intended for oral ingestion, "If swallowed, get medical help right away;" for drugs used topically and intended for oral use, "If more than used for * * * is accidentally swallowed, get medical help right away." * * *

* * * * *

(i) The following terms may be used interchangeably in any of the labeling for OTC drug products provided such use does not alter the meaning of the labeling that has been established and identified in an applicable monograph or by regulation.

(1) "Aggravate(s)" or "makes(s) * * * worse".
(2) "Ask" or "consult" or "contact".
(3) "Asking" or "consulting".
(4) "Assistance" or "help" or "aid".
(5) "Avoid contact with eyes" or "do not get into eyes".
(6) "Avoid inhaling" or "do not inhale".
(7) "Before a doctor is consulted" or "without first consulting your doctor" or "consult your doctor before * * *" or "unless first told to do so by a doctor".
(8) "Clean" or "cleanse".
(9) "Consulting" or "advising".
(10) "Continue(s)" or "persist(s)" or "do(es) not go away" or "last(s)".
(11) "Discard" or "throw away".
(12) "Discontinue * * *" or "stop * * *" or "quit * * *".
(13) "Doctor" or "physician".
(14) "Exceed" or "use more than" or "go beyond".
(15) "Exceed recommended dosage" or "use more than directed".
(16) "Excessive" or "too much".
(17) "Give to" or "use in".
(18) "Immediately" or "right away" or "directly".
(19) "Immediately" or "as soon as".
(20) "Immediately following * * *" or "right after".
(21) "Improve(s)" or "get(s) better" or "make(s) better".
(22) "Indication(s)" or "Use(s)".
(23) "Instill" or "put in (quantity) drop by drop".
(24) "Is (are) accompanied by" or "you also have" (in context only) or "occur(s) with".
(25) "Is persistent" or "continues" or "does not go away" or "lasts".
(26) "Lung" or "pulmonary".
(27) "Medication" or "drug".
(28) "Not to exceed" or "not more than".
(29) "Obtain(s)" or "get(s)".
(30) "Perforation of" or "hole in".
(31) "Persistent" or "that does not go away" or "that continues" or "that lasts".
(32) "Presently" or "now".
(33) "Take" or "use".
(34) "Tend(s) to recur" or "come(s) back".
(35) "To avoid contamination" or "avoid contamination" or "do not contaminate".
(36) "Unless directed by a [the child's] doctor" or "except under the advice of a [the child's] doctor" or "unless told to do so by a [the child's] doctor".
(37) "Worsen(s)" or "get(s) worse" or "make(s) worse".

* * * * *

(k) The following connecting terms may be deleted from the labeling of OTC drug products provided such deletion does not alter the meaning of the labeling that has been established and identified in an applicable monograph or by regulation:

(1) "And".
(2) "As may occur with".
(3) "Associated with".
(4) "Consult a doctor".
(5) "Discontinue use".
(6) "Due to".
(7) "If this occurs".
(8) "Or".
(9) "Occurring with".
(10) "Such as".
(11) "While taking this product".
(12) "Within".
(13) "Unless directed by a doctor".

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

8. The authority citation for 21 CFR part 358 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

9. Section 358.650 is amended in paragraph (d)(1) by revising the information in the brackets to read as follows:

§ 358.650 Labeling of pediculicide drug products.

* * * * *

(d) * * *

(1) * * * [sentence in boldface type].

* * * * *

Dated: December 20, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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

BILLING CODE 4160–01–F

Appendix A.—Examples of Prototype OTC Drug Poducts Labeling

Example 1

Example of Proposed Headings*

Active Ingredient (In Each Tablet) **Purpose**
xxxxxxxxxx **Xmg** xxxxxxxxx

Use:
- xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Warnings

Do Not Use:
- xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
  xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
  xxxxxxxxxxxxxxx

Ask a Doctor Before Use
If You Have:
- xxxxxxxxxxxxxxx

If You Are:
- xxxxxxxxxxxxxxx

When Using This Product:
- xxxxxxxxxxxxxxx

Stop Using This Product If:
- xxxxxxxxxxxxxxx

Ask a doctor. These may be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help right away.

Directions:
- xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

* Note: Headings are in 8 point type, text is in 6 point type

Example 2

Chlorpheniramine Maleate Product Labeling Using Proposed Specifications*
[Based on applicable monograph]

Active Ingredient (In Each Tablet) **Purpose**
Chlorpheniramine Maleate 4 mg..... Antihistamine

Uses: for the temporary relief of these symptoms of hay fever
▶ sneezing ▶ runny nose ▶ itchy, watery eyes

Warnings

Ask a Doctor Before Use
If You Have:
▶ glaucoma
▶ a breathing problem such as emphysema or chronic bronchitis
▶ difficulty in urination due to enlargement of the prostate gland

If You Are:
▶ taking sedatives or tranquilizers

When Using This Product:
▶ marked drowsiness may occur
▶ alcohol, sedatives, and tranquilizers may increase the drowsiness effect
▶ avoid alcoholic beverages
▶ use caution when driving a motor vehicle or operating machinery
▶ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help right away.

Directions:

Adults and children over 12 years:	Take 1 tablet every 4 to 6 hours as needed. Do not take more than 6 tablets in 24 hours.
Children 6 to under 12 years:	Take 1/2 tablet every 4 to 6 hours as needed. Do not take more than 3 tablets in 24 hours.
Children under 6 years:	Ask a doctor.

* Note: Headings are in 8 point type, text is in 6 point type

Example 3

Cough/Cold Product Labeling Using Proposed Specifications*
[Based on applicable monographs]

Active Ingredients (In Each Tablet)	Purposes
Chlorpheniramine Maleate 2 mg	Antihistamine
Dextromethorphan 15 mg	Cough Suppressant
Pseudoephedrine Hydrochloride 30 mg	Nasal Decongestant

Uses: for the temporary relief of these cold symptoms
- sneezing
- runny nose
- nasal congestion, stuffiness
- cough

Warnings

Do Not Use: this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, ask a health professional.

Ask a Doctor Before Use
If You Have:
- heart disease
- excessive phlegm (mucous)
- glaucoma
- high blood pressure
- thyroid disease
- diabetes
- a breathing problem such as emphysema or chronic bronchitis
- difficulty in urination due to enlargement of the prostate gland
- persistent or chronic cough such as occurs with smoking, asthma, or emphysema
- cough with fever, rash, or persistent headache

If You Are: taking sedatives or tranquilizers

When Using This Product:
- marked drowsiness may occur
- alcohol, sedatives, and tranquilizers may increase the drowsiness effect
- avoid alcoholic beverages
- use caution when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

Stop Using This Product If:
- nervousness, dizziness, or sleeplessness occurs
- cough is accompanied by fever, rash, or persistent headache
- nasal congestion does not improve in 7 days

Ask a doctor. These may be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

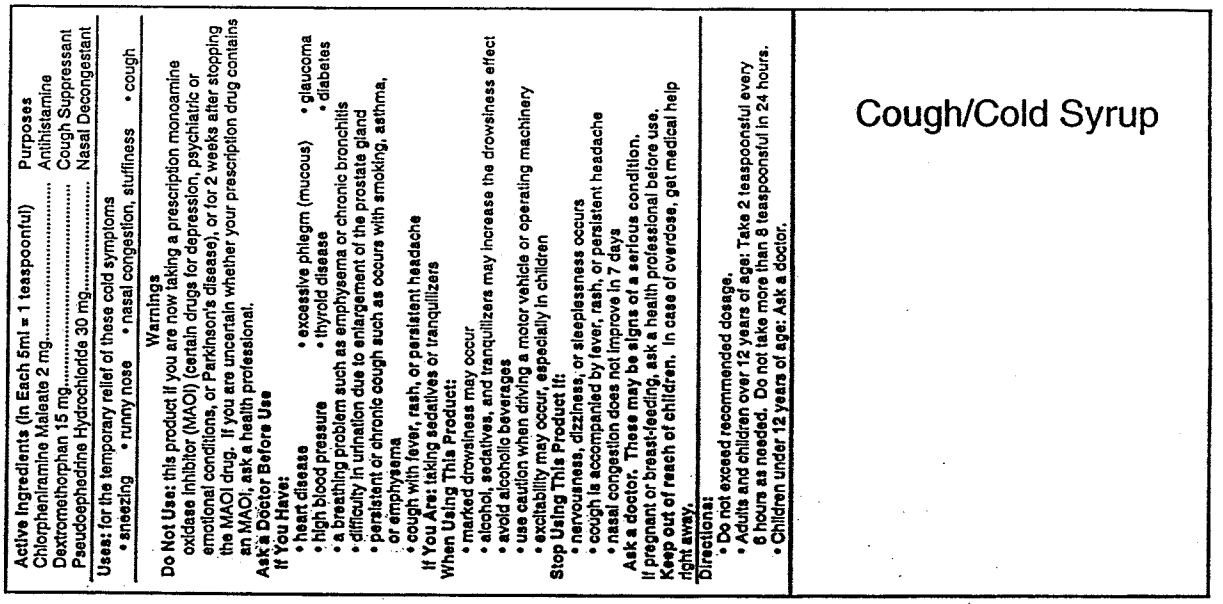
Keep out of reach of children. In case of overdose, get medical help right away.

Directions:
- Do not exceed recommended dosage.
- Adults and children over 12 years of age: Take 2 tablets every 6 hours as needed. Do not take more than 8 tablets in 24 hours.
- Children under 12 years of age: Ask a doctor.

* Note: Headings are in 6 point type, text is in 6 point type

Example 4

Cough/Cold Product Labeling Using Proposed Specifications*
[Based on applicable monographs]



Active Ingredients (In Each 5ml = 1 teaspoonful) **Purposes**
Chlorpheniramine Maleate 2 mg..... Antihistamine
Dextromethorphan 15 mg..... Cough Suppressant
Pseudoephedrine Hydrochloride 30 mg..... Nasal Decongestant

Uses: for the temporary relief of these cold symptoms
• sneezing • runny nose • nasal congestion, stuffiness • cough

Warnings

Do Not Use: this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, **ask a health professional.**

Ask a Doctor Before Use
If You Have:
• heart disease • excessive phlegm (mucous) • glaucoma
• high blood pressure • thyroid disease • diabetes
• a breathing problem such as emphysema or chronic bronchitis
• difficulty in urination due to enlargement of the prostate gland
• persistent or chronic cough such as occurs with smoking, asthma, or emphysema
• cough with fever, rash, or persistent headache
If You Are: taking sedatives or tranquilizers
When Using This Product:
• marked drowsiness may occur
• alcohol, sedatives, and tranquilizers may increase the drowsiness effect
• avoid alcoholic beverages
• use caution when driving a motor vehicle or operating machinery
• excitability may occur, especially in children
Stop Using This Product if:
• nervousness, dizziness, or sleeplessness occurs
• cough is accompanied by fever, rash, or persistent headache
• nasal congestion does not improve in 7 days
Ask a doctor. These may be signs of a serious condition.
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help right away.

Directions:
• Do not exceed recommended dosage.
• Adults and children over 12 years of age: Take 2 teaspoonsful every 6 hours as needed. Do not take more than 8 teaspoonsful in 24 hours.
• Children under 12 years of age: Ask a doctor.

Cough/Cold Syrup

* Note: Headings are in 6 point type, text is in 6 point type

Example 5

Topical Acne Product Labeling Using Proposed Specifications*
[Based on applicable monograph]

Active Ingredients — **Purpose**
Resorcinol 2%
Sulfur 5% ..... Acne Medication Cream

Uses:
- for the treatment of acne
- dries up acne pimples
- helps prevent new acne blemishes

Warnings

Do Not Use: on broken skin or apply to large areas of the body

When Using This Product:
- do not get into eyes
- using other topical acne medications at the same time or right after using this product may increase dryness or irritation of the skin. Only one medication should be used unless directed by a doctor
- apply to affected areas only

Stop Using This Product If: excessive skin irritation develops or increases **Ask a doctor. This may be a sign of a serious condition.**

For external use only.

Keep out of reach of children. If swallowed, get medical help right away.

Directions:
- Clean the skin throughly before applying drug.
- Cover the entire affected area with a thin layer one to three times daily.
- Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two to three times daily if needed or as directed by a doctor.
- If bothersome drying or peeling occurs, reduce application to once a day or every other day.

* Note: Headings are in 6 point type, text is in 6 point type

Example 6

Stannous Flouride Product Labeling Using Proposed Specifications*
[Based on applicable monograph]

Active Ingredient **Purpose**
Stannous Flouride 0.4% ..... Anticavity Flouride Preventive Treatment Gel

Use: Aids in the prevention of dental decay.

Warnings

Keep out of reach of children. If more than used for brushing is accidentally swallowed, get medical help right away.

Directions:
- Adults and children 6 years of age and older: Use once a day after brushing your teeth with a toothpaste.
- Apply the gel to your teeth and brush thoroughly.
- Allow the gel to remain on your teeth for 1 minute and then spit out.
- Do not swallow the gel.
- Do not eat or drink for 30 minutes after brushing.
- Instruct children under 12 years of age in good rinsing habits (to minimize swallowing).
- Supervise children as necessary until capable of using without supervision.
- Children under 6 years of age: Consult a dentist or doctor.

Other Information:
- This is a flouride preventive treatment gel, not a toothpaste.
- Read directions carefully before using.
- This product may produce surface staining of the teeth.
- Adequate tooth brushing may prevent these stains which are not harmful or permanent and may be removed by your dentist.
- The combined daily use of a flouride preventive treatment gel and a flouride toothpaste can help reduce the incidence of dental cavities.

Inactive Ingredients: Anhydrous glycerin, (names of other inactive ingredients listed in order of predominance in the product)

* Note: Headings are in 6 point type, text is in 6 point type

Example 7

Chlorpheniramine Maleate Product Labeling Using Proposed Specifications*
[Based on applicable monograph]

FDA Approved Information:

Active Ingredient (In Each Tablet)	Purpose
Chlorpheniramine Maleate 4 mg	Antihistamine

Uses: for the temporary relief of these symptoms of hay fever
- ▶ sneezing
- ▶ runny nose
- ▶ itchy, watery eyes

Warnings

Ask a Doctor Before Use

If You Have:
- ▶ glaucoma
- ▶ a breathing problem such as emphysema or chronic bronchitis
- ▶ difficulty in urination due to enlargement of the prostate gland

If You Are:
- ▶ taking sedatives or tranquilizers

When Using This Product:
- ▶ marked drowsiness may occur
- ▶ alcohol, sedatives, and tranquilizers may increase the drowsiness effect
- ▶ avoid alcoholic beverages
- ▶ use caution when driving a motor vehicle or operating machinery
- ▶ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help right away.

Directions:

Adults and children over 12 years:	Take 1 tablet every 4 to 6 hours as needed. Do not take more than 6 tablets in 24 hours.
Children 6 to under 12 years:	Take 1/2 tablet every 4 to 6 hours as needed. Do not take more than 3 tablets in 24 hours.
Children under 6 years:	Ask a doctor.

Inactive Ingredients:

Questions: 1-800-555-1234

123456789

* Note: Headings are in 6 point type, text is in 6 point type

Example 9

Chlorpheniramine Maleate Product Labeling Using Proposed Specifications*
Except that the Order is Different
[Based on applicable monograph]

Uses: for the temporary relief of these symptoms of hay fever
▶ sneezing ▶ runny nose ▶ itchy, watery eyes

Directions:

Adults and children over 12 years:	Take 1 tablet every 4 to 6 hours as needed. Do not take more than 6 tablets in 24 hours.
Children 6 to under 12 years:	Take 1/2 tablet every 4 to 6 hours as needed. Do not take more than 3 tablets in 24 hours.
Children under 6 years:	Ask a doctor.

Warnings

Ask a Doctor Before Use
If You Have:
▶ glaucoma
▶ a breathing problem such as emphysema or chronic bronchitis
▶ difficulty in urination due to enlargement of the prostate gland

If You Are:
▶ taking sedatives or tranquilizers

When Using This Product:
▶ marked drowsiness may occur
▶ alcohol, sedatives, and tranquilizers may increase the drowsiness effect
▶ avoid alcoholic beverages
▶ use caution when driving a motor vehicle or operating machinery
▶ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help right away.

Active Ingredient (In Each Tablet) **Purpose**
Chlorpheniramine Maleate 4 mg..... Antihistamine

* Note: Headings are in 8 point type, text is in 6 point type

[FR Doc. 97–4596 Filed 2–26–97; 8:45 am]
BILLING CODE 4160–01–C

Example 8

Cough/Cold Product Labeling Using Proposed Specifications* Except that Directions are Listed Before Warnings [Based on applicable monographs]

Active Ingredients (In Each Tablet)	Purposes
Chlorpheniramine Maleate 2 mg	Antihistamine
Dextromethorphan 15 mg	Cough Suppressant
Pseudoephedrine Hydrochloride 30 mg	Nasal Decongestant

Uses: for the temporary relief of these cold symptoms
- sneezing
- runny nose
- nasal congestion, stuffiness
- cough

Directions:
- Do not exceed recommended dosage.
- Adults and children over 12 years of age: Take 2 tablets every 6 hours as needed. Do not take more than 8 tablets in 24 hours.
- Children under 12 years of age: Ask a doctor.

Warnings

Do Not Use: this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, ask a health professional.

Ask a Doctor Before Use

If You Have:
- heart disease
- excessive phlegm (mucous)
- glaucoma
- high blood pressure
- thyroid disease
- diabetes
- a breathing problem such as emphysema or chronic bronchitis
- difficulty in urination due to enlargement of the prostate gland
- persistent or chronic cough such as occurs with smoking, asthma, or emphysema
- cough with fever, rash, or persistent headache

If You Are: taking sedatives or tranquilizers

When Using This Product:
- marked drowsiness may occur
- alcohol, sedatives, and tranquilizers may increase the drowsiness effect
- avoid alcoholic beverages
- use caution when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

Stop Using This Product If:
- nervousness, dizziness, or sleeplessness occurs
- cough is accompanied by fever, rash, or persistent headache
- nasal congestion does not improve in 7 days

Ask a doctor. These may be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help right away.

* Note: Headings are in 6 point type, text is in 6 point type