DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 330, 331, 341, 346, 355, 358, 369, and 701

[Docket Nos. 98N–0337, 96N–0420, 95N–0259, and 90P–0201]

RIN 0910–AA79

Over-The-Counter Human Drugs; Labeling Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing a standardized format and standardized content requirements for the labeling of over-the-counter (OTC) drug products. This final rule is intended to assist consumers in reading and understanding OTC drug product labeling so that consumers may use these products safely and effectively. This final rule will require all OTC drug products to carry the new, easy-to-read format and the revised content requirements within prescribed implementation periods.

DATES:

Effective Date: April 16, 1999.

Compliance Dates: For compliance dates see section V of the **SUPPLEMENTARY INFORMATION** section of this document.

FOR FURTHER INFORMATION CONTACT: Debra L. Bowen, Food and Drug Administration, Center for Drug Evaluation and Research (HFD–560), 5600 Fishers Lane, Rockville, MD 20852, 301–827–2222, or email ''BOWEND@cder.fda.gov''.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of February 27, 1997 (62 FR 9024), FDA proposed to establish a standardized format for the labeling of OTC drug products that included: (1) Specific headings and subheadings presented in a standardized order, (2) standardized graphical features such as Helvetica type style and the use of ''bullet points'' to introduce key information, and (3) minimum standards for type size and spacing. The proposal included an extensive list of ''connecting terms'' that manufacturers may omit from product labeling, and an expanded list of ''interchangeable terms'' to facilitate the use of more concise and easy to understand language in OTC drug product labeling. The agency also proposed to amend several specific warnings, including the required pregnancy-nursing warning, the ''keep out of reach of children'' warning, and the accidental overdose/ingestion warnings, to make these warnings as direct and understandable as possible. Finally, the agency proposed to preempt State and local rules that establish different requirements than those in the proposed rule, to promote a national, standardized format for all OTC drug product labeling.

The agency discussed at length its basis for proposing to improve labeling design (62 FR 9024 at 9027 through 9031). The agency stated that a standardized labeling format would significantly improve readability by familiarizing consumers with the types of information in OTC drug product labeling and the location of that information. In addition, a standardized appearance and standardized content, including various ''user-friendly'' visual cues, would help consumers locate and read important health and safety information and allow quick and effective product comparisons, thereby helping consumers to select the most appropriate product.

The agency reviewed literature studies that confirmed that OTC drug product labeling often lacks the graphical features and visual cues needed to ensure readability and comprehension. These and other studies recommended ways to make labeling easier to read and understand, described the importance of adherence to directions for use, and reported on a number of preventable adverse drug reactions from OTC drug products (see 62 FR 9024 at 9027 and 9028).

The agency also has benefitted significantly in this proceeding from the experience it gained in redesigning food labeling under the Nutrition Labeling and Education Act of 1990 (NLEA) (Pub. L. 101–535, November 8, 1990). The agency's required nutrition labeling panel (§ 101.9 (21 CFR 101.9)) provides a standardized graphic presentation for food nutrients, allowing consumers to judge the significance of the level of a particular nutrient in a product in the context of a total daily diet. Since its implementation in 1993, the agency has received praise from consumers and nutritionists, noting the impact and utility of the standardized food label.

The agency provided over 7 months for interested persons to comment on the OTC labeling proposal, which included an extension of the comment period from June 27, 1997, to October 6, 1997, published in the **Federal Register** on June 19, 1997 (62 FR 33379). In addition, the agency solicited public comment on two labeling studies it conducted. In the **Federal Register** of December 30, 1997 (62 FR 67770), the agency sought comment (until February 13, 1998) on a study entitled ''Evaluation of Revised Formats for Over-the-Counter (OTC) Drugs'' (Study B). Study B consisted of a survey of more than 900 respondents to evaluate consumer preference for design variations in drug labeling formats. In the **Federal Register** of February 13, 1998 (63 FR 7331), the agency solicited comment (until March 30, 1998) on a second study entitled ''Evaluation of Proposed Over-the-Counter (OTC) Label Format Comprehension Study'' (Study A). Study A consisted of a survey of more than 1,200 consumers on the influence of variations in labeling formats on the communication of directions for use and required warnings.

In response to the proposed rule and the publication of Studies A and B, the agency received more than 1,800 comments from health professionals and students, professional organizations, trade associations, manufacturers, consumers, and consumer organizations. An overwhelming majority of the comments supported the agency's initiative to standardize the format of OTC drug product labeling and to make the labeling easier to read and understand by requiring a minimum type size, user-friendly headings, and other well-accepted visual cues.

However, a number of specific points in the proposal generated extensive, and sometimes divergent, comment: (1) Whether pharmacists, nurses, or other health professionals should be specifically referenced in certain of the proposed headings; (2) an appropriate minimum type size for the required labeling information; (3) application of the proposed labeling format to products traditionally marketed in small containers and products marketed as both drugs and cosmetics; and (4) continued reference to Poison Control Centers in the required accidental ingestion warning. These and other comments are addressed at length in section IV of this document.

The agency has considered the information presented in the proposed rule, the comments received, the results from Studies A and B, and all other relevant information, and concludes that the standardized format and content requirements for OTC drug product labeling, as set forth in this final rule, will enable consumers to better read and understand the information presented and apply this

information to the safe and effective use of OTC drug products.

As discussed in the proposed rule, research on reading behavior and document simplification shows that the use of less complex terminology, presented in shorter sentences with an organized or ''chunked'' structure, is likely to improve consumer processing of the information (Refs. 1, 2, and 3). Research also shows that consumers are more likely to engage in behavior that they believe they can successfully complete than in behavior that appears overwhelming (Ref. 4) or that presents a ''cognitive load,'' such as the task of reading densely worded consumer information (Ref. 5).

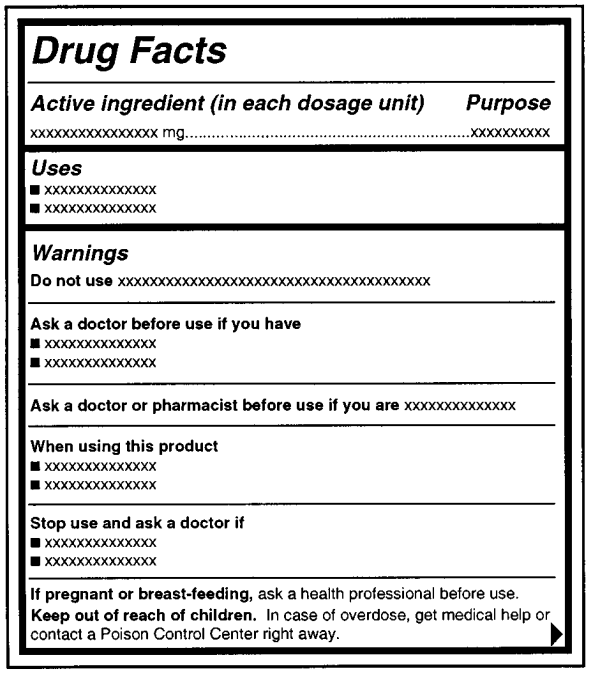
The new OTC drug product labeling is expected to decrease ''cognitive load'' by, among other things, decreasing the memory demands necessary for processing the information. This, in turn, will allow consumers to process the information faster. In addition, the new format offers a more structured, organized, and compact presentation, which places fewer and less imposing processing demands on the reader. The consumer's self-perceived ability to read the labeling will increase significantly and, thereby, result in an improved overall understanding of the information presented. Finally, the new labeling is expected to provide clear signals regarding important information, leading to increased processing and communication of this information.

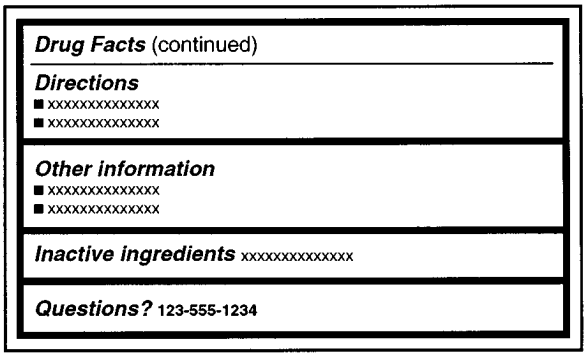
II. Prototype Labeling Based on This Final Rule

An outline of the various labeling provisions for OTC drug products is shown below:

BILLING CODE 4160–01–F

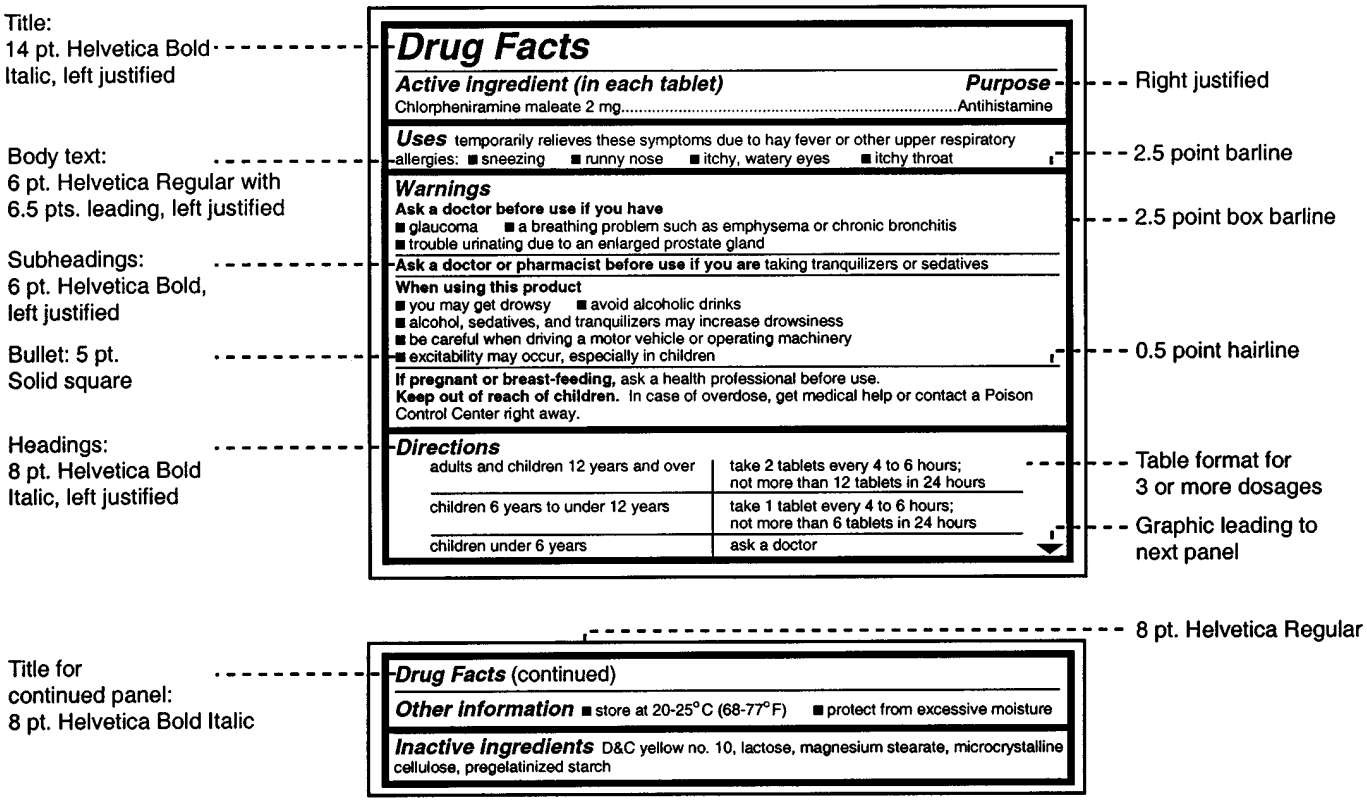
OTC Drug Product Labeling Outline



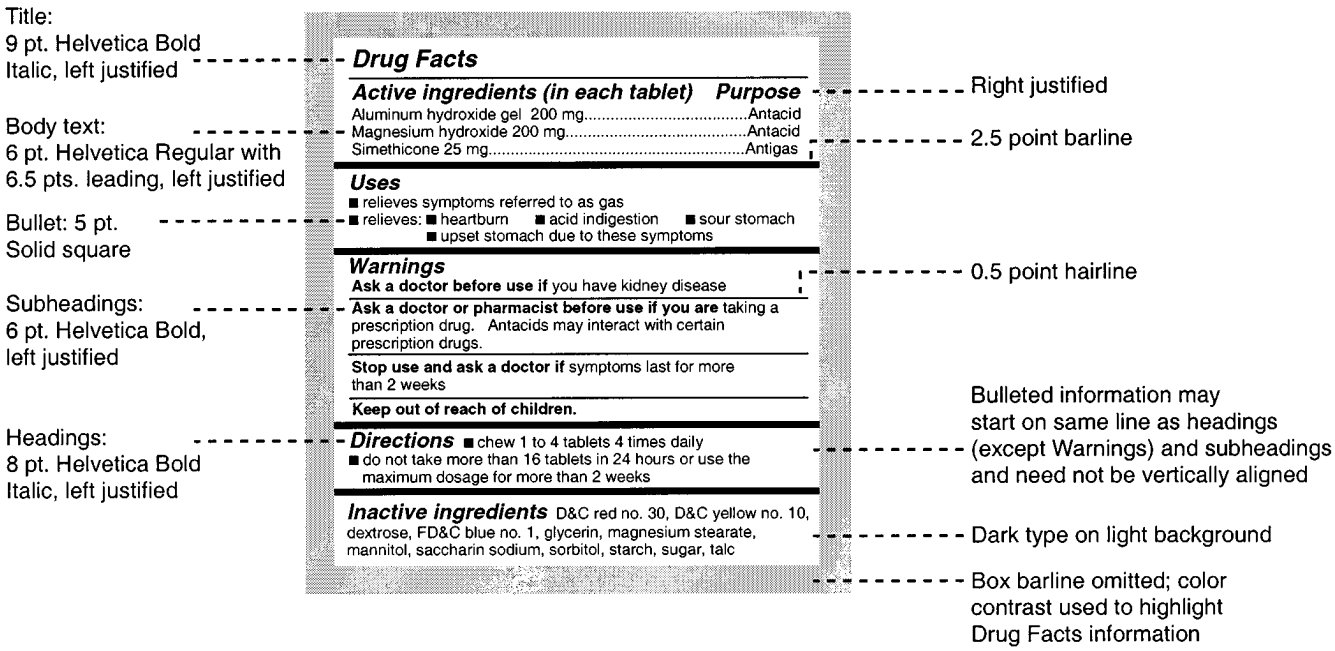


BILLING CODE 4160–01–C

An example of labeling for a single ingredient antihistamine OTC drug product, annotated for illustrative purposes, is shown below. FDA recommends use of the type style and font sizes shown below:



An example of labeling for an antacid OTC drug product, applying the modified, small package labeling provisions in this final rule and annotated for illustrative purposes, is shown below. FDA recommends use of the type style and font sizes shown below:



BILLING CODE 4160–01–C

Examples of prototype OTC drug product labeling are attached in Appendix A of this document. The information in these examples is presented using ordinary package sizes for these types of products. These examples are for illustrative purposes only and are not intended to depict specific products. Some are based on proposed monograph requirements only. Example 1 depicts sample labeling for a single ingredient antihistamine product, using the format and content provisions set forth in this final rule. Example 2 depicts labeling for a combination cough/cold product using the format and content provisions set forth in this final rule. Example 3 demonstrates how the same information shown in Example 2 can be presented directly on the package label for an 8-ounce bottle of syrup, using the small package modifications specified in the final rule. Example 4 depicts a toothpaste that is marketed as a standing tube without an outer carton, using the format and content provisions set forth in this final rule. Example 5 demonstrates labeling for a drug product that is also marketed for cosmetic uses using the format and content provisions set forth in this final rule. Example 5 also demonstrates an acceptable ''similar enclosure'' to a box. Example 6 depicts labeling for a topical acne product that is marketed in a tube and packaged in a carton with a riser, in order to provide additional labeling space. Example 7 depicts labeling for an antacid product, applying the small package modifications.

III. Summary of Studies A and B

Studies A and B tested whether the proposed format improves the readability and understandability of OTC drug product labeling and investigated consumer preference for certain format variations. The studies confirm that the new labeling format will increase communication of OTC drug product information.

A. Study A

Study A examined the influence of labeling formats and the use of selective highlighting on the communication of directions for use and warnings. The study examined two levels of four independent variables in a factorial design: (1) Labeling format (prototypical existing format versus proposed new format), (2) drug type (cough-cold versus pain reliever), (3) the use of highlighting (more versus less emphasis on graphic design features), and (4) consumer attention (divided versus focused). Highlighting, label format, and drug type were varied in the design of the sample product label. Attention (focused or divided) was varied through instructions given to the respondents. Study participants were asked to read a food label, then a drug label to test for divided and focused attention. Half of the participants were told they would be asked questions about both labels (divided attention); the other half were told they would be tested only on the drug label (focused attention) and that the food label was to serve only as reading practice.

The study included 1,202 respondents in 8 geographically distributed shopping malls in the United States, with approximately equal numbers of respondents from each location. Respondents were asked to evaluate the presentation of label information on one OTC drug sample and were asked questions about the labeling to determine their knowledge, opinions, and willingness to read the labeling.

Dependent measures were analyzed using a general linear model analysis of variance. The study demonstrated that the proposed new format took less time and was easier to read and understand than a product that did not follow the new format. Study respondents indicated a general preference for the proposed format and, when their attention was divided, respondents felt more confident in their ability to use the proposed format labeling. When more graphical design features were used, respondents who were instructed to focus on the labeling made more correct product use decisions, compared to respondents whose attention was divided. There were no conditions under which a product with an existing labeling format outperformed the proposed new format.

The results from Study A suggest that consumers who are presented with the new labeling format will be: (1) More confident in their ability to use the information in the labeling, and (2) better able to make correct product use decisions.

B. Study B

This study investigated consumer preferences for format and graphical design variations. The study examined two levels of each of four independent variables in a factorial design: (1) The order of the ''Warning(s)'' and ''Direction(s)'' section (i.e., warnings before directions or warnings after directions), (2) the placement of the ''Active ingredients'' section at the top of the labeling versus bottom, (3) the use of a title as an introduction to the required information (''Medication Facts'' versus no title), and (4) the use of dividing lines between sections (thick versus thin lines).

This study included 904 respondents in 8 geographically distributed shopping malls in the United States, with approximately equal numbers of respondents from each location. The respondents were asked to evaluate 16 labeling variations of either a sample cough-cold or sunscreen drug product. The respondents were also asked to rank the randomly ordered labels from most to least preferred, to specify the reasons for their first and second choices, and to rate a current OTC drug product that did not follow the new format.

The study showed that the presence of a title was the most important factor in determining preference, as participants were more likely to choose labeling with a title than without. When asked why they preferred the label ranked as number one, the respondents indicated that it: (1) Was easy to read, and (2) begins with ''Medication Facts.''

The agency performed a primary conjoint analysis on the preference rankings. A conjoint analysis simultaneously weighs multiple variables and allows for a determination of the relative importance of each particular attribute of a variable, in addition to the level at which each attribute is preferred (SPSS Categories, 1994). Results indicated that, of the four factors examined, title had the greatest impact on rankings, with a utility range from -1.83 for no title and +1.83 for the ''Medication Facts'' title. In this primary analysis, the effect of the other three variables was not significant.

The agency also performed a secondary analysis of the data, to look at differences between variables, independent of context. For labeling with a title, the mean ranks were 6.67 and 10.33 ($Z=-20$, $SD=1.95$, $p<0.001$), clearly confirming that the presence of a title was the most important factor in determining preference rankings. The secondary analysis of the other three format variables showed mean ranks in the middle range (between 8.18 and 8.82, SDs=0.94 to 1.97). However, as stated previously, the primary analysis of these three variables showed that none had a statistically significant influence on preference when the variable was considered in context. Again, the presence of an introductory title proved to be the preferred variable.

IV. Summary and Response to Comments

This section summarizes each section of the final rule and provides the agency's response to comments.

A. Scope (§ 201.66(a))

Section 201.66(a) states that the content and format requirements in § 201.66 apply to the labeling of all OTC drug products. This would include products marketed under a final OTC drug monograph, an approved new drug application (NDA) or abbreviated new drug application (ANDA) under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355), and OTC products for which there is no final OTC drug monograph or approved drug application. Thus, for example, OTC drug products that are the subject of tentative final monographs will, in time, be required to comply with the new labeling requirements.

The proposed rule stated that the new labeling would apply to products that are the subject of a final monograph or an approved drug application. Under both the proposed and the final rule, all OTC drug products in time would be required to adopt the new labeling. The revised wording of the scope provision is consistent with and furthers two central themes of this proceeding. First, the agency has concluded that consistent, standardized labeling of OTC drug products will improve the selection and the safe and effective use of all OTC drug products. Second, all drug products, irrespective of their regulatory status, must bear labeling that is ''likely to be read and understood by the ordinary individual under customary conditions of purchase and use.'' (Section 502 of the act (21 U.S.C. 352(c)).) With all products following the new format, consumers will be able to readily distinguish OTC drug products from other categories of products (such as dietary supplements and foods), make product-to-product comparisons across all therapeutic classes, and will begin to recognize where to find information that is critical to the best use of any OTC drug product. The final rule ensures that by a date certain all OTC drug products will display the new labeling.

The agency has chosen an outside implementation date of 6 years for marketed OTC drug products that are not and do not become the subject of final OTC monographs (see section V of this document). Because most, if not all, drug products undergo at least one major labeling revision every 6 years (see section VIII of this document), the revised scope is not expected to impose any significant additional burdens.

1. Several comments asked that § 201.66 include an express exemption for homeopathic drug products, including those products listed in the Homeopathic Pharmacopeia of the United States. One comment recommended that the labeling requirements should apply to homeopathic drug products to promote their safe use.

Homeopathic drug products generally are subject to the drug provisions of the act, including the misbranding provisions in section 502 of the act, and therefore, the agency has concluded that an express exemption would not be appropriate. However, as emphasized in the proposed rule, the agency's stated policy is that such products ordinarily will not be recommended for regulatory action if the product is a homeopathic drug as described in Compliance Policy Guide 7132.15 entitled ''Conditions Under Which Homeopathic Drugs May Be Marketed'' (62 FR 9024 at 9031), and the product follows the labeling and all other recommendations outlined in that guidance document. By its terms, the policy of generally not recommending homeopathic products for regulatory action will extend to this rule.

B. Definitions (§ 201.66(b))

Section 201.66(b) contains applicable definitions, including explanations of certain printing, typesetting, and graphics terms applicable to this rule. The agency has also added definitions for the terms ''bullet,'' ''title,'' and ''inactive ingredient.'' The definition for inactive ingredient is identical to the definition in the agency's good manufacturing practice regulations in 21 CFR 210.3(b)(8).

C. Content Requirements (§ 201.66(c))

Section 201.66(c) contains the content requirements for the standardized labeling format and states that all information must be organized under the title, headings, and subheadings set forth in paragraphs (c)(1) through (c)(8), and it may contain the information under the heading in paragraph (c)(9), in the order prescribed. This information must appear on the outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper. As discussed below, the agency has amended some of the headings and subheadings and included additional headings and subheadings, including the title ''Drug Facts.''

2. Several comments supported the order for listing information, as prescribed in § 201.66(c). One comment stated that listing active ingredients and their purposes first allows consumers to compare ingredients, avoid certain ingredients for reasons of safety or personal preference, and helps to ensure that products with different active ingredients are not used for the same indication.

Several comments focused on the placement of the inactive ingredient section, with some suggesting that inactive ingredients should be listed separately from active ingredients because the inactive ingredients are of only minor concern to most consumers. Others were opposed to the separation of active and inactive ingredients.

Many comments addressed the relative placement of the ''Directions'' and ''Warnings'' sections. Consumer and professional groups and industry representatives generally preferred that the warnings be presented first, to ensure proper self-selection of the appropriate drug at the point of purchase. A smaller number of comments favored placing the directions first, based on the idea that this section would contain the most important information on the proper use of the product.

As discussed previously in section III.B of this document, the primary statistical analysis performed in Study B did not find a significant respondent preference for the placement of ''Warnings,'' ''Directions,'' and ''Active ingredients.'' Therefore, the order for the placement of information in the final rule is modeled after the decisionmaking process consumers would be expected to follow, and should follow, when selecting and using OTC drug products.

First, consumers need to know what the product is and what it is intended to do. This information often is not apparent from the principal display panel (PDP), especially for combination OTC drug products. This information also is critical to consumers' ability to select the most appropriate product. Therefore, the agency is requiring the listing of the active ingredients and their purposes as the first information presented under the title ''Drug Facts.'' Foremost, the agency believes that consumers need to be able to identify the active drug ingredients, to readily access that information, and to associate the ingredients with their respective purposes.

Next, the consumer needs to select an appropriate product for its intended uses. Therefore, this section, entitled ''Use(s),'' follows the active ingredient and purpose information.

The ''Warnings'' section, which follows the ''Use(s),'' contains information that is relevant to both the product selection decision and to proper use. This section contains information regarding when the product should absolutely not be used, drug-drug and drug-food interactions, when to consult

a doctor or pharmacist before taking the product, possible side effects, and when to stop use and contact a doctor after taking the product.

After a consumer selects an appropriate product, correct administration and dosing is essential. The ''Directions'' section contains dosage and administration information necessary for the safe and effective use of the product. Therefore, this section follows the ''Warnings'' section.

''Other information'' is listed in the next section, for products that need to provide additional information that is important for complete understanding of the product's use, including information for consumers who may be allergic to certain ingredients, such as aspartame, or who restrict the intake of dietary ingredients such as sodium.

The ''Inactive ingredients'' section is listed near the conclusion of the FDA-required information, because some products contain a large number of inactive ingredients. The location of this section will help maintain the systematic presentation of the information listed under the other headings.

Finally, the agency has included a location for a telephone number. The telephone number, if provided, would appear after the header ''Questions?'' (or ''Questions or comments?''), does not need to be a toll-free number, and may include the days of the week and time when someone is available to respond to questions.

As described in section III.B in this document, the agency examined the order of certain headings in Study B, including the relative placement of the ''Warnings'' and ''Directions'' sections and the placement of the ''Active ingredients'' section. When all of the design variables in the study were analyzed simultaneously, the variable placement of these three headings had little relative impact on preference or readability ratings of the entire labeling. The agency selected the order prescribed in § 201.66(c) because it most closely tracks a logical decisionmaking process that would allow for the best selection and best use of OTC drug products.

3. The agency sought comment on whether the new labeling should apply to the immediate container label even if the product is marketed with an outer package or wrapper (62 FR 9024 at 9037 and 9038). Several comments stated that the labeling requirements should not apply to the immediate container, or should be voluntary for the immediate container, when there is an outer package, because space is often especially limited on the container. Some comments supported requiring certain headings in a mandated order, but not imposing the type size and other type style requirements. Others, however, emphasized that the outer carton is often discarded, leaving the immediate container as the sole source for important warnings and dosage information.

For products that are sold with an outer package, the agency encourages manufacturers to try to meet all of the labeling requirements in this rule on the immediate container as well. If the immediate container is too small to meet the format requirements of § 201.66(d)(1) through (d)(9), the agency encourages manufacturers to include the required information as provided in the small package format in § 201.66(d)(10). In addition, manufacturers must include on the immediate container any information that is specifically required by regulation (including an OTC drug monograph) to appear on the immediate container, in the manner described in that regulation or monograph (see, e.g., § 201.314(h)(2) (21 CFR 201.314(h)(2))), requiring Reye's syndrome warning on the immediate container).

1. Title (§ 201.66(c)(1))

Section 201.66(c)(1) requires the title ''Drug Facts'' as the first heading in the standardized format. A title provides an important visual cue for introducing required information. The agency evaluated the use of a title as a graphical design feature in Study B and solicited comment on both the design of Study B and the results of the study. As summarized in section III of this document, respondents in Study B strongly preferred labeling that contained a title, such as ''Medication Facts,'' and considered such labeling to be more credible and reliable than labeling without a title. When the agency analyzed simultaneously the impact of all design variables tested in Study B, the introductory title had the greatest relative impact on preference rankings.

4. The existing regulations governing OTC monograph products allow manufacturers to use titles such as ''FDA Approved Uses'' and ''FDA Approved Information'' to introduce required monograph information. These titles, and the ability to enclose labeling information in a highlighted ''box,'' are available under FDA's ''exclusivity policy.'' Under the policy, manufacturers may include a specified title and box if they follow certain precise or ''exclusive'' language provided by FDA in a final OTC monograph (see § 330.1 (21 CFR 330.1)).

Most manufacturers, however, have preferred to use ''flexible'' language to describe the uses and other information required under the OTC drug monographs. Moreover, the proposed rule itself added more flexibility in selecting language, making it less likely that manufacturers would avail themselves of the labeling features specified in § 330.1. The agency therefore solicited comment on whether to retain the idea of allowing special titles and boxes for manufacturers who follow precise monograph language (62 FR 9024 at 9039).

The agency did not receive substantive comments on this issue. The agency did, however, receive one comment stating that the title ''FDA Approved Uses'' violated section 301(1) of the act and could create confusion between products marketed under new drug applications and similar products marketed under OTC drug monographs. The first issue was rendered moot by the repeal of section 301(1) of the act under section 421 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115), while the second issue was addressed by the agency in the rulemaking for § 330.1(c) (see 51 FR 16258 at 16260 and 16261, May 1, 1986).

The agency agrees, however, that the availability of a title should not be limited to products marketed under OTC drug monographs. The agency also finds, based in part on the strong support for a title under Study B, that consumers would benefit by having a title on all OTC drug products (rather than only on those few products that chose to use certain language specified under an OTC drug monograph). The agency has therefore included a title as part of this final rule to introduce the required information on all OTC drug products. In addition, the agency is revoking the titles and boxed labeling provisions from § 330.1(c).

5. Several comments contended that a title such as ''Medication Facts'' was not specifically discussed in the proposed rule and, therefore, should not be included in this final rule. The comments also contended that this title has not been shown to actually improve consumer use of OTC drug products and would take up too much space.

As discussed, the agency included the title ''Medication Facts'' as a key variable in Study B and provided ample opportunity for interested persons to comment on the design and on the results of the study.

A title on the information panel provides a strong cue to the consumer that important labeling information follows. This is similar to the highly

successful ''Nutrition Facts'' title required on the information panel for food products (§ 101.9). Indeed, respondents in Study B stated that they preferred a label with a title and that they considered the information to be more credible and reliable when introduced by a prominent title.

The agency does not believe that it must prove that the title alone improves consumer use of OTC drug products. A number of factors combined determine consumer use, including format variables, legibility, readability, comprehension, and consumer motivation. It is difficult to separate out the influence of each variable. Nevertheless, it is important to note that when all of the design variables in Study B were considered simultaneously, the title had the most significant impact in determining which label consumers preferred. Overall, a title creates an important, concise visual cue for consumers and serves to reinforce the importance of the information that follows.

The agency has decided to use the title ''Drug Facts,'' in place of the test title ''Medication Facts,'' because the phrase ''Drug Facts'' is short, concise, easy to print in large type, and best signals an OTC drug product. Consumers may use the term ''Medication'' to refer to remedies which may not be marketed as drug products. It is also a four syllable word which requires a higher level of reader comprehension. Consumers, for example, commonly use the term ''drug store'' to refer to a pharmacy. The agency therefore concludes that the word ''drug'' in this title is more precise, readable, comprehensible and, in response to the comments, will require less labeling space.

The title will take up one line of text on each panel that it appears. The previously allowed titles (''FDA APPROVED USES'' and ''FDA APPROVED INFORMATION'') also took up one line of text. Based in part on the results of study data and on the agency's experience with other forms of labeling, the agency concludes that the benefits of having a title outweigh the minimum space required.

2. Active Ingredient(s) (§ 201.66(c)(2))

Section 201.66(c)(2) requires the heading ''Active ingredient(s),'' followed by the established name and the quantity of each active ingredient per dosage unit. For products marketed without a discrete dosage unit, such as topical OTC drug products, the proportion of each active ingredient must be stated instead of the quantity, unless otherwise specified in an applicable monograph or approved drug application.

This provision incorporates a recent amendment to section 502(e) of the act under FDAMA. FDAMA amended section 502(e) of the act to require that the quantity (or the proportion, if determined to be appropriate by the Secretary of Health and Human Services (the Secretary)) of each active ingredient appear in the labeling of all OTC drug products intended for human use. In the proposed rule, the agency provided for the placement and formatting of the quantity of each active ingredient, but requested comment on whether to require all products to include this information. At that time, the agency's regulations encouraged (but did not require) manufacturers to include the quantity per dosage unit in the labeling (§ 330.1(j)). The vast majority of OTC drug products already include such information in their labeling. As a result of the statutory change, this final rule makes clear that the established name and quantity of each active ingredient must be included in the required information set forth in § 201.66(c), in the location and format established by the agency. In an agency guidance document titled ''National Uniformity for Nonprescription Drugs—Ingredient Listing for OTC Drugs (April 1998)'' (Ref. 6), the agency stated that it does not intend to object if manufacturers, packers, and distributors defer relabeling their products to comply with the statutory requirement until the earliest applicable implementation date specified in this final rulemaking document.

6. Several comments favored placing the active ingredient section on the PDP, rather than on another panel. The comments argued that product line extensions (i.e., OTC drug products with the same brand name that contain different active ingredients) invite the need for more prominent placement of the active ingredients. According to these comments, most consumers are able to recognize brand names but are unable to identify the relevant active ingredients. Placement of the active ingredients on the PDP would allow consumers to distinguish products sold under the same brand name.

This final rule requires the listing of active ingredients as the very first information within a clearly defined panel, immediately below a prominent title. This location will enable consumers to quickly and systematically compare ingredients within products for similar uses. In addition, because the respective purposes will be listed next to each active ingredient, consumers will know why the ingredient is in the product. Regardless of placement on the PDP, such uniform and prominent placement will help to ensure proper product selection, especially for product line extensions.

3. Purpose(s) (§ 201.66(c)(3))

Section 201.66(c)(3) requires the heading ''Purpose'' or ''Purposes,'' followed by the general pharmacological category(ies) or the principal intended actions of the drug or of each active ingredient, when more than one ingredient is listed. When an OTC drug monograph contains a statement of identity, the pharmacological action described in the statement of identity shall also be stated as the purpose of the active ingredient. Section 201.66(c)(3) of the final rule does not differ from the proposal.

4. Use(s) (§ 201.66(c)(4))

Section 201.66(c)(4) requires that all OTC drug product labeling include the heading ''Use'' or ''Uses'' followed by the indications for use of the drug product. Section 201.66(c)(4) of the final rule does not differ from the proposal.

5. Warning(s) (§ 201.66(c)(5))

Section 201.66(c)(5) requires the heading ''Warning'' or ''Warnings'' followed by the specific information and subheadings listed in §§ 201.66(c)(5)(i) through (c)(5)(x), as applicable.

7. Several comments requested that the warning ''For external use only'' appear immediately following the ''Warnings'' heading, on the same line of text as the heading. The agency agrees that for topical drug products not intended for ingestion, this warning should appear first. The agency, however, believes that the ''Warnings'' heading should signal the entire warning facts information and, therefore, disagrees with the request to display this statement on the same line as the heading. The agency is also specifying that the placement of the warnings ''For rectal use only'' or ''For vaginal use only,'' where applicable, immediately follow the ''Warning'' heading.

8. The proposed rule would have required certain ingredient-specific warnings, such as the Reye's syndrome warning in § 201.314(h)(1), to be listed first under the heading. Several comments recommended that the agency integrate such warnings into the various subheadings set forth in § 201.66(c)(5). Although the subheadings provide important visual and organizational cues, the agency believes that the warnings listed in § 201.66(c)(5)(ii) of the final rule need to

be given special prominence and should not be combined or grouped with other warnings under a subheading. An effective way to ensure that these special warnings are prominently displayed is to require that they be listed immediately under the ''Warnings'' heading, with a subheading that describes the key aspect of the warning. The agency has incorporated special subheadings for the warnings that will appear in this section. Some of the subheadings appear in current regulations or approved drug applications, and others are being added to provide consumers with signal words that describe the key aspect of the warning statement.

9. One comment suggested that the subheading ''Do not use'' include the word ''if,'' to read ''Do not use if.'' Another suggested listing allergic reaction warnings under this subheading.

The agency disagrees with adding ''if'' to this subheading because conditional words other than ''if'' may be part of certain warnings (e.g., ''on broken skin''). With respect to allergic reactions, the agency considers serious allergic reactions (e.g., immediate hypersensitivity reactions) to be of such importance that it is requiring these warnings to appear immediately under the ''Warnings'' heading, preceded by the subheading ''Allergy alert.''

In the labeling examples included in the proposed rule, the agency showed the prescription monoamine oxidase inhibitor (MAOI) warning under the ''Do Not Use'' subheading. No comments to the contrary were received, and the agency concludes that the warning should appear after this subheading.

The MAOI warning appears in several places in the cough-cold monograph (§§ 341.74(c)(4)(v) and (c)(4)(vi), 341.76(c)(4), and 341.80(c)(1)(i)(D) and (c)(1)(ii)(D) (21 CFR 341.74(c)(4)(v) and (c)(4)(vi), 341.76(c)(4), and 341.80(c)(1)(i)(D) and (c)(1)(ii)(D)). The agency has determined that the words ''Drug Interaction Precaution'' and ''this product,'' which are currently included in these sections, need not appear when the information appears after the new ''Do not use'' heading. Therefore, the agency is including the words ''Drug Interaction Precaution'' and ''this product'' in new § 330.1(j) in this final rule, which lists connecting terms that can be deleted from the labeling of OTC drug products. The MAOI warning would now appear in labeling as follows ''Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) * * * .''

10. The agency received numerous comments on the subheading, ''Ask a doctor before use.'' The agency specifically sought comment on whether the phrase ''or pharmacist,'' as in ''Ask your doctor or pharmacist,'' should be included in OTC drug product labeling and, if so, in what section of the labeling, and for which products (62 FR 9024 at 9039). A majority of the comments supported the inclusion of the pharmacist in OTC drug product labeling. Other comments suggested phrases such as ''other health professional,'' ''other healthcare professional,'' or ''other healthcare practitioner.''

Those comments favoring the phrase ''or pharmacist'' stated that pharmacists often are immediately accessible at the time of OTC drug purchase, are well equipped to provide information regarding benefits and risks associated with OTC drug products, have extensive training, and in many instances have immediate access to patient profiles and prescribing histories. The comments added that when pharmacists do not have enough information about a person's medical condition, or otherwise recognize the need to contact a doctor, they are trained to advise the consumer to speak with a doctor before taking an OTC drug product. Several comments noted that about 60 percent of OTC drug products are purchased in retail pharmacies.

Those supporting phrases such as ''other health professional'' or ''other healthcare professional'' or ''other healthcare practitioner'' stated that for many consumers the primary healthcare provider is a nurse practitioner, clinical nurse specialist, nurse midwife, physician assistant, or other healthcare professional, and not a physician. The comments argued that limiting the reference to ''doctor'' sends the message that only a ''doctor'' is qualified to know about a drug product's benefits, risks, side effects, and precautions.

A few comments stated that a subheading such as ''Ask a doctor or pharmacist before use'' would equate the role of a pharmacist with that of a doctor. These comments contended that pharmacists do not have the same level of knowledge or training regarding patient specific conditions, symptoms, side effects, and concomitant therapies. Further, only a physician is trained in medical history-taking, physical examination, and diagnosis. The comments stated that although a pharmacist may be qualified to help consumers select OTC drug products, a phrase such as ''or pharmacist'' is likely to confuse consumers about the role of their doctor and may seriously and adversely impact health.

This issue was also presented to the FDA's Nonprescription Drugs Advisory Committee at its July 14, 1997, meeting. The committee did not reach consensus whether ''pharmacist'' should be included in the labeling. However, several presenters suggested a specific consultative role for the pharmacist when considering drug-drug and drug-food interactions.

The agency has determined that warnings for persons with certain preexisting conditions (e.g., glaucoma) and symptoms (e.g., cough with fever, rash, or persistent headache) be listed under the subheading, ''Ask a doctor before use if you have,'' and that warnings concerning drug-drug or drug-food interactions be listed under the subheading, ''Ask a doctor or pharmacist before use if you are.'' However, the pregnancy/breast-feeding warning in § 201.63 (21 CFR 201.63) will continue to use the term ''health professional.''

As stated in the proposed rule, the agency recognizes that pharmacists are knowledgeable about OTC drug products. Also, pharmacists are readily accessible to a majority of consumers who purchase OTC drug products and are a valuable resource for general questions. Survey studies submitted to the docket for this proceeding suggest that direct consumer counseling by pharmacists may change initial OTC drug purchasing decisions and may prevent potential adverse events (Refs. 7 and 8). In addition, pharmacists are trained to provide advice about drug-drug and drug-food interactions and often have access to computer data bases which contain (and frequently update) this information. Therefore, the agency concludes that warnings concerning interactions be listed under the subheading, ''Ask a doctor or pharmacist before use if you are.'' The drug interaction precautions in 21 CFR 331.30(d) and 346.50(c)(7)(ii) have been revised to fit this new subheading.

If a consumer has a preexisting disease or clinical symptoms, the agency concludes that the subheading, ''Ask a doctor before use if you have,'' should be retained. The agency has decided not to include the phrase ''or pharmacist'' in this subheading because questions concerning preexisting diagnoses or clinical symptoms are best answered by a healthcare provider who is trained and licensed specifically to make differential diagnoses and to treat disease entities.

The agency has also decided to use only the term ''doctor'' in this subheading, rather than a longer list of

healthcare providers. The agency acknowledges that in addition to physicians, surgeons, and dentists, other licensed professionals play important roles in delivering clinical services directly to consumers and that nurse practitioners and physician's assistants may sometimes serve as primary medical care providers. However, the agency has decided not to endeavor to list each specific practitioner who is licensed and qualified in the clinical practice of medicine and in disease management. For OTC drug products, the term ''doctor'' in this subheading is sufficiently broad and inclusive (Ref. 9).

The agency is retaining the phrase, ''health professional'' in the revised pregnancy/breast-feeding warning in § 201.63(a), which requires, when appropriate, the warning, ''If pregnant or breast-feeding, ask a health professional before use.'' In establishing this warning (47 FR 54750, December 3, 1982), the agency noted that certain health professionals (e.g., physicians, nurses, certified nurse midwives, nurse practitioners, and physician's assistants) may be familiar with problems related to medication use during pregnancy and nursing because they receive specific training in this area and they directly deliver healthcare to women who are pregnant or nursing. As a consequence, for these specific physiologic conditions, these health professionals may be appropriately relied upon as sources of information advising caution concerning drug use while pregnant or nursing. The agency has amended § 201.63(a) in this final rule by requiring that the first four words of the warning appear in bold type, to ensure that this warning is as prominent and conspicuous as the required subheadings.

Finally, the agency is including in this final rule a conforming amendment to the MAOI warning (§§ 341.74(c)(4)(v) and (c)(4)(vi), 341.76(c)(4), and 341.80(c)(1)(i)(D) and (c)(1)(ii)(D)), substituting the words ''doctor or pharmacist'' for the words ''health professional.'' This change is consistent with the respective roles of pharmacists, doctors, and health professionals in assisting consumers of OTC drug products.

11. Several comments recommended consolidating the subheading ''Ask a doctor before use if you have'' (proposed § 201.66(c)(iii)(A)) with the subheading ''Ask a doctor before use if you are'' (proposed § 201.66(c)(iii)(B)), to allow greater flexibility in labeling design.

The subheading ''Ask a doctor before use if you have'' (§ 201.66(c)(5)(iv) in this final rule) cautions consumers about preexisting conditions when consumers should not use the product before a doctor is consulted. The subheading ''Ask a doctor or pharmacist before use if you are'' (§ 201.66(c)(5)(v) in this final rule) cautions consumers about potential drug-drug or drug-food interactions when consumers should not use the product before a doctor or pharmacist is consulted. Organizing or ''chunking'' the information under separate subheadings makes it more likely that the information will be read and understood by consumers who have certain conditions or are taking other drugs.

12. Section 201.66(c)(5)(vi) requires the subheading ''When using this product,'' followed by any side effects that the consumer may experience and the substances (e.g., alcohol) or activities (e.g., operating machinery, driving a car) to avoid while using the product. One comment suggested that because this subheading is not parallel in grammar with the other subheadings, it should read, ''Be aware when using this product.'' Another comment requested that warnings for drugs in dispensers pressurized by gaseous propellants be included under this subheading.

Although the subheading ''When using this product'' is not grammatically parallel with the other subheadings, the phrase ''Be aware'' is implied in the subheading because it appears under the general heading, ''Warnings.'' Consumers are already cautioned that they need to read and take note of the warning information that follows. In addition, the words ''Be aware'' would unnecessarily lengthen the subheading.

The agency agrees with the comment that the warnings for drugs in dispensers pressurized by gaseous propellants (§ 369.21 (21 CFR 369.21), 21 CFR 310.201(a)(11) and (a)(18)) would appear under this subheading.

13. Section 201.66(c)(5)(vii) requires the subheading ''Stop use and ask a doctor if,'' followed by any signs of toxicity or other serious reactions that would necessitate immediately discontinuing use of the product. This subheading, as proposed, read ''Stop using this product if,'' followed by the required warnings, followed by ''Ask a doctor. These may be signs of a serious condition.'' Several comments raised the concern that the ''Ask a doctor'' portion of this warning may be de-emphasized within the proposed labeling format. The agency agrees and has amended the subheading to ensure that consumers are adequately advised to contact a doctor if they experience certain signs of toxicity or other reactions.

The agency has also added to the final rule a ''catch-all'' provision in § 201.66(c)(5)(viii) that directs the placement of any other required warning that does not fit within the categories listed in § 201.66(c)(5)(i) through (c)(5)(vii), (c)(5)(ix), and (c)(5)(x), to appear following the warnings described in (c)(5)(vii).

14. Many comments disagreed with the proposal to eliminate the reference to Poison Control Centers in the accidental overdose/ingestion warning in § 330.1(g), which is incorporated by reference in § 201.66(c)(5)(x) of the final rule. The comments cited several factors, including: (1) Medical professionals may lack complete knowledge about treating an accidental overdose of an OTC drug product; (2) advising consumers to ''get medical help right away'' is likely to encourage consumers to proceed immediately to a hospital emergency room when Poison Control Centers can often help treat such exposures at home; and (3) Poison Control Centers in appropriate circumstances can direct consumers to an emergency provider, inform hospital personnel of a patient's imminent arrival, and provide hospital staff with critical information. One comment indicated that Poison Control Centers now serve the entire U.S. population, 24 hours a day, 7 days a week, providing immediate free advice to consumers and health professionals.

The agency agrees that Poison Control Centers are a valuable resource in the event of an accidental overdose or ingestion of an OTC drug product. Accordingly, the agency is retaining, and adding where needed, the reference to Poison Control Centers in revised § 330.1(g), 21 CFR 369.9, 21 CFR 369.20, §§ 369.21, and 201.314(a) and (g)(1).

6. Directions (§ 201.66(c)(6))

Section 201.66(c)(6) requires the heading ''Directions'' followed by the applicable directions for use.

15. One comment suggested that this heading read ''Follow these directions,'' to give consumers a stronger cue. The agency believes that the heading ''Directions'' is an implicit instruction to not only read the directions for use, but also to follow the directions. Accordingly, the agency prefers the more concise heading.

7. Other Information (§ 201.66(c)(7))

Section 201.66(c)(7) requires the heading ''Other information,'' when appropriate, followed by information that does not fall within any of the other categories in § 201.66(c), but which is required by or is made optional under an applicable OTC drug monograph,

other OTC drug regulation, or an approved drug application.

16. One comment asked whether information regarding proper storage of an OTC drug product must appear under this heading. The agency recognizes that there are space constraints for placement of information on OTC drug product labeling. For products that include United States Pharmacopeia (USP) or manufacturer's storage information in their labeling, this information may be placed under the ''Other information'' heading or outside the ''Drug Facts'' labeling. However, if an OTC drug monograph contains storage requirements (e.g., wart remover drug products in 21 CFR 358.150(c)(3) and corn and callus remover drug products in 21 CFR 358.550(c)(3)), then that information must be included in the ''Drug Facts'' labeling under this heading.

17. Several comments suggested that other required information for OTC drug products (such as the identification of certain inactive ingredients and the required tamper-resistant packaging statement) appear below the ''Other information'' heading. The agency is requiring inactive ingredients to be listed in a separate section. However, required information about certain ingredients (e.g., the sodium content) will appear as the first required statement in the ''Other information'' section. The required tamper-resistant labeling statement (now referred to as ''tamper-evident'' labeling (see 63 FR 59463, November 4, 1998) must be prominently placed to alert consumers about the product's tamper-evident features (see (21 CFR 211.132(c)). The agency will continue to allow flexibility as to where this statement appears in labeling and is not requiring that it be included within the ''Drug Facts'' area. However, if the statement is included in the ''Drug Facts'' area, it should be placed under ''Other information.''

18. The agency also received comments asking whether a ''sell copy'' statement or other promotional information, such as a statement of approval of the American Dental Association, may appear under ''Other information.'' Although promotional copy may be important to the sale of a drug product, it is generally not necessary for the safe and effective use of the product. Therefore, this information may not appear under the ''Other information'' heading or within the ''Drug Facts'' area, but may appear elsewhere in the labeling (e.g., PDP or side or end panel) if otherwise permitted by law.

19. FDA regulations require or will require in the future that certain information about specific ingredients be included in the labeling of OTC drug products. Examples include sodium content (21 CFR 201.64), proposed calcium content (§ 201.72 (21 CFR 201.72)), proposed magnesium content (§ 201.71), proposed potassium content (§ 201.72), and phenylalanine/aspartame content (21 CFR 201.21(b)). The agency did not include a separate heading for such dietary information in the proposed rule. However, the agency requested comment on the appropriate placement of this information. Several comments suggested that a separate heading would help ensure appropriate product selection and reduce health risks associated with certain nutrients. Other comments disagreed with the need for such a heading, arguing that this information can be placed in the ''Other information'' section.

The agency has determined that this information can appropriately appear after the heading ''Other information.'' This information is significant for individuals who monitor their intake of certain nutrients, including persons with hypertension and renal insufficiency, and for persons who want to increase their intake of certain nutrients (e.g., calcium). The agency is requiring this important information to be the first statement under ''Other information'' to draw attention to it. The information will appear as follows: ''each (insert appropriate dosage unit) contains:'' [in bold type] (insert name(s) of ingredient(s) and the quantity of each ingredient), (e.g., sodium 50 mg). The phenylalanine/aspartame content, if applicable, should appear as the next item of information. Additional information that is authorized to appear under this heading shall appear as the next item(s) of information. There is no required order for this subsequent information.

8. Inactive Ingredients (§ 201.66(c)(8))

Section 201.66(c)(8) requires the heading ''Inactive ingredients,'' followed by a listing of the inactive ingredients. If the product is an OTC drug product that is not also a cosmetic, then the established name of each inactive ingredient (any ingredient that is not an active ingredient as defined in § 201.66(b)(2)) shall be listed in alphabetical order. If the product is both a drug and a cosmetic, then the inactive ingredients would be listed in accordance with § 701.3 (21 CFR 701.3). However, because § 701.3 includes format requirements that may not be consistent with this final rule, the agency has enumerated the paragraphs within § 701.3 that would apply to the listing of ingredients in OTC drug products that are also cosmetics. Manufacturers may follow § 701.3(a), which generally requires the listing of ingredients in descending order of predominance, or § 701.3(f), which allows ingredients to be grouped in certain categories. The provisions in § 701.3 in paragraphs (e), (g), (h), (l), (m), (n), and (o) and 21 CFR 720.8, may also apply, as appropriate. The names of cosmetic ingredients are to be determined in the manner described in § 701.3(c).

This final rule incorporates the recent amendment to section 502(e) of the act under section 412 of FDAMA. Section 502(e)(iii) of the act, as amended, authorizes the Secretary to require the listing of the established name of each inactive ingredient in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary, on the immediate container as well, as prescribed in regulations issued by the Secretary. Further, the amendment to section 502(e) of the act provides that if the drug product is also a cosmetic, then the inactive ingredients need not be listed in alphabetical order.

In a guidance document entitled ''National Uniformity for Nonprescription Drugs—Ingredient Listing for OTC Drugs'' (April 1998), the agency stated that it would consider whether to provide an additional opportunity for comment before finalizing provisions implementing new section 502(e)(1)(iii) of the act. Because the final rule essentially codifies the provisions of the statute, and because the final rule requires the listing of inactive ingredients in the same location as that described in the proposal, an additional opportunity to comment is not needed at this time. However, the agency recognizes the possibility that more detailed regulations or guidance on the listing of inactive ingredients may prove necessary. The agency also intends to consider whether to consolidate, to the extent permitted under the act, the requirements for listing inactive ingredients in OTC drug products with the requirements for OTC drug products that are also marketed as cosmetics. Either or both of those initiatives, if they resulted in rulemaking, would provide further opportunities for public comment.

Finally, the agency is not requiring at this time the listing of inactive ingredients on immediate containers when the product is marketed with an outside retail package that includes the required list of inactive ingredients.

9. Questions or Comments? (§ 201.66(c)(9))

Section 201.66(c)(9) identifies where manufacturers may include a telephone number for consumers. The telephone number would appear after the header ''Questions?'' (or ''Questions or comments''), is in a minimum 6-point bold type (but preferably larger), and does not need to be a toll-free number. It is recommended that the days of the week and the times when someone is available to respond to questions also be included. A graphic of a telephone or telephone receiver may appear before the heading.

20. Several comments urged the agency to allot space for the manufacturer's toll-free telephone number in bold Helvetica type. At least one comment also requested the agency to require a telephone number in clear braille over-print, to assist those with impaired eyesight in obtaining usable labeling.

Many OTC drug products already include a section entitled ''Questions or Comments?'' and provide a telephone number. The agency considers this information very beneficial because it provides a place to report concerns after product use and a source to contact when the product is not purchased in a pharmacy. A telephone number also provides a contact for the elderly or visually impaired who may not be able to read the product's labeling, and for individuals who do not use English as a primary language.

The agency has allotted space for a telephone number within the ''Drug Facts'' area. While this labeling is not required, the agency strongly encourages all manufacturers, distributors, and packers to include a telephone number. The agency also encourages the use of a point size greater than 6 to display the information, to help those unable to read 6-point type. Further, the telephone number, if shown, must appear in bold type. As requested by the comments, a Helvetica type style may be used. The agency recommends that the days of the week and the time of the day when a person is available to respond to questions (e.g., Monday to Friday, 9 a.m. to 5 p.m.) also be included. Braille labeling is discussed in comment 43 of this document.

D. Format Requirements (§ 201.66(d))

Section 201.66(d) prescribes the required format for presenting the title, headings, subheadings, and information set forth in § 201.66(c)(1) through (c)(9).

Although the comments on balance strongly support the conclusion that a standardized presentation of information will benefit consumers and health professionals, several comments raised concerns regarding specific features of the format. These concerns included the need to: (1) Further improve readability; (2) maintain internal consistency with respect to periods, spacing, and other type setting features; (3) increase usable labeling space without decreasing readability; (4) provide flexibility to accommodate required information on small packages; and (5) minimize the potential for consumer confusion.

1. Alignment and Punctuation of Headings (§ 201.66(d)(1))

Section 201.66(d)(1) requires that the first letter of each word of the title in § 201.66(c)(1) appear in uppercase. Section 201.66(d)(1) also requires that only the first letter of the first word of each heading and subheading set forth in paragraphs (c)(2) through (c)(9) appear in upper case, and that the title, headings, and subheadings set forth in paragraphs (c)(1), (c)(2), and (c)(4) through (c)(9) must be left justified.

21. Several comments recommended the use of upper case letters only for the first letter of the first word in each heading and subheading to be consistent with conventional rules of graphics and labeling design. The agency agrees that limiting the use of upper case letters to the first word in the phrases in § 201.66(c)(2) through (c)(9) will enhance readability. The agency has incorporated this recommendation into the final rule. The length of the title, however, is sufficiently short to allow the first letter of both words to appear in uppercase without compromising readability. However, when the title appears on additional panels, the term ''(continued)'' will appear in lowercase letters.

22. Several comments recommended that all headings be left justified, rather than centered, to enhance readability. The comments contended that information that is centered may be missed or overlooked, particularly when most of the information presented is left justified. In general, the agency agrees. However, to preserve the association of each active ingredient with its purpose, the agency has retained in the final rule the requirement that the heading ''Active ingredients'' appear immediately adjacent and to the left of the heading ''Purpose(s)'' (§ 201.66(d)(6)).

2. Type Size (§ 201.66(d)(2))

Section 201.66(d)(2) requires that the letter height or type size for the title ''Drug Facts'' must appear in a type size greater than the largest type size used within the ''Drug Facts'' area. The type size for the title ''Drug Facts (continued)'' must appear in no smaller than 8-point type. The headings in paragraphs (c)(2) through (c)(9) must appear in 8-point or greater type, or in a type size that is at least 2-point sizes greater than the text, whichever type size is larger. Thus, if the required information is presented in 7-point type, the headings must appear in at least 9-point type. This will ensure that the headings, which serve as important visual cues, stand out from the balance of the text, while preserving flexibility for manufacturers to use larger type sizes to enhance readability. The subheadings and all of the information described in § 201.66(c)(2) through (c)(9) must appear in at least 6-point type.

23. Many comments, particularly from consumers, urged the agency to adopt the 6-point minimum type size for all required OTC labeling, except for the manufacturer's name and address. Some comments argued that anything less than 6-point type is not readable, especially for elderly consumers. Other comments contended that a 6-point minimum should be required because, if industry is allowed to use anything less than 6-point, smaller type size will become the standard. A study (Ref. 7) was submitted demonstrating that many OTC drug products did not conform with the Nonprescription Drug Manufacturers Association (NDMA) Readability Guidelines (Ref. 10) recommended for use by the industry for OTC drug products.

Manufacturers and several trade associations argued that the 6-point minimum should be optional, to allow flexibility in fitting all of the required information into the proposed format. Manufacturers urged that a 6- point type be used where feasible, but that smaller types (down to 4.5 point) be permitted when necessary. At least one comment claimed that if 6-point type is required, the OTC labeling information would not fit on nearly 33 percent of the branded products and 95 percent of generic products. Data were not submitted to support these figures. The comments also noted that the agency has allowed 4.5-point type for dietary supplements in certain situations.

Upon careful review of the comments and supportive studies and the rationale set forth in the proposed rule (see 62 FR 9024 at 9027), the agency has determined that the type size for required OTC drug product labeling information must be no smaller than 6-point, under the conditions set forth in this final rule, including format

exceptions for small packages as defined in this final rule.

The proposed rule summarized literature studies that demonstrated how important type size is in evaluating readability, as well as the difficulty consumers have in reading OTC drug product labeling because of small type (see 62 FR 9024 at 9027 to 9029). For example, a survey of consumers' ability to read OTC drug product labeling printed with the minimum type sizes recommended by NDMA's Readability Guidelines demonstrated that a significant portion 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. Further, only 48 percent of the public who currently purchase OTC drug products 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 4.5-point type size, with only 32 percent able to read them, and only 63 percent of people under age 51 were able to read the existing (or tested) labels (62 FR 9024 at 9029).

Another study evaluated the ability of persons over 60 years of age to read OTC drug product labeling (Ref. 11). The study found a significant portion of this population cannot adequately read the print on certain existing OTC drug products due to small type size (vertical height) and horizontal letter compression (type style). The study concluded that to maximally enhance readability for this target population, OTC drug information should be presented in a minimum vertical type size of 6.7-point and a letter compression of no more than 39 characters per inch. Recognizing the space constraints in existing labeling, the agency chose to require a minimum type size of 6-point and type styles which ensure letter compression of no more than 39 characters per inch.

Finally, the agency acknowledges that it has allowed 4.5-minimum type size under certain conditions in dietary supplement labeling for small packages (see § 101.36(i)(2) (21 CFR 101.36(i)(2)). In these instances, however, much of the required labeling consists of numerical information regarding the content of the product. With limited exception, this information may be presented in a well-defined tabular format with ample white space to enhance readability. OTC drug product labeling, on the other hand, consists largely of running text, including descriptive information essential to the safe and effective use of the product. This information often occupies one or more full panels of the product's packaging. It also tends to vary considerably from product to product, and is no less important on small packages than it is on larger packages. As a result, OTC drug product labeling places particularly significant demands on the reader. The agency therefore believes that while 4.5 point type may be appropriate in exceptional cases for nutritional information on a dietary supplement product, it is not an appropriate minimum type size for OTC drug products.

The agency recognizes the delicate balance between: (1) The need for the required information to fit within customary labeling and packaging constraints, and (2) the need to ensure that the required information is prominent and readable under customary conditions of purchase and use. The agency believes it has selected type sizes and styles that are consistent with the need for readable OTC drug product labeling by a majority of OTC drug consumers, while at the same time taking into account the manner in which OTC products are marketed and the economic impact posed by setting these minimum requirements (see section VIII of this document).

24. Some comments suggested a sliding scale for type size based on package size, similar to the requirements for dietary supplements and food labeling (§§ 101.9(j)(13) and 101.36(i)(2)). The agency generally supports the approach of requiring larger type sizes and more generous formatting for products marketed in progressively larger packages. There is, however, less of need to develop such an approach for OTC drug products than for food products because the range of package sizes for OTC drug products is much smaller than the range for food packages. Therefore, the agency has focused in this rulemaking on developing minimum requirements suitable for typical OTC drug products. Nevertheless, the agency encourages drug manufacturers to enlarge point size wherever the package may accommodate larger labeling text. To that end, the agency has specified in § 201.66(d)(2) the relative increase in point size for the title and headings when a larger type size is used for the required text.

3. Font, Leading, Kerning, Contrast, and Highlighting (§ 201.66(d)(3))

Section 201.66(d)(3) contains font, leading, kerning, contrast, and highlighting requirements. The agency has determined that at least 0.5-point leading (i.e., the space between two lines of text) is needed to ensure readability. While the proposal would have limited type style to Helvetica, the final rule will allow any single, clear, easy-to-read, type style. The agency notes that san serif type styles have been adopted by at least one trade association as the industry standard. The agency believes that san serif types styles are the most likely to be considered clear and easy-to-read. The agency also is requiring the title ''Drug Facts'' and the ''Drug Facts'' part of the ''Drug Facts (continued)'' title to appear in bold italic print to draw even more attention to the required information panel and, thereby, contribute to the goal of ensuring that consumers are appropriately signaled to read and use the information which follows. The agency is requiring the type to be all black or one dark color, printed on a white or other light, neutral color, contrasting background.

25. Several comments requested that the agency allow the use of any sans serif type style in OTC drug product labeling.

The agency is allowing any single, clear, easy-to-read, type style. Because font styles vary in their stroke weight characteristics (i.e., the thickness of the character of each letter is variable). Helvetica and Univers font styles in particular have consistent and uniform stroke weight characteristics and are both commonly available. The agency therefore recommends the use of either one of these font styles.

26. Several comments requested that only the format layout should be required and not the graphical features (i.e., type size, leading, kerning, and highlighting). If graphical features are required, the comments requested reduced type size and leading.

Based on the discussion in the proposed rule (62 FR 9024 at 9036), the agency has determined that both format layout and graphical features are necessary to ensure that labeling information is conveyed in a manner that enables the consumer to readily notice and comprehend such information. The agency has revised the leading requirement from the proposed 1-point leading to 0.5-point leading in this final rule.

4. Bullets (§ 201.66(d)(4))

Section 201.66(d)(4) specifies the style and format for using bullet points to introduce and highlight statements of information. The bullet style is limited to solid squares or solid circles of 5-point type size and must be presented in the same shape and color throughout the labeling. The use of a solid circle or square will avoid selection of an icon that may have an independent meaning, such as an octagon (stop) or inverted

triangle (caution). This format provides a valuable visual cue for introducing each required ''chunk'' of information, without unnecessarily distracting or confusing the reader. The bullets and bulleted statements under each heading or subheading must be vertically aligned, to ensure visual separation and adequate white space between discrete information chunks. This section also establishes standards for presenting more than one bulleted statement in the same horizontal line of text and for the vertical alignment of such additional bulleted statements.

27. To increase usable labeling space, several comments requested that the agency allow more than one bulleted labeling statement per line and not require that bulleted phrases be separated by at least two square ''ems'' (two squares of the size of the letter ''M''). The agency agrees that allowing more than one bulleted statement per line is an effective way to optimize labeling space. The agency has incorporated this into the final rule. However, if more than one bulleted statement appears on the same horizontal line, each statement must be separated by at least two square ems.

5. Multiple Panels (§ 201.66(d)(5))

The proposed rule would have required that all of the information presented under the ''Warnings'' heading appear in one continuous space, on one panel. As described in the following paragraphs, § 201.66(d)(5) of the final rule provides increased flexibility with respect to the presentation of the required labeling information on more than one panel of the retail package.

28. Several comments requested that the agency allow the warnings section to appear on more than one panel if: (1) Text or a visual graphic such as an arrow leads the consumer to the continuation onto the next adjacent panel, (2) the adjacent panel has an appropriate heading, and (3) there is no intervening copy or symbols. One comment noted that the Universal Product Code (UPC) symbol should not be allowed to interrupt the flow of information in the required OTC drug product labeling.

The agency agrees with these comments. Section 201.66(d)(5) of this final rule provides that the headings, subheadings, and information required under § 201.66(c), including the warnings section, may appear on more than one panel. However, appropriate visual cues must be provided, so that the flow of information is retained. The title ''Drug Facts (continued)'' must appear on each subsequent panel with a graphic such as an arrow, directing the consumer to the continuation of the information on the next panel. The continuation of the required content and format onto multiple panels must retain the required order and flow of headings, subheadings, and information. The UPC symbol may appear on the same panel as some of the information, but must be outside the box or enclosed. Section 201.66(d)(7) provides that graphical images, such as the UPC symbol, and information not set forth in paragraphs (c)(1) through (c)(9) and (d)(1) through (d)(10), may not appear in or otherwise interrupt the content and format required by these parts of the final regulation.

6. Active Ingredient, Purpose, and Warning Headings (§ 201.66(d)(6))

Section 201.66(d)(6) establishes the required format for listing the established name, the quantity or proportion, and the ''purpose'' of each active ingredient. This section also provides that no other text is permitted to appear on the same line as the ''Warning'' or ''Warnings'' heading.

29. Several comments recommended that the agency allow products containing more than one active ingredient with the same purpose to list the purpose only once, adjacent to the listing of the last active ingredient. The agency agrees. However, the presentation must allow the reader to readily associate each active ingredient with its purpose. The agency has incorporated this recommendation into the final rule.

7. Graphical Images and Interruptions (§ 201.66(d)(7))

Section 201.66(d)(7) requires that graphical images, such as the UPC symbol, and any information that is not set forth under § 201.66(c), must not interrupt the required information panel or panels. The UPC symbol may appear on the same panel as required information but must be outside the box or enclosure.

8. Required Lines (§ 201.66(d)(8))

Section 201.66(d)(8) sets forth the placement and style of lines that define the title, headings, subheadings, and information described in § 201.66(c)(1) through (c)(9). The proposed rule requires a horizontal line to separate the information under each major heading (62 FR 9024 at 9036 and 9051). In this final rule, the agency is including more specific requirements for the use of these hairlines and is requiring a barline to set off the ''Drug Facts'' labeling from other information that appears in the labeling.

Under § 201.66(d)(8), a barline must be used to form a box or similar enclosure around the information described in § 201.66(c). Example 7 of the sample labeling in the proposed rule (62 FR 9024 at 9060) depicted the required information surrounded by a hairline forming a box. Also under § 201.66(d)(8), a horizontal hairline extending within two spaces on either side of the ''Drug Facts'' box or similar enclosure must immediately follow the title set forth in § 201.66(c)(1). A distinctive horizontal barline extending to each end of the ''Drug Facts'' box or similar enclosure must provide separation between each of the headings listed in § 201.66(c)(2) through (c)(9). And, a horizontal hairline extending within two spaces on either side of the ''Drug Facts'' box or similar enclosure must immediately precede the subheadings set forth in § 201.66(c)(5), except the subheadings in § 201.66(c)(5)(ii)(A) through (c)(5)(ii)(G).

The placement and style of barlines and hairlines set forth in § 201.66(d)(8) will highlight the information, making it more prominent and easier to read and process. Section 330.1(c)(2) previously provided for the use of a boxed area, in conjunction with titles such as ''FDA Approved Uses'' and ''FDA Approved Information,'' to set off this information from other OTC labeling information. The agency has used the box technique to highlight information in several other notable instances (see, e.g., § 101.9(d)(1)(i)).

9. Directions (§ 201.66(d)(9))

Section 201.66(d)(9) adds the requirement that dosage directions, when provided for three or more age groups or populations, must be presented in a table format. The agency displayed this labeling technique in example 2, 7, and 9 of the proposed rule (62 FR 9024 at 9055, 9060, and 9062 and in the sample cough-cold product used in Study B.

30. Several comments requested that the agency allow flexibility in the arrangement of information under ''Direction(s)'' and not mandate a table format. One comment added that other formats, e.g., running text, can adequately convey the information while maximizing text in a minimal amount of space.

Study A confirmed that consumers are less likely to make a dosing error when dosing information for multiple populations is separated within an easy-to-read table as compared to such information appearing in a paragraph format. Tables are now widely used in the labeling of many OTC drug products, including those marketed

under NDA's and ANDA's. The agency therefore has incorporated into this final rule a requirement that a table be used when dosing information is complex, as when separate dosing instructions are presented for three or more age groups. A text format may be used when there are less than three dosage directions.

10. Small Packages (§ 201.66(d)(10))

Section 201.66(d)(10) establishes a modified labeling format for packages that cannot meet the format requirements of paragraphs (d)(1) through (d)(9).

31. Several comments urged the agency to adopt a broad, blanket small package exemption from the proposed content and format requirements. The comments described small packages as those products that are marketed in unit doses, convenience sizes, samples, minimal net content packages, analgesic products with less than 6 square inches of usable labeling space, uniquely shaped containers (e.g., envelope packaging, which has a front and back panel only), tubes, roll packs commonly used for antacids, some ophthalmic products, a number of drug-cosmetic products, and bottles without an outer carton.

Many comments suggested graphical flexibility to accommodate products marketed in small packages, such as: (1) Use of more than one panel, (2) use of sans serif fonts or more than one font, (3) reduced type size (to 4.5-point), (4) reduced or no leading, (5) interlined spacing such that one line's ascenders do not touch the preceding line's descenders, (6) eliminate hairlines and required bullet spacing, and (7) consolidate warning information. One comment suggested that graduated type size requirements could be adopted depending on the available label space and cited the dietary supplement labeling provisions in § 101.36(c)(6) (amended and recodified at § 101.36(i), effective March 23, 1999 (62 FR 49826, September 23, 1997)). Another comment pointed out that the dietary supplement labeling provisions allow a minimum 4.5-point type size.

Some comments contended that relying on a subjective standard to support an exemption would be inefficient. These comments recommended that a small package be defined as any outer package: (1) Where the total surface area available to bear labeling is less than 12 square inches (including the PDP); or (2) where more than 60 percent of the total surface area available for labeling on the back and side panels must be used to satisfy the ''content requirements'' in proposed § 201.66(c); or (3) that is a trial size package, packet, or single use unit. Some comments proposed that any drug or drug-cosmetic product that meets this definition be exempt from the new format and content requirements, but should still bear all required labeling. Some comments stated that a performance standard, as described in the proposed rule (62 FR 9024 at 9036), has not been established or validated and would be impractical to use for small packages at this time.

The agency agrees that some manufacturers may have difficulty providing important drug information, which is prominent and easy to read, on packages that are irregular (i.e., bottle labels) or small (i.e., unit does). However, the agency also considers the required OTC drug labeling information essential for the safe and effective use of OTC drug products, irrespective of the size or the shape of the package.

Because readability is especially dependent on vertical letter height and letter compression, the agency disagrees that less than 6-point type or letter compression allowing more than 39 characters per inch should be permitted (Ref. 11), even on ''small packages.'' As discussed in response to comment 23 in section IV.D of this document, the agency considers 6.0 type the minimum allowable for OTC drug product labeling.

The agency, however, is including in § 201.66(d)(10) of this final rule several modifications that may be used with packages that are too small to meet the format requirements of paragraphs (d)(1) through (d)(9). Under § 201.66(d)(10), headings may be presented in a minimum 7-point or greater type size. The leading may be adjusted so that the ascenders and descenders of the letters do not touch, rather than the 0.5-point leading required under § 201.66(d)(3). Also, bulleted statements may continue to the next line of text and need not be vertically aligned. Finally, the box or similar enclosure required in § 201.66(d)(8) may be omitted if the headings, subheadings, and information in § 201.66(c)(1) through (c)(9) are set off from the rest of the label by color contrast.

As suggested by the comments, a product will be considered ''small,'' and will be permitted to apply these modifications, if more than 60 percent of the total surface area available to bear labeling on the entire outside container or wrapper, or the immediate container label if there is no outside container or wrapper, would be needed to present FDA required labeling. This consists of the labeling required by § 201.66(c)(1) through (c)(9), in accordance with the minimum specifications in § 201.66(d)(1) through (d)(9) and any other FDA required information for drug products and, as appropriate, cosmetic products, other than information required to appear on a principle display panel. This formula is consistent with the idea that 40 percent of available labeling space is generally reserved for the UPC symbol and PDP (see, e.g., 21 CFR 101.1 and § 201.60 (21 CFR 201.60)).

In determining whether more than 60 percent of the available surface area is needed, the indications listed under the ''Use(s)'' heading must be limited to the minimum required uses allowed under the applicable monograph. Also, for purposes of this rule, the ''total surface area available to bear labeling'' does not include the flanges at the tops and bottoms of cans and the shoulders and necks of bottles and jars. All other surface areas are considered to be ''available to bear labeling.''

32. Several comments stated that the format under the proposed rule would require manufacturers to increase the package or container size of a significant number of OTC drug products. NDMA, for example, reported that a survey of its members showed 33 percent of branded products and 95 percent of private label products could not comply with the proposed format without making some change in package or container size. Some comments also opposed the mandatory use of alternative packaging designs, such as extending a single side panel of a package to increase labeling space, as had been suggested by the agency in the proposed rule (62 FR 9024 at 9036). According to these comments, the cost of adding such packaging features, and the additional environmental waste associated with increasing package size or configuration, outweighs the need to set a minimum 6.0 type size and other minimum format requirements. Several comments made general reference to state ''slack fill'' laws, which prohibit the use of oversized containers to mislead consumers.

Other comments, however, encouraged the use of alternative packaging to ensure that important information is presented in a readable type size with user-friendly visual cues. They emphasized that consumers need the information, and need to be able to read and understand the information, for proper self-selection and self-medication, and that these concerns support the required use of alternative packaging to increase available labeling space.

As discussed in section VIII of this document, the comments that oppose the required use of alternative packaging

design greatly overestimated the number of products that would not be able to accommodate the proposed format within the confines of current packaging. In addition, the modified format authorized under § 201.66(d)(10) of the final rule is expected to enable many small package products to comply without increasing container or package size.

For those remaining products that are unable to accommodate the modified, small package format, a number of design techniques are available to increase labeling space. As suggested in the proposed rule, labeling space can be increased by, for example, extending a single side panel or widening the label affixed to a bottled drug product (62 FR 9024 at 9036). In a survey described in section VIII of this document, the agency found that many products are now marketed with extended panels, peel back or fold out labels, or are otherwise mounted on cardboard cards or placards. These alternative packaging techniques often increase labeling space for promoting the sale of the product and could also be used to accommodate FDA required information. The agency likewise expects that any packaging changes needed to conform to this rule will be sufficiently minimal, and can be done in a manner, as to not render the product misleading under a ''slack fill'' law or similar provision (see, e.g., section 502(i)(1) of the act).

Thus, products that are unable to meet the labeling format described in § 201.66(d)(1) through (d)(9), or the modified format authorized under § 201.66(d)(10), will be expected to be reconfigured to meet the format requirements of this rule. The agency will not routinely grant exemptions or deferrals under § 201.66(e) for products that claim to be too small to meet the requirements of this rule.

Finally, the agency is not requiring manufacturers to increase the size of immediate containers (for those products that are marketed with outside retail packages) in order for the required format to be applied to the immediate container (see 62 FR 9024 at 9037). As stated in response to comment 3 in section IV.C of this document, for products that are sold with an outer package, the agency is encouraging, but not requiring, the use of the modified, small package format in § 201.66(d)(10) on the immediate container.

E. Exemptions and Deferrals (§ 201.66(e))

Proposed § 201.66(e) provided that the required labeling information 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. As explained in the following paragraphs, the agency has eliminated this requirement to give manufacturers more flexibility. In addition, the agency has codified proposed § 201.66(f), Exemptions and deferrals, as § 201.66(e) and has made several changes to make the exemption process less burdensome on manufacturers and on the agency.

33. Several comments recommended that the agency allow the inclusion of a brand name and product attributes anywhere on the information panel as long as they do not interrupt the flow of the required information and as long as the labeling is in compliance with the type size requirements. Several comments requested that the product brand name be the first text allowed on the information panel and that the equivalent of three lines of type be allocated at the top of the panel for a brand name and product attributes such as: (1) Information about dosage form, flavor, the absence of certain ingredients, directions for opening the package, and reference to the importance and benefits of proper use; (2) references to alternative products that are available; and (3) information from organizations endorsing the product. Other comments raised concerns about whether adequate space would be allowed for guarantee statements, signage, and sell copy. Another comment suggested that the space for a brand name and product attributes should be equivalent to the greater of either: (1) Three lines of the minimum size copy across the width of the information panel; or (2) 10 percent of the main information panel, at the option of the manufacturer. The comments maintained that this information is important to consumers for comparative purposes and for identification of products with desired features.

The agency has determined that the required OTC drug product labeling information need not appear as the first information on the back or side panel, provided there is adequate space on the outside container or wrapper for the labeling to conform with § 201.66(c)(1) through (c)(9) and § 201.66(d)(1) through (d)(10). Accordingly, the agency is not including proposed § 201.66(e) in this final monograph. Thus, a brand name and product attributes may appear anywhere on the labeling outside of the boxed area.

34. A number of comments suggested that FDA establish an exemption process other than a citizen petition. The comments contended that the petition process is too slow and burdensome for both industry and the agency, and would cause marketing delays. Some comments suggested a simple notification process when a company is unable to comply with the final rule. The company would notify the agency, a certain time would be allowed for the agency to respond with any objections, and, if no objections were provided, marketing could then proceed.

Section 201.66(e) in this final rule provides that FDA, on its own initiative, or in response to a written request from any manufacturer, packer, or distributor, may exempt or defer, based on the particular circumstances presented, one or more specific requirements set forth in § 201.66(a) through (d), on the basis that the requirement is inapplicable, impracticable, or would be contrary to public health or safety.

The agency agrees that the exemption process need not require a citizen petition. However, the process should be a matter of public record and requests for exemptions must be granted by the agency prior to marketing. Requests for exemptions must be submitted in three copies in the form of an ''Application for Exemption'' to the agency. The requests shall be clearly identified on the envelope as a ''Request for Exemption from 21 CFR 201.66 (OTC Labeling Format)'' and with Docket No. 98N–0337. A separate request must be submitted for each OTC drug product. In addition to the three copies of the exemption request submitted to the agency, manufacturers of a product marketed under an approved drug application must also submit a single copy of the exemption request to their application. Decisions on exemptions and deferrals will be maintained in a permanent file in this docket for public review.

The request for exemption or deferral must: (1) Document why a particular requirement is inapplicable, impracticable, or would be contrary to public health or safety, and (2) include a representation of the proposed label and labeling, including outserts, panel extensions, or other graphical or packaging intended to be used with the product.

35. In the proposed rule, the agency asked for comment on whether there are particular types of products or packages that should be granted a regulatory exemption (62 FR 9024 at 9038). At least one comment, from a trade association, requested that ''drug-cosmetic products,'' and particularly those that do not have a dosage limitation (e.g., antidandruff shampoos, anticaries

toothpastes, antiperspirants, and sunscreens), be exempted from the new labeling requirements. The comment argued that these products do not raise serious adverse event concerns, are not used to treat serious health problems, do not raise serious misuse concerns, do not have the potential for significant new therapeutic uses in the future, and are limited in the space available for other information concerning product attribute labeling. Several comments contended that some drug-cosmetic products are used primarily for their cosmetic effects, and one comment argued that most of the required information on these products consists of ''common-sense'' statements and, therefore, do not need to be subject to this rule.

One comment also argued that drug-cosmetic products must include more mandatory labeling information than other OTC drug products, leaving even less space on drug-cosmetic products for the required format. In particular, the comment stated that drug-cosmetic products, unlike other products, must include a full list of all ingredients (see § 701.3). According to the comment, the proposed format would force this information to be listed on more than one panel, making it difficult for consumers (particularly those who may be allergic to certain ingredients) to find important ingredient information. This comment, however, has largely been superseded by the recent amendment to section 502(e) of the act, which authorizes the agency to require that all OTC drug products bear a full list of ingredients. The final format includes a prominent location for the listing of this information on all OTC drug products, including those that may also be intended for cosmetic uses.

The agency also received comments questioning whether the factual record supports the need to standardize the labeling format for drug-cosmetic products, especially those without a specified dosage limitation. One comment noted that the agency failed to include drug-cosmetic products in its consumer research studies, and that the agency lacks a factual basis for applying this rule to these products.

Finally, several comments provided additional reasons why sunscreens, in particular, should be exempted: (1) The names of sunscreen active ingredients have little meaning to consumers; and (2) the prominent display of words such as ''Active ingredients,'' ''Uses,'' and ''Warnings'' may discourage the use of traditional cosmetic products containing a sunscreen or cause manufacturers to leave out the sunscreen ingredient.

The agency disagrees and finds no basis for including a broad exemption because a product is marketed both as a drug and a cosmetic, because a product does not require a precise dosage limitation, or because the labeling of the product includes ''common-sense'' statements. When therapeutic claims are made for a product, the drug provisions of the act apply to ensure the safety and effectiveness of the drug ingredients, whether or not these products may also be used for other purposes (see sections 201(g)(1) and (p) (21 U.S.C. 321(g)(1) and (p)), 502, and 505 of the act). The agency also does not agree that it lacks a sufficient factual basis for requiring the new format and content requirements on all OTC drug products.

The agency does not believe that consumers should be denied the benefits of the new labeling requirements simply because a product may have both drug and cosmetic attributes. Moreover, under the approach suggested by the comment, a manufacturer who markets a standard sunscreen product for sunscreen (i.e., ''drug'') uses and for moisturizing (i.e., ''cosmetic'') uses, would not be required to follow the new labeling requirements, while a manufacturer whose product is marketed solely as a sunscreen would be required to follow those requirements. Both products, nevertheless, are regarded as drug products and share the intended use of sunburn prevention. The agency is concerned that consumers may be unneccessarily confused if the rule would allow these products to bear markedly different labeling.

The agency also disagrees with the comment that products without dosage limitations do not raise safety issues and, therefore, the agency lacks a rational basis for applying the new labeling requirements to such products. While the agency takes steps to ensure that all OTC drug products are safe for their intended uses, adverse reactions do occur in the categories of products for which a blanket exemption has been requested. For example, certain sunscreen ingredients have the potential to cause photo allergenicity; certain antidandruff ingredients may promote sunburn or cause even more serious events if used for prolonged applications; and fluoride-containing preparations may contribute to fluorosis or may cause acute symptoms in overdose ingestions. Thus, even products that do not require discrete dosage limitations contain ingredients that raise safety risks which the labeling must convey to the consumer.

The agency also disagrees with the suggestion that the required labeling in such products consists of nothing more than ''general common-sense limitations'' such as ''if condition persists, consult a health professional'' or ''if a rash develops, stop use.'' For example, a number of acne medications (which are marketed for both drug and cosmetic uses) contain important warnings for persons who are sensitive to or have a known allergy to salicylic acid. Dandruff products that contain coal tar likewise must bear important drug-drug and sunburn warnings (see 21 CFR 358.750). In any case, the agency does not accept the argument that ''common-sense'' precautions need not be prominent and readable. However, the agency will continue to consider whether required labeling for these products can be simplified and condensed even more.

The agency has an ample factual record, discussed elsewhere in this document and in the proposed rule, to support the conclusion that current labeling conventions are inadequate. The act requires readable and understandable labeling, irrespective of a specific showing of harm. The agency endeavors to require the least amount of information possible to assure proper self-selection and use. Nevertheless, the information the agency does require under the act must be prominently and conspicuously displayed (section 502(c) of the act) and must be readable and understandable to ensure that all material facts are provided to consumers (sections 201(n) and 502(a) of the act). Moreover, improved labeling is needed not only to address potential safety issues, but also to ensure selection of the most appropriate product and use of that product in an effective manner.

With respect to whether sunscreen ingredient names have little meaning to consumers, the same argument can currently be made for many OTC drug active ingredients. The new format requires prominent listing of the active ingredients for all products, together with the purpose of each active ingredient. The agency believes that this element of the new format will improve consumer understanding of the names and purposes of active drug ingredients, including those typically used in sunscreens. This will assist the consumer and pharmacist in identifying changes in formulation (and purpose) of many combination OTC drug products so that medication errors can be avoided and consumers can appropriately self-select an OTC drug product for their condition(s).

The agency also emphasizes that with drug-cosmetic products, self-selection is

very important because consumers often must choose between a cosmetic or a drug-cosmetic product. A consumer who has dandruff should select an antidandruff-conditioner shampoo rather than a conditioner shampoo; a consumer who wishes to prevent sunburn should select a sunscreen-moisturizer rather than a moisturizer; a consumer who perspires heavily should select an antiperspirant-deodorant rather than a deodorant; a consumer who needs to prevent caries should select a fluoride toothpaste rather than a nonfluoride toothpaste. This final rule provides a format for presenting information that will allow consumers to readily distinguish among seemingly similar products and to readily access important drug information.

The agency agrees that there may be limited instances in which a labeling requirement may discourage manufacturers from marketing certain products for a drug use (e.g., lipsticks containing sunscreens or lip balms containing skin protectant ingredients). These products, when they contain an ingredient intended to provide a therapeutic effect, do provide significant public health benefits to consumers.

When developing drug labeling, the agency considers the risks and benefits of the drug, the intended use, and the need to communicate limitations or restrictions about the use of the product to the target population. The quantity and complexity of information which must be communicated to ensure appropriate product selection, convey the effectiveness of the drug, communicate risks, and provide complete directions for use, varies with the drug ingredient, the target population, the disease or symptoms the product is intended to treat or prevent, and related information about the conditions which must be provided for the safe and effective use of the drug.

In some cases (e.g., lipsticks or lip balms containing sunscreen), minimal information is needed for the safe and effective use of the product. Such products may typically be packaged in small amounts, have a high therapeutic index, carry extremely low risk in actual consumer use situations, provide a favorable public health benefit, require no specified dosage limitation, and require few specific warnings and no general warnings (e.g., pregnancy or overdose warnings). The agency will identify products with these characteristics and will consider appropriate exemptions in their respective monographs and drug marketing applications to the extent possible. In addition, under new § 201.66(e), FDA, on its own initiative, or in response to a written request from any manufacturer, packer, or distributer, may exempt or defer one or more specific requirements set forth in § 201.66 (a) through (d).

36. One comment noted that OTC drug product labeling varies among different countries, particularly for products that are considered drug-cosmetics in the United States but are regulated as cosmetics in other countries. The comment contended that these variations make it difficult to label products intended to be sold in more than one country. The comment pointed out that FDA is increasingly focused on international harmonization as a matter of policy. However, requiring products to meet the new OTC labeling content and format requirements represents a barrier to trade and harmonization. Another comment requested that FDA exempt OTC drug products intended for export from the new labeling requirements.

The agency disagrees with these comments. As discussed, sound public policy and the dictates of the act require that drug-cosmetic products present readable, understandable, prominent, and conspicuous drug labeling. With respect to export issues, section 802 of the act (21 U.S.C. 382) sets forth those instances in which exported drug products are not required to be labeled in accordance with the requirements for domestic marketing. The agency notes that an OTC drug product exported in accordance with section 802 of the act would not be required to meet labeling requirements for domestic marketing (such as the requirements imposed by this rule), except to the extent that the import country itself has adopted U.S. requirements (see section 802(b)(1) and (f) of the act).

F. Interchangeable and Connecting Terms (§§ 201.66(f) and 330.1(i) and (j))

Section 201.66(f) permits specific terms codified in § 330.1(i) (''interchangeable terms'') to be used interchangeably in the labeling of OTC drug products, provided such use does not alter the meaning of labeling established in an applicable OTC drug monograph or regulation. Section 201.66(f) also permits the terms listed in § 330.1(j) (''connecting terms'') to be deleted from the labeling of OTC drug products, provided again that such deletion does not alter the meaning of established labeling. However, the title, headings, and subheadings listed in § 201.66(c)(1) through (c)(9) cannot be changed through the use of interchangeable or connecting terms.

Proposed § 330.1(i) has been modified in the final rule to include 43 additional interchangeable terms. In addition, two of the proposed terms were combined and seven others were modified slightly in this final rule. (See § 330.1(i)(12), (i)(16), (i)(48), (i)(49), (i)(52), (i)(54), (i)(68), (i)(69), and (i)(72).)

Although the agency specifically sought recommendations on additional connecting terms that should be added to the list (62 FR 9024 at 9039), no terms were submitted. Proposed § 330.1(k) has been redesignated as § 330.1(j) in this final rule and modified to include seven additional connecting terms based on further analysis of OTC drug monograph labeling. The agency recognizes that there may be other connecting terms that can be deleted and that will help required statements and clauses fit into the new format. The agency encourages manufacturers, packers, and distributors to submit these terms to the agency as soon as possible so this list can be further amended before the implementation dates for this final rule.

37. One comment requested that an interchangeable term be added to accommodate products intended for use only in children under 12 years of age, because the information should be directed to the child's guardian or care giver.

The agency agrees that for products intended for use only in children under 12 years of age the information should be directed to a care giver, rather than to the child. Accordingly, for such products, the term ''the child'' may be interchanged with ''you'' or the term ''the child's'' may be interchanged with ''your.''

G. Liable to Regulatory Action (§ 201.66(g))

Section 201.66(g) states that an OTC drug product that is not in compliance with the format and content requirements is subject to regulatory action. The wording in § 201.66(g) of the final rule is changed slightly from the proposal, but the meaning remains the same.

H. Flexibility for Uses (§ 330.1(c)(2))

Section 330.1(c)(2) retains flexibility of labeling for the OTC drug product's ''Uses'' section by allowing alternative truthful and nonmisleading statements describing those indications for use that have been established in an applicable OTC drug monograph. The agency, however, is shortening and simplifying the previous labeling requirements in § 330.1(c)(2). This reflects the decision to require the title ''Drug Facts'' and the boxed or similar enclosure format for all OTC drug products, in place of the ''Approved Uses'' or ''Approved Indications'' title and format. The

agency is consolidating into a new § 330.1(c)(2) the ''exact language'' requirement currently in § 330.1(c)(2)(vi) for language (other than indications) established and identified by quotation marks in an applicable OTC drug monograph or by regulation (e.g., § 201.63), except as provided in § 330.1(i) and (j). A number of comments expressed their support for the existing flexibility policy, which is being retained in this final rule.

I. Miscellaneous Comments

38. Several comments requested that OTC drug product labeling include information on: (1) When to take the drug, e.g., morning or night, before or after meals; (2) whether the drug can be taken with liquids; (3) whether analgesics or antibiotics interfere with effectiveness; and (4) a warning to the elderly that a smaller dosage may be needed. The comments argued that these facts should be in the labeling because many consumers may not ask, and some health professionals do not provide, this information.

The agency notes that this information is currently included in OTC drug product labeling when the information is known and when it is considered to be necessary for the safe and effective use of the product. For example, labeling for an OTC drug product containing naproxen sodium includes information on how to reduce the dosage for the elderly. The labeling for acid reducer products indicates how the drug should be taken in relation to foods or beverages. In addition, the warnings section for OTC analgesic products must indicate when particular drinks (e.g., alcohol) or substances (e.g., caffeine) should be avoided while taking these products.

39. Several comments recommended that OTC drug product labeling should state how long a drug remains in the body.

The agency believes that information about how long a drug remains in the body is important. However, it is difficult to state the actual time that a drug remains in the body in terms meaningful to consumers because of the variability of metabolism in individuals and because the time may vary depending on whether the drug is taken with or without food. Instead, when known and when relevant, the agency requires labeling that tells consumers when to redose, the maximum number of doses to take per day, and which drugs or foods to avoid to obtain maximum effectiveness and safety in the use of their OTC drug products.

40. Several manufacturers requested that FDA allow voluntary warnings to appear under the appropriate headings to further protect consumers from possible misuse of the product. Otherwise, placement of such information outside of the headings could create the impression that these warnings are less or more important than the required warnings.

The agency encourages manufacturers to discuss with the agency the addition of voluntary warnings to OTC drug products. As a general matter, FDA agrees that consumers may be confused if an appropriate warning were placed outside of the Drug Facts area. Thus, the agency expects such warnings to appear under the ''Warnings'' heading, preceded by an appropriate subheading.

41. In the proposed rule, the agency invited 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 (62 FR 9024 at 9035 to 9036) as requested by a citizen petition (Ref. 12).

The agency evaluated the petition and concluded in a letter dated April 22, 1997 (Ref. 13) that the expiration date should be readily seen under usual and customary circumstances but did not require that it be placed in a specific location in the labeling. Comments to the proposed rule provided no new information for the agency to revise this conclusion.

42. Several comments were uncertain about whether the proposed rule would affect the PDP. This final rule does not affect the PDP requirements set forth in § 201.60, and 21 CFR 201.61 and 201.62.

43. Several comments requested that products with multilingual or braille labeling be exempted from the requirements of the final rule because space is not available on these labels to follow the requirements.

Current regulations (21 CFR 201.15) set forth the requirements for using foreign languages in labels and labeling. (Although analogous to multilingual labeling, braille is not specifically addressed in current regulations.) The regulations provide that ''No exemption depending on insufficiency of label space, as prescribed in regulations promulgated under section 502(b) or (e) of the act, shall apply if such insufficiency is caused by: * * * The use of label space for any representation in a foreign language.'' When multilingual or braille labeling is used, the agency considers it important that all labeling on the package be readable and understandable because it is not known which language the purchaser will use. Therefore, the agency will not categorically exempt multilingual or braille labeling from the new format.

44. Several comments recommended that the agency continue to permit voluntary use of symbols or pictograms in addition to required warning language. Some stated that symbols and pictograms may confuse consumers because they may have different meanings for different people. One comment recommended that if pictograms are used, USP pictograms should be adopted.

The use of symbols and pictograms will remain voluntary, provided their use is not a substitute for required OTC drug product labeling. In addition, a symbol or pictogram that directs attention away from required information, or one that is ambiguous or can be misunderstood by consumers, may render the product misbranded. The agency is allowing voluntary use of a telephone or telephone receiver in § 201.66(c)(9).

45. One comment recommended field testing new OTC drug labels to: (1) Assist in the development of criteria that define good OTC drug labeling; and (2) confirm, with representative consumer groups, that the new labels are readable, understandable, and cause the desired drug use behavior.

The agency agrees. Over the past several years, the agency has approved OTC drug product labeling, similar to the format required in this final rule, for new drugs that have moved from prescription to OTC marketing status. This labeling often is field tested by manufacturers under OTC usage conditions, and is presented to the agency in supplemental ''switch'' applications. The agency has incorporated in this rule content and format elements that have emerged through that process. Studies A and B (see section III.A and B of this document) also involved field testing which led to refinements of earlier labeling prototypes.

J. Reporting Requirements

Products that are marketed under an OTC drug monograph are not required to submit labeling to the agency for preapproval. However, if manufacturers have questions about how to implement the new requirements, they are encouraged to seek FDA guidance from the Division of OTC Drug Products.

Labeling changes to an OTC drug product marketed under a NDA or ANDA must be made in accordance with § 314.70 (21 CFR 314.70). Manufacturers of these products are also encouraged to seek agency guidance.

46. The agency specifically requested comment on whether labeling changes

required by the rule, for products marketed under approved applications, should be made under § 314.70(b), (c), or (d), and whether these changes should require agency preapproval (62 FR 9024 at 9042).

Several comments stated that the changes should be considered ''editorial'' or ''minor.'' The comments contended that the rulemaking itself takes the place of approving product-specific supplements, and that the filing of a supplement would impose an unnecessary burden. One comment favored preapproval supplements as the appropriate mechanism, because close collaboration between the agency and drug sponsors will be needed to ensure that final OTC drug product labeling meets the requirements of the new rule. Another comment argued that the appropriate process under § 314.70 would vary from product to product depending upon the nature and extent of the changes needed.

The agency agrees that it should not single out one process because the nature and extent of the changes needed to conform to the new format and content labeling requirements will vary depending on the product class and uses. The agency expects, however, that the majority of the changes required by this final rule can be submitted under § 314.70(d)(3). Section 314.70(d)(3) would cover any labeling changes that precisely follow § 201.66(c) and (d) and that require editorial changes specified in § 330.1(i) or (j). All other labeling changes would be submitted under § 314.70(b)(3) or (c)(2), as appropriate. However, most changes to required content beyond those specified in § 330.1(i) or (j) are expected to require preapproval under § 314.70(b).

K. Implementation Plan

47. Several comments urged that the time allowed for implementation of a final regulation on OTC drug labeling be extended to 3 years, with one comment urging an extension to 4 years. The comments argued that the number of product lines and stock keeping units (SKU's) involved creates a tremendous workload, especially in the case of private label manufacturers who may have to change hundreds of labels and must obtain approval of changes from their clients. One comment presented data intended to show that incremental costs to comply with a final rule in 2 years would be $140 million but would drop by half to only $70 million for a 3-year implementation date. No cost data were presented for a 4-year implementation date.

The final implementation plan, set forth in section V of this document, generally retains a 2-year implementation period for currently marketed products that are the subject of final monographs or approved drug applications. An additional year is allowed for low volume products. The economic basis for retaining this implementation plan is discussed in section VIII of this document. In addition, an outside date of 6 years from the effective date of this rule, or the next major labeling revision (whether required or voluntary) after the rule has been in effect for 2 years, whichever comes first, is set for all marketed OTC drug products (except those marketed under final monographs or approved drug applications) to comply with the new format and content requirements.

The plan is intended to minimize the economic burden on the industry while providing consumers with the benefit of more readable and understandable OTC drug product labeling at the earliest feasible date. As discussed in section VIII of this document, this implementation plan provides manufacturers with sufficient time to design and print new labeling and to deplete existing stock. Products that do not comply with the format and content requirements in this final rule on or after the applicable implementation date may be considered for regulatory action. The agency will review and, as needed, initiate steps to revise existing statements of enforcement policy to be consistent with this final rule document.

L. Preemption

In the proposed rule, the agency tentatively concluded that State and local laws that would establish different or additional format or content requirements than those in the proposed rule should be preempted (62 FR 9024 at 9041 to 9042). The agency is not finalizing the proposed preemptions sections (proposed § 201.66(h) and (i) as a result of a recent amendment to the act under FDAMA.

48. The agency received a significant number of comments supporting the proposed preemptive effect of the labeling requirements. Several comments suggested that the agency extend the scope of the preemption and preempt State requirements on safety and efficacy, dosage form, and packaging.

Subsequent to the issuance of the proposed rule, Congress enacted section 412(a) of FDAMA, which added to the act section 751 (21 U.S.C. 379r), titled ''National Uniformity for Nonprescription Drugs.'' Section 751(a) of the act provides that no State or political subdivision of a State may establish or continue in effect any ''requirement'' that relates to a nonprescription drug that is ''different from or in addition to, or that is otherwise not identical with'' a requirement under the act. A ''requirement'' that relates to a nonprescription drug is defined in section 751(c)(2) of the act as ''any requirement relating to public information or any other form of public communication relating to a warning of any kind for a drug.'' Similar to the preemption provision in the proposed rule, section 751(b) of the act establishes a process by which a State or political subdivision may seek an exemption from the preemptive effect of section 751(a) of the act.

Section 751 of the act also addresses the two issues on which FDA had specifically requested comment, i.e., the preemptive effect of the proposed OTC drug product labeling requirements on product liability lawsuits and the preemptive effect of the proposed labeling requirements on State initiatives such as California Proposition 65. On the issue of product liability suits, section 751(e) of the act states that ''[n]othing in [section 751] shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State.'' On the issue of whether the proposed labeling requirements preempt State initiatives, section 751(d)(2) of the act specifically provides that the national uniformity requirements in section 751 ''shall not apply to a State requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997.''

This amendment to the act supersedes the agency's proposed regulation preempting State and local labeling requirements. The agency, therefore, has removed the preemption provision from this final rule and will, at this time, rely on the terms of the statute in addressing preemption issues.

M. Comments on Studies A and B

49. Two comments stated that it is generally accepted by industry and by experts in label readability that a format that includes a standard order of information, standard headings, bullet points, and interchangeable terms is superior to the ''old'' format. However, the comments maintained that the results of Studies A and B should be given little or no weight in FDA's deliberations because these studies covered only a small segment of all label readability issues.

The agency agrees that a number of format variables can affect readability,

and that Studies A and B did not evaluate all format variables that affect readability. The agency has been mindful of the limitations of these studies in its deliberations. Indeed, all of the significant conclusions in this proceeding have been informed by data gathered from a variety of sources. In addition to the two studies, the agency has considered and relied upon information provided by comments, information gathered from the leading literature on label design, graphics, and readability, and information drawn from the agency's own expertise in drug labeling.

50. The comments requested that the agency provide an extension to the comment period for Studies A and B. The comments also requested that the agency provide its analyses of the studies for public comment.

The agency provided two 45-day comment periods for these studies (see section I of this document). In order to facilitate public comment, the agency also made available in electronic format all of the data collected for these studies, including full tabulations of the data organized along key variables. The agency's summary analyses for these studies are contained in this document and an expanded review will be placed on file in the Dockets Management Branch (Ref. 14).

In light of the opportunities for comment already provided on the design and outcome of the studies, and the extent to which the agency in the end relied on the studies, the agency disagrees that there is a need for one more opportunity for comment.

51. One comment stated that the data from Study A are irrelevant to whether the proposed new OTC labeling is necessary for ''drug-cosmetic products,'' because no such product was evaluated in the study. The comment contended that consumer research concerning OTC analgesic and cough-cold drug products is not relevant to drug-cosmetic products. The comment urged the agency to undertake consumer research relevant to drug-cosmetic labeling, taking into account the differences between OTC drug products and OTC drug-cosmetic products.

For several recent prescription-to-OTC switches of drug-cosmetic products, the agency has observed labeling comprehension results similar to that seen in Study A. The results of several of these studies have been presented and discussed at open public advisory committee meetings (e.g., Rogaine). Given this experience, the agency believes that the findings from Study A can be applied to all OTC drug products, including those marketed as drug-cosmetics.

Study A evaluated the influence of label format, comparing the existing style formats to the proposed new format. This comparison demonstrated that the new format takes less time to read and helps people make better product use decisions. This comparison also found that consumers preferred the new format to the existing format. The agency believes that these findings would not differ if the product were marketed as a drug-cosmetic because the drug information would appear in the ''Drug Facts'' labeling format (see also comment 35 section IV.E of this document).

Study A also evaluated how the amount of information affected the time it takes to find information needed to answer specific questions. This was done by examining two drug types, a three-ingredient cough-cold product and a single-ingredient analgesic. The study demonstrated that the greater the amount of information, the longer it takes to find relevant information in the labeling. Again, although a drug-cosmetic was not evaluated in Study A, there is no reason to expect the results to be different if the product were a multi-ingredient drug-cosmetic versus a single ingredient drug-cosmetic.

Finally, Study A evaluated the influence of highlighting, or graphic design emphasis, on communication of important OTC drug product labeling information. The results showed that more, compared to less, highlighting helped participants make correct product use decisions when there is a large amount of information in the labeling. Labeling with more highlighting was also considered more useful. The agency considers the use of highlighting equally applicable to drug-cosmetic products that contain a large amount of information in the labeling.

52. One comment maintained that Study B is flawed in design and rationale because of its complexity and its intention to use consumer preferences as indicators of important labeling elements. The comment stated that the order of information should not be determined by consumer preference.

The agency carefully designed the protocol for Study B and solicited public comment on the design prior to initiating the study. The agency agrees, however, that consumer preference should not be the sole determinant of labeling design or information (Ref. 15). Thus, the final order and placement of label information in this rule is intended to follow a logical decisionmaking process that assists the consumer in the appropriate selection and use of OTC drug products.

However, Study B clearly indicated that the presence of a title for OTC labeling information was the most important factor in determining preference rankings. Consumers are the ultimate users of the OTC drug product labeling. They stated that they preferred the title because it drew their attention to the required information and made the required information appear more credible. The agency considers such unequivocal consumer input very important and useful in the design of OTC drug product labeling format.

53. One comment stated that because inactive ingredients were not included in Study B and because the terms for the active ingredients were not authentic, there was no way to determine whether these omissions or fabrications would have any impact on consumer label preference.

The agency used fabricated names for the active ingredients to reduce the influence of preconceived knowledge about specific OTC drug products. Because new drug ingredients are novel to consumers when these products first enter the marketplace, use of novel names for active ingredients would simulate this condition. The agency has no reason to believe that not including inactive ingredients or using fabricated names for the active ingredients influenced consumer preference in Study B.

V. Final Implementation Plan

The applicable implementation dates vary according to the regulatory status of the product. Any product that does not comply with this final rule as of the applicable implementation date may be considered for regulatory action. The agency will review and, as needed, initiate steps to revise existing statements of enforcement policy to ensure consistency with this implementation plan.

A. Products in the OTC Drug Review

Products marketed under final OTC drug monographs must comply with this rule as of April 16, 2001. Products for which a final monograph becomes effective on or after April 16, 1999, must comply with this rule as of: (1) The applicable implementation date for that final monograph, (2) the next major revision to any part of the label or labeling after April 16, 2001, or (3) April 18, 2005, whichever occurs first.

Combination drug products in which all of the active ingredients are the subject of a final monograph or monographs must comply with this rule as of April 16, 2001. Combination

products in which one or more active ingredients are the subject of a final monograph, and one or more ingredients are still under review as of the effective date of this rule, must comply with this rule as of the implementation date for the last applicable final monograph for the combination, or as of April 16, 2001, whichever is earlier. Combination products in which none of the active ingredients is the subject of a final monograph or monographs as of the effective date of this rule, must comply with this rule as of: (1) The implementation date of the last applicable final monograph for the combination, (2) the next major revision to any part of the label or labeling after April 16, 2001, or (3) April 18, 2005, whichever comes first.

B. Products Marketed under NDA's and ANDA's

Products that are the subject of an approved drug application (NDA or ANDA) before April 16, 1999, must comply with this rule as of April 16, 2001. Products that become the subject of an approved marketing application (NDA or ANDA) on or after April 16, 1999, must immediately comply with this rule.

C. Additional Provisions

Any OTC drug product not described in section V.A. and B of this document must comply with this rule as of: (1) The next major revision to any part of the label or labeling after April 16, 2001, or (2) April 18, 2005, whichever occurs first.

Products (including combinations) marketed under a final OTC drug monograph or monographs, or under an approved drug application (NDA or ANDA), with annual sales of less than $25,000, must comply with this rule as of April 16, 2002. This is intended to provide marketed products with a low level of distribution an additional year to come into compliance with this final rule.

Finally, irrespective of the regulatory status of the product, the agency strongly encourages all manufacturers, distributors, and packers of OTC drug products to voluntarily implement the new content and format requirements as soon as possible, particularly when existing labeling is exhausted and relabeling would occur in the normal course of business. The agency also encourages sponsors of products marketed under NDA's and ANDA's to submit any required labeling supplements as soon as possible, to ensure timely review.

Provided below is a chart that summarizes the time periods within which the various categories of marketed OTC drug products must be in compliance with this final rule. Unless otherwise stated, all time periods begin on the effective date of this final rule.

TABLE 1.—IMPLEMENTATION CHARTS

Products	Time Periods
Single entity and combination products subject to drug marketing applications approved before April 16, 1999.	Within 2 years (or within 3 years if annual sales of the product are less than $25,000).
Single entity and combination products subject to drug marketing applications approved on or after April 16, 1999.	Immediately upon approval of the application.
Single entity products subject to an OTC drug monograph finalized before April 16, 1999.	Within 2 years (or within 3 years if annual sales of the product are less than $25,000).
Single entity products subject to an OTC drug monograph finalized on or after April 16, 1999.	Within the period specified in the final monograph. However, if a monograph has not been finalized as of April 16, 2001, then the product must comply as of the first major labeling revision after April 16, 2001 or within 6 years, whichever occurs first.
Combination products subject to an OTC drug monograph or monographs in which all applicable monographs were finalized before April 16, 1999.	Within 2 years (or within 3 years if annual sales of the product are less than $25,000).
Combination products subject to an OTC drug monograph or monographs in which at least one applicable monograph was finalized before April 16, 1999 and at least one applicable monograph was finalized on or after April 16, 1999.	Within the period specified in the last applicable monograph to be finalized, or within 2 years (or 3 years if annual sales of the product are less than $25,000), whichever occurs first.
Combination products subject to an OTC drug monograph or monographs in which all applicable monographs are finalized on or after April 16, 1999.	Within the period specified in the last applicable monograph to be finalized. However, if the last monograph is not finalized as of April 16, 2001, then the product must comply as of the first major labeling revision after April 16, 2001 or within 6 years, whichever occurs first.
All other single entity and combination OTC drug products (e.g., products in the OTC Drug Review that are not yet the subject of proposed OTC drug monographs).	If a monograph has not been finalized as of April 16, 2001, then the product must comply as of the first major labeling revision after April 16, 2001 or within 6 years, whichever occurs first.

VI. The Paperwork Reduction Act of 1995

This final rule contains information collections 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). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

With respect to this collection of information, FDA invited 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. FDA received no comments concerning the proposed burden estimates of this rulemaking under the Paperwork Reduction Act of 1995 (62 FR 9024 at 9044).

Regarding OMB's concerns about various label formats informing consumers about purchasing and using OTC drug products in a manner that will improve their health, FDA discussed this subject in the February 27, 1997 (62 FR 9024 at 9031) proposal. The agency points out that the required label format (i.e., the order for the placement of information) is modeled after the decisionmaking process consumers would be expected to follow, and should follow, when selecting and using OTC drug products. This new required labeling format should help consumers to more efficiently and better use OTC drug products.

OMB, in its notice of action did state that it wished to allow the industry and the public to consider the notice of proposed rulemaking, specifically its concerns about the utility of various label formats to inform consumers about purchasing and using OTC drug products in a manner that will improve their health. FDA has met with the industry on numerous occasions over the past 4 years to discuss various aspects of the new labeling formats and believes that the industry and public sector has had ample opportunity to express their views and be aware of the reporting burdens established by this final rule. Throughout the preamble, the agency has addressed numerous comments received concerning information collection. The agency adds that many manufacturers of OTC drug products have begun on their own initiative implementing the labeling format provided in this rule as part of their routine labeling redesign practice.

Title: Over-the-Counter Human Drugs; Final Rule for Labeling Requirements.

Description: FDA is amending its regulations governing labeling requirements for human drug products to establish a standardized format and standardized content requirements for the labeling of all marketed OTC drug products. The rule requires that the outside container or wrapper of the retail package (or the immediate container label if there is no outside container or wrapper) of all OTC drug products include uniform headings and subheadings, presented in a standardized order, with minimum standards for type size and other graphical features. FDA is issuing these requirements because it has determined that the design and format of labeling information varies considerably among OTC drug products and consumers may have difficulty reading and understanding the information presented on OTC drug product labeling. The rule 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.

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, 503, 505, 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 conveys all material information to the consumer (sections 201(n) and 502(a) of the act), and that labeling communicates this information in a manner that is ''likely to be read and understood by the ordinary individual under customary conditions of purchase and use'' (section 502(c) of the act).

FDA concludes that the labeling statements required under this rule are not subject to review by the OMB because they are ''originally supplied by the Federal government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)) and therefore do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

Section 201.66 requires all OTC manufacturers to format labeling as set forth in subsections (c) and (d). FDA has learned from the industry that OTC manufacturers routinely redesign the labeling of OTC products as part of their usual and customary business practice. This rule provides varied timeframes for implementing the OTC labeling requirements. Therefore, the majority of respondents will be able to format OTC labeling in accordance with § 201.66 as part of their routine redesign practice, creating no additional paperwork or economic burden. However, of the 39,310 SKU's currently marketed under a final monograph, FDA has determined that approximately 32 percent, or 12,573 products, may necessitate labeling format changes sooner than provided under their usual and customary practice of label redesign. FDA has estimated that of the 400 respondents who produce OTC products, including the 12,573 products described above, each may be required to respond approximately 31.4 times to this rule outside of their usual and customary practice. Each response is estimated to take, on the average, 4 hours, for a total of 50,292 hours per year. This burden is expected to be a one-time burden.

Although the usual and customary practice of label redesign will minimize the burden for the remainig 68 percent of SKU's currently marketed, or 26,737 products, additional time may be necessary for each company to make the format changes under this rule. FDA has estimated that of the 400 respondents who produce OTC products, each may be required to respond approximately 66.8 times to bring the 26,737 products into compliance with this rule. FDA estimates that for this group, each response will take an average of 2.5 hours for a total of 66,842 hours. This is expected to be a one time burden. The chart reflects this group on the second line.

Section 201.66(c) and (d) will also trigger the requirement that OTC manufacturers with approved or pending new drug applications (NDA's) and abbreviated new drug applications (ANDA's) must submit to FDA supplements and amendments regarding labeling changes under 21 CFR 314.60(a), § 314.70, 21 CFR 314.96(a), and 21 CFR 314.97. In the proposed rule, the agency attributed this paperwork burden to these specific NDA and ANDA regulations. For the final rule, the agency has redesignated the burden under § 201.66(c) and (d). Based on its records and experience, FDA estimates that approximately 61 respondents hold applications (41 NDA holders and 20 ANDA holders) for which supplements and amendments will be required. FDA expects that approximately 522 submissions (350 to NDA's and 172 to ANDA's) will be required regarding labeling changes under § 201.66(c) and (d), which averages to 8.5 submissions per respondent. Based on information and experience, FDA further estimates that each submission will take an average of 2 hours to prepare, for a total of 1,040 hours annually. This burden is also expected to be a one-time burden.

Under § 201.66(e), respondents subject to this rule will be required to submit requests in writing for exemptions and deferrals from the specific requirements of § 201.66. Based on its experience with exemption and deferral requests under similar provisions, FDA estimates that

approximately 16 percent of the total number of respondents, or 25 manufacturers, packers, or distributors, could be expected to submit such requests on the average of one time per year. Such requests may take an average 24 hours each for a total of 2,400 hours annually.

The agency estimates that approximately 59,329 SKU's are moving towards publication of a final monograph. The burden associated with label reformatting for these products is not included below. The burden below will be adjusted after these products become final.

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
201.66[2]	400	31.43	12,573	4	50,292
201.66	400	66.8	26,737	2.5	66,842
201.66(c) and (d)[2]	61	8.5	522	2	1,044
201.66(e)	25	4	100	24	2,400
Total					120,578

[1] There are no capital costs or operation and maintenance costs associated with this collection of information.
[2] One-time burden.

VII. Environmental Impact

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

VIII. Analysis of Impacts

A. Background and Summary

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*). 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 requires that agencies prepare a written assessment and economic analysis before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this final rule is consistent with the principles set out in the Executive Order and in these two statutes. The final rule is a significant regulatory action as defined by the Executive Order due to the novel policy issues it raises. It is also an economically significant regulatory action because of its substantial benefits. With respect to the Regulatory Flexibility Act, the following analysis constitutes the agency's Final Regulatory Flexibility Analysis. Because the rule does not impose any mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any 1 year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

The standardized format and easier-to-read labels established by this rule will have a positive effect on the nation's public health by enhancing the ability of consumers to find, read, and understand important safety and use information. The expected benefits of the rule will include: (1) Improved drug effectiveness for labeled indications, (2) reduced adverse drug reactions, and (3) more efficient consumer search activities. The health benefits that will result from improved drug effectiveness could not be quantified, but FDA believes that they are substantial. With respect to the anticipated reduction in adverse drug events, the agency finds that if the rule prevents just 5 percent of the hospitalizations associated with the unintended consequences of self-medication, the economic savings could be $39 million annually in direct benefits and $52 million annually from indirect benefits. In addition, by reducing consumer search time, the uniform format could lead to consumer time savings valued at from $19 million to $38 million per year. The total benefits of this rule range from $110.5 million to $129.6 million per year.

The costs of the product redesign and relabeling imposed by this rule will be incurred by the manufacturers of OTC drug products. FDA estimates that the required labeling redesign will cost about $19.4 million. In addition, the minimum print size and other format changes will require a small percentage of products (estimated at 6.4 percent) to increase the size of their label and/or package. These size-related adjustments will add about $38 million in one-time costs and $11.5 million in annually recurring costs. Overall, therefore, the agency estimates that the one-time costs of this rule will amount to about $58 million and the annual recurring costs about $11.5 million.

B. Benefits of Regulation

The purpose of this final 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. Thus, the final rule will enhance the safe and effective use of OTC drug products by improving the ability of consumers to find, read, and understand important safety and use information. As discussed in section III.A of this document, the agency conducted a study (Study A) to examine the influence on comprehension of the new versus the previously used OTC labeling format. That study supports the conclusion that the new format will take less time to read and will help consumers make a greater number of correct product use decisions when such decisions require a simple search for information in the product labeling. The study found that individuals like a format with strong visual cues and consider information easier to use when presented in easy to read ''chunks.'' Especially when attention is divided, individuals felt more confident in their ability to use such a format.

Both the variability and the presentation of existing OTC drug product labeling make it difficult for consumers to select the most appropriate OTC drug product and to use the product safely and effectively. For consumers to gain the greatest benefit from these products, relevant information must be easy to find, readable, readily understood, noted, and acted upon. Despite the critical importance of safety and use information, OTC drug product labeling is often printed in small type with a crowded layout and minimal white space. Although the OTC drug industry has developed voluntary labeling standards encouraging a minimum 6-point type size, many OTC drug product labels fail to meet this standard. Moreover, the placement of the information varies, making it harder for consumers to find and compare similar information on competing products.

The revised labeling will produce at least three important benefits: (1) The new label will enhance the therapeutic value of OTC drug products by helping consumers select appropriate products and adhere to proper dosage regimens; (2) consumers will find it easier to avoid ingredients or products that in some circumstances cause adverse events such as allergic reactions, adverse drug interactions, or other unintended outcomes, ranging from minor discomfort to hospitalization; and (3) consumers will increase the economic efficiency of their OTC drug purchases by more quickly locating and identifying key elements of product information, such as appropriate ingredients, uses, and warnings.

1. Improved Product Selection and Use

The number of consumers relying on self-diagnosis and self-treatment has increased rapidly over the past decade, due in part to the rising cost of health care and the increasing number of drug products switched from prescription to OTC status. Consumers, however, are faced with a growing number of choices for purchase decisions and often find it difficult to determine the product that is best for their particular condition. The absence of uniform and easily readable product information complicates product comparisons and can result in less than optimal health outcomes. Moreover, even informed product selections can produce disappointing results if directions for use are misread. Inappropriate product selections or illegible dosage directions can postpone relief from aches or pains, or permit other discomforts to persist longer than necessary. Study A suggests that the standardized labeling format will reduce such incorrect product use decisions. Although FDA cannot quantify the value of the health improvements that would result, the agency is confident that the more informed OTC drug selection and use produced by this rule will increase consumer satisfaction and, at times, reduce health care costs for additional or supplemental medications, doctor visits, and hospitalizations.

2. Savings From Reduced Adverse Drug Reactions

Although adverse events associated with some OTC drug products are not systematically tracked and recorded, substantial documentation does exist for the more serious events. Numerous studies in the literature have documented drug-related hospitalizations (60 FR 44182 at 44232, August 24, 1995). One comprehensive review of 36 articles focused specifically on adverse drug reactions (ADR's) as the primary cause of hospitalization. This study counted the number of events attributed to the unintended consequences of drug therapy, excluding admissions due to overdose, intentional poisoning, attempted suicides, drug abuse or intoxication, and found that the percentage of hospitalizations due to ADR's ranged from 0.2 to 22 percent, with a mean of 5.5 percent (Ref. 16). Of those studies that distinguished between prescription and OTC drugs, the reported OTC share ranged from between 4 (Ref. 17) and 18 percent (Refs. 18 and 19). Thus, FDA estimates that unintended OTC drug-related hospitalizations may account for about 0.55 percent (5.5 percent x 10 percent), or 170,500 of the nation's 31 million annual hospital admissions. Investigators have determined that between 48 and 55 percent of all hospital admissions related to adverse reactions are preventable (60 FR 44182 at 44232). (A recent study of in-hospital adverse drug reactions also found that almost 50 percent were preventable.) (Ref. 20). Consequently, on the assumption that 50 percent of the hospitalizations attributable to OTC drug adverse reactions are preventable and that the cost of an average hospital stay is $9,191 (Ref. 21), FDA finds that $784 million (170,500 x 50 percent x $9,191) is spent annually on hospitalizations due to potentially avoidable OTC drug ADR's.

The realized benefits of the rule will depend on the degree to which consumers are better able to read and understand OTC drug product labeling and to act on that information to make choices that would reduce drug side effects, drug interactions, allergic reactions, and other unintended consequences of self-medicating. If the improved labeling format and larger print size contributed to the avoidance of only 5 percent of these hospitalizations, the economic savings would amount to $39 million annually.

The indirect benefits from reduced drug-related illnesses include avoided costs due to lost work time or reduced productivity. Roughly 58 percent of adverse drug reaction admissions were for patients aged 20 to 59. The remaining 42 percent of admissions were for patients under 20 years (<10 percent) and over 59 years old (Refs. 17, 18, and 22). To calculate productivity losses, the agency assumed 56 hours per admission for the patients aged 20 to 59 years (40 hours of lost work per hospitalization plus 16 additional hours for recovery and followup doctor visits) and 14 hours for the remaining group (to account for lost volunteer time or for time away from work for the care givers of dependent patients). Using the average hourly production workers earnings plus 30 percent for fringe benefits of $15.96, the estimated value of lost productivity is $44.2 million patients for aged 20 to 60 and $8 million for the remaining patients or their care givers (Ref. 23). These estimates may somewhat overstate the value of lost productivity for the 20 to 59 age group because all patients are assumed to be employed. On the other hand, indirect benefits for the remaining age groups are understated because many of these patients are in the workforce and for those who are not, data are inadequate to measure their contribution to society.

Although less severe adverse incidents have not been systematically tracked and recorded, they likely occur frequently, as over 5 billion OTC drug products are purchased annually. The crowded format and small print size found on many of these products obscures important directions and warnings that might otherwise be heeded by consumers. For example, certain OTC drug products contain warnings about not driving or operating heavy equipment when using those products. Some consumers inadvertently overdose because they are unaware that a particular ingredient was also contained in a multi-symptom product. In the case of combination products with multiple active ingredients, especially in the cough/cold category, consumers often treat symptoms that are not present, raising the likelihood of an adverse drug event. The new label format will establish a consistent order of presentation and group similar information (such as ingredients, warnings, and directions) together under relevant headings so that

it will be easier for consumers to find and read this information, thus helping to reduce the number of adverse event occurrences.

3. Savings From More Efficient Product Search

By facilitating product comparisons, easier-to-read labeling will reduce those suboptimal purchases that result from inappropriate price-quality relationships and competitive inefficiencies. For example, the uniform format will reduce consumer search and transaction costs, because all products will display information in the same order. In turn, consumers will find it easier to purchase more economical items by comparing products with similar ingredients and uses. Although FDA could not assign an economic value to this expected efficiency gain, Study A found that the time required to read the complete safety and use information in the proposed format was reduced by a statistically significant 10 seconds compared to traditional formats. The total time saved searching for specific information components, such as ingredients and their therapeutic benefits, or for conducting product comparisons, should be even greater at the point of purchase.

According to A.C. Nielsen (Nielsen), a recognized provider of market research business information and analysis, consumers purchased 5.6 billion units of OTC drug products in 1995. (This figure excludes dandruff shampoos and facial makeup and lipstick with sunscreen.) If 10 percent of these purchases represent first time or annual evaluations of purchase decisions, 0.6 billion product decisions are made annually. If consumers save only the reported 10 seconds per purchase decision, they would save 1.6 million hours annually. Using 1997 average hourly production worker earnings of $12.28, the approximate economic value of this time savings is $19.1 million per year (Ref. 23). If consumers compare two products, the additional time could double, with a value of $38 million per year.

4. Summary of Expected Benefits

In summary, FDA expects revised OTC drug product labeling to generate substantial benefits, many of which the agency could not quantify. While the majority of the costs attributed to this rule are one-time costs associated with labeling redesign and packaging reconfiguration, the benefits from improved labeling will accrue annually. Better informed product selection and use will raise the likelihood that OTC drugs will produce desired health outcomes. The standardized format and easier-to-read labeling is expected to reduce the number of ADR's associated with OTC drug products. A 5 percent decrease, for example, would reduce annual hospital costs by about $39 million and reduce annual productivity losses by $59 million. Finally, FDA expects that easier-to-read information will lead to more efficient marketing transactions, because product and price comparisons will be simpler and faster, permitting consumers to obtain comparable results in less time. The value of the reduced search time could range from $19 to $38 million annually. The total benefits of this rule range from $110 million to $129 million annually.

C. Costs of Regulation

For its analysis of the proposed rule, FDA determined that the cost of revising labeling for thousands of OTC drug products would be substantial, involving numerous levels of review and verification, in addition to extensive graphic redesign. The agency found, however, that regulatory costs would be moderated by the standard business practice of periodic redesign. Because a majority of the labeling would undergo design changes even in the absence of a new rule, FDA estimated the costs of redesign by counting only the value of the label-years that would be lost, after adjusting for the length of the traditional labeling cycle. The regulatory cost was calculated as the product of the number of SKU's, which are the individual products, packages, and sizes affected; the number of years of labeling life lost; and the value of each year of labeling life lost (see 62 FR 9024 at 9045 through 9049). As explained below, upon review of the comments, FDA has concluded that its methodology for estimating the cost of a labeling change was sound. The agency has, however, refined its earlier cost estimates, based on the comments and other supplemental information, and has added costs for increasing the size of certain packages and labeling.

1. Number of Products Affected

Once the rule is fully effective, a new OTC drug product labeling design will be required for each SKU. For its initial analysis, FDA based its estimate of the size of the affected OTC drug market on data from Nielsen. According to Nielsen, OTC drug products in 1995 accounted for $18.7 billion in sales in grocery stores, drug stores, and mass merchandise outlets. FDA allocated the products in Nielsen's inventory into review categories based on their monograph review status. This categorization indicated that almost 30,000 brand name SKU's were regulated under the OTC drug monograph review process. The breakdown of these branded SKU's by monograph review status showed: 10,910 under a final monograph (including products switched from prescription to OTC status), 8,241 scheduled to become final before this final rule, and the remaining 8,488 scheduled to become final after this final rule is published. (The latter figure was subject to greater uncertainty because of incomplete coverage of products with sunscreens in the Nielsen data base.) (See Table 3 of this document.)

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

	Brand name	Private	Total
Marketed under final monograph	10,910	28,400	39,310
Under review, scheduled for final monograph	8,241	21,300	29,541
Remaining	8,488	21,300	29,788
Total	27,639	71,000	98,639

Because the Nielsen data base did not break out SKU's for private label store brands, FDA estimated the number of private label SKU's using data on the number of retail chains likely to market private label brands (Ref. 24) and Nielsen data on the average number of SKU's carried by firms that relabel generic OTC drug products. The agency estimated 71,000 private label SKU's (62 FR 9024 at 9046 to 9047) and assumed the same regulatory status distribution as for branded SKU's.

While this rule will ultimately affect all OTC drug products, the implementation dates for the labeling changes will vary according to the

regulatory status of the product. For its analysis of the proposed rule, FDA assumed that products currently covered by a final OTC drug monograph or marketing application, or about 39,310 SKU's, would incur labeling design costs. A second group of up to 29,541 SKU's was thought to be potentially affected, depending on the timing of the publication of their final OTC drug monographs. The agency assumed that monographs for the remaining 29,788 SKU's would become final only after publication of the final rule. Because products marketed under this latter group of OTC drug monographs would require labeling changes regardless of the final rule, no design-related costs were assigned to this group of products. Although FDA received no comments questioning this SKU allocation, the agency has now determined that the 29,541 SKU's in the review category will not be finalized before this rule is published. As a result, only those 39,310 SKU's currently covered by final OTC drug monographs are expected to incur incremental labeling design costs.

2. Original Agency Estimate

a. *Cost of labeling redesign*. FDA's previous analysis (62 FR 9024 at 9045 to 9049) found that redesign cost estimates varied 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 and generally included redesign of the PDP. FDA assumed that the PDP accounted for 50 percent of the cost to redesign branded product labeling and reduced the estimated redesign costs by one-half, on the presumption that the rule would not affect the PDP. To derive an average cost, the agency weighted the affected share of private label and branded SKU's at 80 and 20 percent, respectively, based on FDA's estimate of 71,000 private label SKU's and an analysis of Nielsen sales data covering the remaining 27,639 branded SKU's. Because the analysis found that a substantial proportion of the branded products were regional and/or low sales volume items, FDA assumed that the redesign costs for regional and low sales volume branded products would be similar to that for private label products. Using the midpoints of the cost ranges, and reducing the cost for branded products by 50 percent to account for the PDP adjustment, the analysis calculated an average redesign cost of $1,500 per SKU. However, as described in section VIII.E.3 of this document, based on additional information, the agency's final analysis eliminates the PDP adjustment.

b. *Methodology*. The agency's assessment of the proposed rule found that frequent labeling redesigns are recognized as a cost of doing business in the OTC drug industry. Thus, labeling that would normally be redesigned within the implementation period was assumed to incur no additional costs. To represent the distribution of typical labeling replacement intervals, the agency had estimated that the labeling for 20 percent of the affected SKU's would be redesigned at least every 2 years, 40 percent every 3 years, and 40 percent every 6 years. Both the number of OTC drug products requiring redesign and the market value of the labeling were assumed to be evenly distributed over their labeling lifetimes. That is, for labeling with a 6-year lifetime, one-sixth would be redesigned in year 1, one-sixth in year 2, and so on. FDA then measured the economic cost of the proposed labeling redesign requirement as the lost value of the remaining life-years of the existing labeling designs. For example, given a 2-year phase-in period, product labeling with a remaining 3-year lifetime would lose the value of 1 year of labeling-life.[1]

FDA found that, with a 2-year implementation period, the cost of the proposed requirements would be $19.7 million. To reduce the economic impact on small entities, the agency proposed an additional 1 year extension for OTC drug products with sales of less than $25,000 per year. Based on the Nielsen data, this extension applied to about 40 percent of OTC drug products, but only about 1 percent of OTC drug retail sales. With this added deferral, FDA estimated the cost of the proposed rule at $14.2 million.

3. Response to Comments

A number of comments from the OTC drug industry asserted that the agency understated the cost of the proposed rule. These comments stated that: (1) FDA's estimated average cost to redesign labeling was too low, (2) FDA's methodology to calculate the economic impact of the proposal was inappropriate, and (3) FDA incorrectly assumed that package and label sizes would not need to be increased. The following section addresses each of these issues while focusing primarily on the comments and alternative economic analysis submitted by NDMA. Appendix G of NDMA's comment provides a full description of its explanatory data and methodology (Ref. 25).

NDMA stated that the cost to comply with the proposed rule, assuming a 2-year implementation period, would be a minimum of $140 million, even without changes to package and label sizes. NDMA subsequently recommended the use of a net present value approach, which reduced its cost estimate to $114 million. Further, FDA had proposed an additional implementation year for SKU's with annual sales below $25,000. This adjustment reduces NDMA's cost estimate (assuming no package or label size changes) to $86 million, substantially less than the originally stated $140 million figure, but still far above FDA's estimate of $14.2 million.

a. *Cost of redesigning drug label*. NDMA agreed that FDA ''approached the very complex task of assessing the economic costs resulting from the proposed rule in a rational, data-based manner'' and that ''many of the parameters that FDA used as a basis to determine label design costs were supported by reliable market research data.'' For example, NDMA accepted FDA estimates for both the number and life cycle of the affected drug labels. Nevertheless, NDMA asserted that the agency had understated the cost of redesigning a label for the following reasons: (1) FDA's unit cost estimate was based on a small, nonrandom sample; (2) FDA was incorrect in eliminating PDP redesign from the cost of relabeling branded OTC drug products; and (3) FDA did not consider either the cost of scrapping label inventory or the administrative burden that would be incurred by firms in developing compliance strategies.

i. *Unit cost estimate (without scrap)*. NDMA reports that it developed a cost estimate by surveying 74 member firms regarding the average cost of redesigning an OTC drug product label. The survey (Ref. 25) requested information on minor and major label changes. Thirty-four firms responded, of which 31 were brand label manufacturers and 3 were private label manufacturers. The reported cost per SKU to redesign a label ranged from $500 to $420,000. Excluding three extreme outliers,

[1] Mathematically, the following formula was used to calculate the costs:

$Cost_{yx} = \Sigma j N_x A_x (1/x)$, where j = 1 to (x-y)

Total $Cost_y = Cost_{y6} + Cost_{y3} + Cost_{y2}$

where:

x = life of labeling in years (2, 3, or 6),

y = implementation period in years,

N_x = number of SKU's with labeling life of x years, and

A_x = amortized annual value of labeling with a life of x years.

(A_x is equivalent to the annuity value to pay off an initial investment, i.e., $A_x = C \times \{ I / [1 - (1/(1 + I)^x)]\}$; where C = the average weighted cost to redesign a labeling ($1,500); I = the discount rate (7%); and x = the life of a labeling in years (2, 3, or 6).)

NDMA projected an average cost (omitting scrap) of $15,154 per SKU to redesign a branded label and $1,261 for a private label. Assuming a 20/80 market split for branded and private label products, NDMA calculated a weighted average cost per SKU of $4,039, roughly double the earlier FDA estimate (without a PDP adjustment) of $2,070.

To validate its estimate, NDMA cited a cost model that had been developed by the Research Triangle Institute (RTI) to estimate the regulatory impact of the NLEA. The RTI model assumed that the cost of changing a food product label was a function of administrative, analytical, marketing, printing, and label inventory costs. Printing costs depended on the type of printing process, the frequency of redesign, the number of SKU's affected, the complexity of the label changes, and the length of the compliance period (Ref. 26). NDMA estimated, based on responses from 21 member firms, that about 50 percent of the industry's SKU's are printed using lithography, 47 percent by flexography, 1 percent by gravure, and the remaining by other methods. Applying these proportions to the RTI model for complex printing tasks with four or more color changes, NDMA derived a label printing cost of $3,458 per SKU for an average OTC drug product and concluded that this result verified its estimate of $4,039 per SKU (without scrap).

The agency agrees that the cost data used in FDA's economic analysis of the proposed rule were not drawn from a random sample, although they were supplied by sources familiar with the OTC drug industry, including smaller and private label manufacturers. FDA notes, however, that the survey underlying the NDMA cost estimates was likewise not based on a random sample of manufacturers. While NDMA member firms include a range of large, small, brand-label, and private-label manufacturers, many smaller firms do not belong to NDMA. Indeed, NDMA indicates that its 74 members (which may represent less than 20 percent of all OTC drug manufacturers), account for 90 to 95 percent of all OTC drug sales. A survey limited to this membership necessarily over-represents large manufacturers of nationally branded products and under-represents smaller manufacturers of regionally branded products.

Following review of the survey data provided by NDMA, FDA concludes that NDMA's figures overstate the industry average cost of redesigning OTC drug labels. For example, the survey reports unreasonably large differentials between branded and private label manufacturers, with survey costs for branded SKU's from 3 to 40 times greater than those for private label SKU's. For graphics development (directions for studio, draft/mock-ups, review, and concurrence), the average SKU cost reported was $6,215 for branded and $291 for private label products. Assuming an hourly wage rate of $40 for branded and private product personnel, manufacturers of branded products spend 155 hours per SKU on this function compared to 7 hours by private labelers. For separations (color mock-ups created and reviewed), the survey reported the per SKU cost for branded and private label companies at $3,210 and $82, respectively, almost a 40-fold difference. The agency acknowledges that large manufactures of nationally branded products involve more personnel in decision making and may use higher quality packaging materials. Nevertheless, in view of the substantial degree of market competition in this industry, private labelers typically package goods to resemble the competing national brand. Moreover, while questioning the size of the reported range, FDA could not review the basis for NDMA's estimates, because the supporting data, such as the number of labor hours or labor costs used in its calculations, were not submitted.

Furthermore, while the proposed rule required manufacturers to reformat the information panels, the NDMA survey instructed respondents to include the cost of changing all labeling, including certain promotional materials. Thus, some manufacturers may have reported costs for developing new product identities, advertising campaigns, etc. Also, survey respondents were asked to estimate the cost to redesign only one SKU, which ignores both learning curve and economy of scale effects. For the most part, the same industry personnel are responsible for copy and layout decisions for numerous product lines and SKU's. Moreover, FDA does not agree that the RTI model necessarily validates NDMA's redesign cost estimate. The portion of the RTI model used by NDMA was developed to estimate the cost of printing food labels, which are often considerably larger than OTC drug labels.

NDMA's recent estimate also differs from the average cost of $7,900 per SKU submitted by the Cosmetic, Toiletry, and Fragrance Association to change a drug-cosmetic label (Ref. 27). OTC drug-cosmetics are generally considered to have more expensive labeling than OTC drugs alone, because they compete with other elaborately packaged cosmetic products.

To finalize its estimate of the average cost of redesigning an OTC drug label, FDA considered several approaches. First, the agency maintained its initial estimating methodology, but adjusted the estimated unit cost per SKU. Based on all available information, FDA concludes that the cost of redesigning nationally branded products manufactured by large companies ranges from $5,000 to $15,000 per SKU. The cost to redesign regional or low sales volume brands of smaller manufacturers is considerably less, ranging from about $1,000 to $8,000 per SKU. The cost to redesign labels for private label brands is smaller still, but approximates FDA's original estimate of $1,000 and NDMA's survey estimate of $1,261 per SKU. Accordingly, to calculate a final estimate, the agency divided OTC drug products into three classes: (1) Branded products manufactured by large NDMA member companies, with a midpoint cost estimate of $10,000 per SKU; (2) branded products manufactured by smaller companies, with a mid-point cost estimate of $4,500 per SKU; and (3) private label products, assumed to cost $1,261 per SKU, as reported by NDMA.

The agency used its original estimate of the SKU distribution, which indicated that about 30 percent of all OTC drug SKU's are branded, and the NDMA member survey to determine costing weights to apply to each industry sector. Respondents to NDMA's survey reported that they account for about 4,000 branded SKU's, which amount to 15 percent of all branded SKU's. As these survey respondents comprise almost half of NDMA's membership, FDA assumed that branded products of all NDMA members may account for about 30 percent of all branded SKU's, or approximately 10 percent of all affected SKU's (30 percent branded x 30 percent NDMA members). The remaining branded products, therefore, account for 20 percent of all affected SKU's, and the private label products account for the remaining 70 percent. This calculation results in a weighted average cost of $2,783 (without scrap) to redesign a label (i.e., ($10,000 x 10 percent)+($4,500 x 20 percent)+($1,261 x 70 percent)), a figure higher than the prior FDA estimates but below the NDMA survey estimate of $4,039.

A second approach was developed by the Eastern Research Group, Inc. (ERG), a private economics consulting firm under contract to FDA. ERG developed its model based on data collected during site visits to several large and small drug

companies and through discussions with other industry consultants (Ref. 28). ERG assumed a more complex distribution of various types of SKU's among firms of different sizes and included specific cost variables for regulatory affairs, art/graphics, manufacturing changes, and inventory losses by firm size (by employment), firm type (branded or private label), and type of label changed (carton, container, etc.). Under ERG's model, the estimated weighted average cost of label redesign (without scrap) is $1,210 per SKU (Ref. 28).

Because the OTC industry is so diverse and the relevant cost data are so limited, no single model or single estimate can be viewed as definitive. Nevertheless, the agency continues to believe that its overall approach represents a rational basis for estimating the redesign costs associated with this rule. The agency in its proposed analysis arrived at an estimate of $2,070 per SKU (without a PDP adjustment). That figure, when revised to take into account certain data from the NDMA survey, is increased to $2,783 per SKU. ERG employed a more complex model and arrived at a figure of $1,210 (or half that of FDA), while NDMA arrived at a weighted average of $4,039 (or twice that of FDA). Given this spread, and given the agency's concerns about NDMA's methodology and input data, the agency is adopting the revised figure of $2,783 as its base average cost estimate. The agency acknowledges that it has adopted a conservative figure, relative to that derived by ERG. However, nothing in the ERG model, or in the NDMA model, suggests that FDA should discard its methodology or its assumptions for estimating unit costs.

ii. *Principal display panel.* In its original analysis, FDA assumed that the PDP need not be altered and therefore adjusted its unit cost estimate for branded products downward by 50 percent. NDMA argued that this correction was inappropriate as it failed to account for many commonly used labeling and packaging configurations. NDMA pointed out that, with the exception of labels with separate front and back panels, all PDP's must be reprinted when the information panel is changed. Based on a poll of 7-member companies, NDMA estimated that about 90 percent of all OTC drug SKU's require the PDP to be reprinted when changes are made to the information panel.

The fact that the PDP needs to be reprinted when the information panel is changed does not mean that it has to be redesigned. For the majority of labels, the PDP and information labeling are printed as a single label, with one printing plate required for each of the colors used. For many products, only one or two colors will be changed on the information panel to accommodate the new requirements; consequently, only those plates would need to be redesigned, the others could be reused or simply copied at significantly reduced cost. Nevertheless, the agency acknowledges that many manufacturers would, at the time of redesigning the information panel, also make incremental changes to the PDP. Therefore, the agency has adopted the NDMA position and eliminated any downward PDP adjustment from its calculation of the cost of the final rule.

iii. *Scrap.* NDMA also argued that the cost of scrapping unused inventory should be included as a regulatory cost. Based on its survey, it estimated that scrap labeling inventory adds about $1,000 to the weighted redesign cost per SKU ($2,968 per SKU for higher cost firms and $576 per SKU for lower cost firms), raising its average unit cost estimate to about $5,000. NDMA declared this a conservative estimate that would underestimate the cost of scrap label inventory if the implementation date were less than 2 years.

FDA agrees that some scrap label inventory loss is inevitable when label changes are made, but notes that the longer the implementation period the easier it is for manufacturers to minimize the cost. The final rule allows either a 2- or 3-year implementation phase (depending on sales volume), which is sufficient time to minimize inventory losses. Because the NDMA survey question failed to state the length of the phase-in period, the survey response cannot be considered reliable. Nonetheless, because a better estimate of the average scrap cost is not available, FDA accepts NDMA's figures, but adjusts the weighting to 10 percent for the higher cost firms and 90 percent for the lower cost firms, for a weighted average of $800. This weighting is based on the assumption that both small brand name manufacturers and private label manufacturers have less expensive labels and smaller inventories than large brand-name companies. The consideration of scrap, therefore, raises FDA's weighted average design cost estimate to approximately $3,600 per SKU.

iv. *Administrative costs.* NDMA suggested that the agency also include administrative costs in its calculation of the cost to redesign the label. NDMA provided no estimate of these costs, but noted that there would be a burden to manufacturers to manage the additional required redesign of labels.

FDA agrees that the rule will impose administrative costs, but concludes that these costs are adequately accounted for in the previous estimates. OTC drugs are highly regulated products and manufacturers are expected to have regulatory personnel on staff or consultants available to address compliance matters. The complexity of the rule is not unusual compared to other OTC drug regulations and the requirements will be clear to graphics design and regulatory personnel. Moreover, the rule is expected to receive widespread publicity when issued and most OTC drug firms belong to trade associations or have access to trade publications that provide additional sources of information. Because the rule permits a 2- to 3-year implementation period, FDA continues to believe that managing the label changes will not impose burdens beyond the costs included in the agency's estimate.

b. *Methodology for calculating economic impact.* NDMA disagreed with the methodology the agency used to calculate the economic impact of the proposed rule for two reasons: (1) FDA treated the cost to redesign as a financed rather than an expensed cost and calculated the impact using an amortized cost rather than a net present value, and (2) FDA treated label redesign as an accelerated change rather than an additional change.

i. *Economic versus accounting costs.* NDMA asserted that FDA used an incorrect valuation method to assess the economic impact of the rule, because the agency's valuation of amortized lost label life incorrectly implies that the costs of label redesign are financed costs, rather than sunk costs expensed in the year they incur. According to NDMA, the proper approach is not to amortize, but to calculate the net present value of the incremental costs of label redesign.

FDA does not agree that the amortization of lost label life is inappropriate. Executive Order 12866 charges Federal agencies to determine the economic cost of its rules, but such costs are not necessarily identical to financial costs, as interpreted by accounting convention. According to the U.S. Office of Management and Budget (Ref. 29), the preferred measure for economic analyses is ''the opportunity cost' of the resources used or the benefits forgone as a result of the regulatory action.'' Whether firms expense label design costs in the year they occur is largely irrelevant to the proper calculation of economic costs, i.e., the opportunity cost of the rule.

Moreover, FDA's calculation yields results that are identical to those obtained through a net present value approach. To derive its results, FDA estimated a net present value and then, for ease of exposition, converted this figure into an equivalent stream of annual costs.

ii. *Additive versus accelerated costs.* The primary reason that NDMA's methodology produces substantially higher costs than FDA's estimate is that NDMA's approach assumes a ''market driven'' label cycle that is independent of the design changes required by the rule. For example, if the average lifetime of a particular label type is 3 years and a design change costs $3,000 per SKU, both FDA and NDMA agree that a 2-year phase-in would allow two-thirds of the labels to be replaced under normal business conditions without additional costs (assuming no package size changes). FDA's methodology, however, also assumed that the remaining one-third of the labels lose only 1-year of their expected lifetime, so that the economic cost (ignoring any discounting adjustment) would be $1,000 per SKU (1/3 x $3,000) for one-third of these SKU's. This approach, however, implicitly assumes that the label design cycle would resume at a 3-year interval, so that the next voluntary label redesign, on average, would not occur until 3 years after the mandated change.

In contrast, NDMA argues that voluntary label redesign occurs in response to external ''market driven'' factors that would be independent of this mandated change. According to NDMA, such redesigns are to change product attribute copy; change graphics; add litigation-driven warnings; delete ''new'' flags after 6 months; add multilingual labeling; change labeling information, such as manufacturer, distributor, or inactive ingredient; or add or change SKU's in a product line. NDMA contends that, because the mandated changes required by this rule would not affect the underlying ''market driven'' design cycle, the full cost of the redesign, rather than just the value of the remaining life of the former label, measures the economic cost of the regulation.

With respect to the previous numerical example, NDMA's methodology implies that those labels that were redesigned in year 2 for regulatory reasons would, on average, be redesigned again in year 3 for ''market driven'' reasons. (FDA would assume that the labels that had to be redesigned in year 2 would not, on average, be redesigned again until year 5.) NDMA's methodology, therefore, would calculate the economic cost at about $3,000 per affected SKU, compared to FDA's estimate of about $1,000.

The agency does not dispute the theoretical possibility of NDMA's argument. If ''market driven'' reasons for label adjustments always compelled an immediate response, companies could not coordinate voluntary label updates with mandatory label redesign; the regulatory cost for each affected label, therefore, would be the full cost of the design change. However, FDA does not agree that such abrupt shifts in marketing strategies are the industry norm. Many of the examples of ''market driven'' label changes NDMA cited are for exactly the kind of incremental adjustments that would be deferred and consolidated in a major redesign effort. For example, the demand for most changes to product attribute copy or graphics mounts gradually in response to shifting advertising and marketing styles. Once changed, such modifications postpone the need for future change. Revisions for litigation-driven warnings are less common events that would be expected to have a small effect on industry averages. According to the RTI study (Ref. 26), line copy changes or changes affecting just one color are minor changes that, in most cases, are made without the assistance of a label artist and cost one-sixth the cost of a four-or-more color change. Such minor adjustments would not be expected to alter the underlying design cycle.

The agency finds it more likely that the demand for most major label changes is a steadily increasing function of the time that has elapsed since the last labeling revision and that manufacturers continually refine marketing techniques and strategies. As most companies will find it cost-effective to complete these incremental labeling changes concurrently with the mandatory redesign required by this rule, FDA's revised analysis maintains the assumption that the current labeling change cycle will continue unaltered. Moreover, it is important to note that the agency's decision not to exclude PDP design costs is based on its finding that incremental style modifications accompany mandated changes. If firms would not bundle incremental style changes with the mandated changes, the PDP design costs should be subtracted from the regulatory cost estimate.

c. *Cost of increasing size of packages and/or labels.* Several comments objected to FDA's assumption that the proposed rule would require few changes to the size or configuration of OTC drug packages or labels. NDMA reported that its survey indicated that 33 percent of branded and 95 percent of private label SKU's could not accommodate the proposed label format. NDMA estimated that exemption petitions would be filed for 33,500 SKU's, that 32,600 SKU's would alter package configuration at a cost of over $1 billion, and that about 15,500 SKU's would be removed from the market. While not including administrative costs for feasibility studies to determine cost-effective packaging and labeling configurations, NDMA stated that they would be large. One manufacturer suggested that a new packaging line to accommodate a label change for just one product line would result in a one-time equipment expenditure of about $2.5 million (including equipment, installation, validation, depreciation of old equipment, facility renovation, and inventory loss) and recurring costs of almost $500,000 for the more expensive labeling.

The previously mentioned projections greatly overestimate the percentage of SKU's that will not be able to accommodate the new format and the cost of increasing the size of the labeling, where necessary. In particular, the assertion that 95 percent of private label SKU's could not accommodate the proposal requirements is difficult to understand, as the vast majority of private label OTC drug products are packaged almost identically to the leading branded products for competitive reasons. Moreover, the agency carefully reviewed labels submitted as examples of those that would not fit the proposed format and found that many could, in fact, accommodate the final rule without a change in label or package size.

FDA also questions the methodology for calculating the costs of package size changes. Although details of these calculations were not submitted, it appears that NDMA estimated the cost of purchasing or modifying equipment by multiplying the unit costs by the number of affected SKU's, with no allowance for multiple SKU's packaged on a given production line, or for the widespread usage of contract packagers. Although agreeing that such factors should be considered when determining costs, NDMA nonetheless assumed substantial equipment requirements for each SKU. Moreover, NDMA does not differentiate between the costs of branded and private label manufacturers. Most private label products are manufactured by firms that produce hundreds of SKU's on the same equipment, as most packaging machines can accommodate a spectrum of changes with only minor modification or retooling. As firms will choose the most cost-effective means of implementing

package changes, only in rare cases, or when equipment is already obsolete, should the rule lead to the purchase of new equipment.

For some small SKU's, the impact of this rule will be moderated by the more flexible leading and formatting provisions in the final rule and the modified small package format allowed in 201.66(d)(10). FDA further believes that any reduced consumer choice, should a small package product not be able to meet the new requirements, will be relatively insignificant because most manufacturers offer products in more than one package size.

To respond fully to the estimates offered by NDMA, FDA asked its economics consultant, ERG, to survey (Ref. 28) all of the OTC drug products found on the shelves in three retail outlets in the Boston area. These outlets included: (1) A large pharmacy chain, (2) an independent pharmacy, and (3) a convenience store. ERG examined each of the 2,689 distinct SKU's found on the store shelves, and recorded data on the package size and type, the available labeling space, and the font size. ERG then compared these data to generic mock-ups of the revised monographs to estimate the percent of the SKU's that might need to increase the size of either the label or package. ERG also estimated the amount of the additional space needed to accommodate the new format for those SKU's that lacked sufficient labeling surface area, using an expansion factor to derive estimates for SKU's for which no adequate mock-ups were available.

The results of the survey are shown by type of package in Table 4 of this document. The vast majority of SKU's, 92 percent, have sufficient labeling space to accommodate the revised format. Of these, 16 percent will require some reconfiguration of the current information presentation, such as moving, reducing, or eliminating certain marketing information. Another 1.7 percent of the SKU's would increase the size of their label to accommodate the new format and 6.4 percent either would not fit or were indeterminate (too close to call) and, thus, might require a new packaging configuration. (SKU's were judged indeterminate when the available labeling area was within 5 square centimeters of the required area.)

TABLE 4.—FINDINGS FOR 6.0-POINT FONT, CONDENSED TYPE ALLOWED[1]

Labeling outcome	Percent of SKU's
Revised label can fit using existing area allotted for regulatory information	75.9
Revised label fits if area allotted for regulatory information is increased	16.0
Revised label fits if expanded on existing container	1.7
Revised label will not fit	4.5
Indeterminate	1.9
Total	100

[1] Horizontal width of the characters reduced by approximately 20 percent while the vertical height of the characters is unchanged.

To evaluate the estimate of reconfiguration costs (i.e., changes to the size of the labeling or packaging) presented in the comments, ERG considered several options for packaging changes, including adding a carton (if not already present), adding a fifth panel, increasing the size of the packaging, or switching to a nonstandard form of labeling such as peel-back or accordion labels (Ref. 28). Where applicable, the costs for changing a container size included container inventory loss, adjustment of the packaging line, and stability testing. The estimated packaging change costs varied with the option chosen (for example, adjustment or retooling of existing machinery versus the purchase of new equipment), although the lower cost options had a higher probability of selection. ERG also considered the recurring annual costs that would be associated with the need for larger labels or packages. A detailed description of ERG's assumptions, calculations, and unit costs is presented in the full report.

4. Total Incremental Costs

The costs of labeling redesign apply only to products covered by final OTC drug monographs or applications. Currently there are about 39,310 SKU's in this category (see Table 3 of this document). No redesign costs are assigned to the remaining 59,330 SKU's because the 6-year implementation period for these products will allow manufacturers to incorporate the design changes in their usual redesign cycle. Using a weighted average cost to redesign a label of $3,600 per SKU and assuming labels are redesigned voluntarily every 2, 3, or 6 years, the total incremental costs for redesigning labeling using the methodology discussed earlier is $19.4 million.

Reconfiguration costs apply to those products that cannot accommodate the small package format allowed in § 201.66(d)(10). These costs include the one-time cost to increase labeling size (the label or package, where applicable) to accommodate a minimum 6.0 condensed font, plus the recurring cost of producing larger labeling. Because these costs are applied to this rule regardless of the monograph status of the product, all 98,639 SKU's are potentially subject to label reconfiguration costs; 39,310 within 2 years of the effective date of this final rule, the remaining 59,330 within 6 years of the effective date of this final rule. The estimated reconfiguration costs amount to $38.1 million in one-time costs and $11.5 million in annual recurring costs. The latter reflects the incremental increases in labeling or packaging materials to accommodate the format requirements.

Table 5 of this document presents FDA's estimate of the one-time and annual recurring costs and the total annualized cost by compliance activity. The total one-time costs of $57.5 million include $19.4 million for label redesign and $38.1 million for packaging changes. The annual costs are $11.5 million. The total annualized cost to industry (using a 7 percent discount rate) is estimated at $18.4 million. The cost to individual firms will vary with the number of SKU's, the type of changes needed, and the timing of the changes.

TABLE 5.—TOTAL INDUSTRY COMPLIANCE COSTS

Activity	One-Time ($Million)	Annual ($Million)	Total Annualized
Label redesign	19.4	NA	1.4
Packaging	38.1	11.5	17.0
Total	57.5	11.5	18.4

These estimates may overstate the costs attributable to this rule. First, reconfiguration costs will be reduced to the extent that companies opt to eliminate some smaller packaging sizes within a product line. In these instances, however, consumers will bear some of the added costs. Second, the recent amendment to section 502(e) of the act under FDAMA requires that OTC drug manufacturers list the inactive ingredients in their labeling. The ERG retail outlet survey (Ref. 28) found that about 7 percent of the SKU's currently do not include inactive ingredients on their labels. Some of these products may need larger label or package sizes irrespective of this rule.

D. Small Business Impact

Manufacturers and those entities that engage in the relabeling of OTC drug products will be required to redesign the labeling of their products to comply with this rule. 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 drugs. Over 92 percent of the roughly 700 establishments and over 87 percent of the 650 firms in this sector have fewer than 500 employees. The Small Business Administration (SBA) considers firms with fewer than 750 employees in this industry to be small, but the U.S. Census size categories do not correspond to the SBA designation. An alternative data source, IMS, identified roughly 400 firms as manufacturers of OTC drug products. Using the SBA size designation of 750 employees, about 70 percent of the 400 affected manufacturing firms would be considered small.

This regulation will 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 and may need to increase the size of the packaging or labeling for a few SKU's. These costs will be mitigated, however, by the several year implementation period, which will permit many of these changes to be coordinated with those labeling changes conducted in the normal course of business. OTC drug products subject to new drug and ANDA's will need to submit revised labeling to the agency in accordance with § 314.70. This is a standard procedure that companies routinely follow for labeling changes. The final rule will not require new reporting and recordkeeping activities. Therefore, no additional professional skills are necessary.

The economic impact of this rule on small firms is particularly difficult to measure, because published financial data do not distinguish between firms manufacturing mostly OTC drugs and firms manufacturing mostly prescription drugs. ERG adopted Census data on firm size and revenue for SIC 2834, Pharmaceutical Preparations, and assumed 400 manufacturers of OTC drug products to derive the figures in Table 6 of this document. These data indicate that if 90 percent of the OTC drug product firms meet the SBA size criteria for small businesses, the annualized industry cost attributed to small businesses would amount to $12.3 million out of the total $18.4 million. If revenues of small OTC drug product manufacturers are similar to those of all small manufacturers in SIC 2834, these costs represent only 0.17 percent of small business OTC drug revenues.

TABLE 6.—SMALL BUSINESS IMPACT

	OTC Manufacturing Total	OTC Small Business Total
Firms	400	357
Establishments	478	374
Employees	86,849	18,942
Average employees per firm	217	53
Percentage of total small business employment	NA	100%
Receipts ($000)	$42,363,000	$7,411,000
Receipts per firm ($000)	$106,000	$21,000
Total SKU's affected	98,639	65,792
As percentage of all SKU's	100%	66.7%
Total annualized compliance costs ($ millions)	$18.4	$12.3
Total annualized compliance costs as percentage of annual revenues	0.0004	0.0017

These calculations, however, assume that small businesses can finance the one-time outlays over time. In fact, some small firms may have difficulty raising the funds. FDA finds that, on average, the incremental one-time cost per SKU is about $600 ($57.5 million ÷ 98,639 SKU's). If a small firm manufactures 10 or 20 SKU's, it might need to raise from $6,000 to $12,000 within the permitted implementation period. In view of the figures developed for Table 6 of this document, which imply that the annual revenue per SKU averages about $100,000 for small businesses, such one-time outlays should be manageable for most small firms.

The agency has taken a number of steps to minimize the impact on small entities, including: (1) A 2- to 6- year implementation period to allow the sale of existing product inventories and to permit coordination of required labeling changes with routine industry-initiated labeling changes, (2) a modified format for small packages, (3) an additional phase-in year for OTC drug products covered by a final monograph or an

approved drug application if yearly sales are less than $25,000, and (4) coordination of the FDAMA requirement for listing inactive ingredients with the implementation of this rule. These provisions will provide additional flexibility and cost savings for small entities.

E. Alternatives

The major regulatory alternatives considered included various implementation periods and graphics features, including font sizes and print types. As shown in Table 7 of this document, redesign costs for the 39,310 SKU's with a final monograph decrease substantially with longer implementation periods for products covered by final monographs or approved drug applications. One-time costs for a 1-year implementation period would be about $59.1 million. A 2-year implementation period reduces this figure to $27 million and a 3-year period to $11.9 million. The selected alternative, which includes the 2-year implementation period, but permits a third year for products with low volume sales, reduces these redesign costs to $19.4 million. The agency believes this implementation period will provide substantial relief to industry while achieving important consumer safety and use goals in a timely manner.

TABLE 7.—EFFECT OF IMPLEMENTATION PERIOD ON REDESIGN COSTS

Implementation Period for Final Monographs	Cost ($ Millions)	Redesign Cost With 1 Additional Year for Low Volume Products ($ Millions)
1 year	59.1	46.9
2 years	27.0	19.4
3 years	11.9	8.9

FDA also considered alternative requirements for minimum font sizes and print types. Table 8 of this document presents, for several alternatives, ERG's estimates of the percent of SKU's with current labels too small to fit, the one-time costs for labeling reconfiguration, and the recurring label, carton, and container costs, under varied font size and print requirements. The annualized cost for a minimum 6.0 font but not condensed type (i.e., the horizontal width of the characters reduced approximately 10 to 20 percent while the vertical height of the characters is unchanged) requirement would be $25 million. The final rule allows condensed print, which reduces this cost to $17 million. The agency considered but rejected labeling with smaller than 6-point type size because of the readability issues associated with such labeling.

TABLE 8.—EFFECT OF PRINT REQUIREMENTS ON LABELING RECONFIGURATION COSTS

Minimum Font Size, Print Type Required	Percent of SKU's That Cannot Fit or Are Indeterminate	One-Time Packaging Reconfiguration ($ Millions)	Recurring Incremental Label, Carton and Container Materials ($ Millions)	Total Annualized Packaging Cost ($ Millions)
6.0, not condensed	9.5	45.9	18.3	25.0
6.0, condensed allowed	6.4	38.1	11.5	17.0
4.5, not condensed	3.4	21.0	5.1	8.2
4.5, condensed allowed	2.3	14.0	3.4	5.4

This final rule has been determined to be a major rule for purposes of 5 U.S.C. 801 *et. seq.*, subtitle E of the Small Business Regulatory Enforcement Fairness Act of 1996 (Pub. L. 104–121). FDA is submitting the information and reports as required by the statute.

IX. References

The following references are 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. Miller, G. A., ''The Magical Number Seven, Plus or Minus Two: Some limits on Our Capacity for Processing Information,'' *Psychological Review*, 101(2):343–352, 1994.

2. Shiffrin, R. M., and R. M. Nosofsky, ''Seven Plus or Minus Two: A Commentary On Capacity Limitations,'' *Psychological Review*, 101(2):357–361, 1994.

3. Allen, P. A., and L. C. Crozier, ''Age and Ideal Chunk Size,'' *Journal of Gerontology: Psychological Sciences*, 47(1):47–51, 1992.

4. Wood, R., and A. Bandura, ''Impact of Conceptions of Ability on Self-Regulatory Mechanisms and Complex Decision Making,'' *Journal of Personality and Social Psychology*, 56(3): 407–415, 1989.

5. Chandler, P., and J. Sweller, ''Cognitive Load Theory and the Format of Instruction,'' *Cognition and Instruction*, 8(4):293–332, 1991.

6. Food and Drug Administration, ''National Uniformity for Nonprescription Drugs—Ingredient Listing for OTC Drugs,'' April 1998, Docket No. 98D–0149, Dockets Management Branch.

7. Comment No. 718, Docket No. 96P–0318, Dockets Management Branch.

8. Comment No. 684, Docket No. 96P–0318, Dockets Management Branch.

9. *Webster's Ninth New Collegiate Dictionary*, p. 371, 1990.

10. Nonprescription Drug Manufacturers Association, ''Label Readability Guidelines,'' May 1996, in OTC vol. 28FR, Docket No. 96N–0420, Dockets Management Branch.

11. 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.

12. Comment No. CP1, Docket No. 96P–0318, Dockets Management Branch.

13. Letter from R. G. Chesemore, FDA, to B. Nakutin, dated April 22, 1997, coded PDN1, Docket No. 96P–0318, Dockets Management Branch.

14. Food and Drug Administration ''Consumer Comprehension and Preference for Variation in the Proposed Over-the-Counter Drug Labeling Format,'' in OTC vol. 28FR, Docket No. 96N–0420, Dockets Management Branch.

15. Levy, A. S., S. B. Fein, and R. E. Schucker, ''More Effective Nutrition Label Formats Are Not Necessarily More Preferred,'' *Journal of the American Dietetic Association*, 92(10):1230–1234, 1992.

16. Einarson, T. R., ''Drug-Related Hospital Admissions,'' *The Annals of Pharmacotherapy*, 27:832–840, 1993.

17. Ives, T. J., E. J. Bentz, and R. E. Gwyther, ''Drug-Related Admissions to a Family Medicine Inpatient Service,'' *Archives of Internal Medicine*, 147:1117–1120, 1987.

18. Caranasos, G. J., R. Stewart, and L. E. Cluff, ''Drug-induced Illness Leading to

Hospitalization,'' *Journal of the American Medical Association*, 228:713–7171, 1974.

19. Mitchell, A. A. et al., ''Adverse Drug Reactions in Children Leading to Hospital Admission,'' *Pediatrics*, 82:24–29, 1988.

20. Classen, D. C. et al., ''Adverse Drug Events in Hospitalized Patients,'' *Journal of the American Medical Association*, 277(4):301–306, 1997.

21. Agency for Health Care Policy and Research, ''National Medical Expenditure Survey: Annual Expenses and Sources of Payment for Health Care Services Research Findings 14,'' p. 7, 1995.

22. McKenney, J. M., and W. L. Harrison, ''Drug-related Hospital Admissions,'' *American Journal of Hospital Pharmacists*, 33:792–795, 1976.

23. U.S. Department of Commerce, ''Statistical Abstract of the United States 1998,'' *The National Data Book*, Table 683, 118:426, 1998.

24. U.S. Department of Commerce, ''1992 Census of Retail Trade; Establishment and Firm Size,'' Table 3, pp. 56, 57, and 68, 1992.

25. Comment No. 716, Supplement No. 2 (attachment 1, appendix G), Docket No. 96N–0420, Dockets Management Branch.

26. Research Triangle Institute, ''Compliance Cost of Food Labeling Regulations: Final Report (January, 1991),'' FDA contract number 223–87–2097, Docket Nos. 90N–0134 and 90N–0135, Dockets Management Branch.

27. Comment No. C717, Docket No. 96N–0420, Dockets Management Branch.

28. Eastern Research Group, Inc., ''Cost Impacts of the Over-the-Counter Pharmaceutical Labeling Rule,'' in OTC vol. 28FR, Docket No. 96N–0420, Dockets Management Branch.

29. Office of Management and Budget, ''Economic Analysis of Federal Regulations Under Executive Order 12866,'' 1996.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 330

Over-the-counter drugs.

21 CFR Parts 331, 341, 346, 355, and 358

Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

21 CFR Part 701

Cosmetics, Labeling, Reporting and recordkeeping requirements.

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, 21 CFR parts 201, 330, 331, 341, 346, 355, 358, 369, and 701 are amended as follows:

PART 201—LABELING

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

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

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

§ 201.63 Pregnancy/breast-feeding warning.

(a) The labeling for all over-the-counter (OTC) drug products 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.'' [first four words of this statement in bold type] * * *

* * * * *

(e) The labeling of orally or rectally administered OTC aspirin and aspirin-containing drug products must bear a warning that immediately follows the general warning identified in paragraph (a) of this section. The warning shall be as follows:

''It is especially important not to use'' (select ''aspirin'' or ''carbaspirin calcium,'' as appropriate) ''during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.''

3. Section 201.64 is amended by revising the last sentence in paragraph (b) to read as follows:

§ 201.64 Sodium labeling.

* * * * *

(b) * * * The sodium content per dosage unit shall follow the heading ''Other information'' as stated in § 201.66(c)(7).

* * * * *

4. Section 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 content and format requirements for the labeling of all OTC drug products. Where an OTC drug product is the subject of an applicable monograph or regulation that contains content and format requirements that conflict with this section, the content and format requirements in this section must be followed unless otherwise specifically provided in the applicable monograph or regulation.

(b) *Definitions*. The following definitions 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. 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) *Approved drug application* means a new drug (NDA) or abbreviated new drug (ANDA) application approved under section 505 of the act (21 U.S.C. 355).

(4) *Bullet* means a geometric symbol that precedes each statement in a list of statements. For purposes of this section, the bullet style is limited to solid squares or solid circles, in the format set forth in paragraph (d)(4) of this section.

(5) *Established name* of a drug or ingredient thereof means 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 ingredient is recognized in an official compendium, the official title of the drug or ingredient in such compendium, or, if there is no designated official name and the drug or ingredient is not recognized in an official compendium, the common or usual name of the drug or ingredient.

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

(7) *Heading* means the required statements in quotation marks listed in paragraphs (c)(2) through (c)(9) of this section, excluding subheadings (as defined in paragraph (a)(9) of this section).

(8) *Inactive ingredient* means any component other than an active ingredient.

(9) *Subheading* means the required statements in quotation marks listed in paragraphs (c)(5)(ii) through (c)(5)(vii) of this section.

(10) *Drug facts labeling* means the title, headings, subheadings, and information required under or otherwise described in paragraph (c) of this section.

(11) *Title* means the heading listed at the top of the required OTC drug product labeling, as set forth in paragraph (c)(1) of this section.

(12) *Total surface area available to bear labeling* means all surfaces of the outside container of the retail package or, if there is no such outside container, all surfaces of the immediate container or container wrapper except for the flanges at the tops and bottoms of cans and the shoulders and necks of bottles and jars.

(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, shall contain the title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(8) of this section, and may contain the information under the heading in paragraph (c)(9) of this section, in the order listed.

(1) (Title) ''Drug Facts''. If the drug facts labeling appears on more than one panel, the title ''Drug Facts (continued)'' shall appear at the top of each subsequent panel containing such information.

(2) ''Active ingredient'' or ''Active ingredients'' ''(in each [insert the dosage unit stated in the directions for use (e.g., tablet, 5 mL teaspoonful) or in each gram as stated in §§ 333.110 and 333.120 of this chapter])'', followed by the established name of each active ingredient and the quantity of each active ingredient per dosage unit. Unless otherwise provided in an applicable OTC drug monograph or approved drug application, products marketed without discrete dosage units (e.g., topicals) shall state the proportion (rather than the quantity) of each active ingredient.

(3) ''Purpose'' or ''Purposes'', followed by 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 categories or the principal intended actions of each active ingredient. When an OTC drug monograph contains a statement of identity, the pharmacological action described in the statement of identity shall also be stated as the purpose of the active ingredient.

(4) ''Use'' or ''Uses'', followed by the indication(s) for the specific drug product.

(5) ''Warning'' or ''Warnings'', followed by one or more of the following, if applicable:

(i) ''For external use only'' [in bold type] for topical drug products not intended for ingestion, or ''For'' (select one of the following, as appropriate: ''rectal'' or ''vaginal'') ''use only'' [in bold type].

(ii) All applicable warnings listed in paragraphs (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section with the appropriate subheadings highlighted in bold type:

(A) Allergic reaction warnings set forth in any applicable OTC drug monograph or approved drug application for any product that requires a separate allergy warning. This warning shall follow the subheading ''Allergy alert:''

(B) Reye's syndrome warning for drug products containing salicylates set forth in § 201.314(h)(1). This warning shall follow the subheading ''Reye's syndrome:''

(C) Flammability warning, with appropriate flammability signal word (e.g., §§ 358.150(c) and 358.550(c) of this chapter). This warning shall follow a subheading containing the appropriate flammability signal word described in an applicable OTC drug monograph or approved drug application.

(D) Water soluble gums warning set forth in § 201.319. This warning shall follow the subheading ''Choking:''

(E) Alcohol warning set forth in § 201.322. This warning shall follow the subheading ''Alcohol warning:''

(F) Sore throat warning set forth in § 201.315. This warning shall follow the subheading ''Sore throat warning:''

(G) Warning for drug products containing sodium phosphates set forth in § 201.307(b)(2)(i) or (b)(2)(ii). This warning shall follow the subheading ''Dosage warning:''

(iii) ''Do not use'' [in bold type], followed by all contraindications for use with the product. These contraindications are absolute and are intended for situations in which consumers should not use the product unless a prior diagnosis has been established by a doctor or for situations in which certain consumers should not use the product under any circumstances regardless of whether a doctor or health professional is consulted.

(iv) ''Ask a doctor before use if you have'' [in bold type] or, for products labeled only for use in children under 12 years of age, ''Ask a doctor before use if the child has'' [in bold type], followed by all warnings for persons with certain preexisting conditions (excluding pregnancy) and all warnings for persons experiencing certain symptoms. The warnings under this heading are those intended only for situations in which consumers should not use the product until a doctor is consulted.

(v) ''Ask a doctor or pharmacist before use if you are'' [in bold type] or, for products labeled only for use in children under 12 years of age, ''Ask a doctor or pharmacist before use if the child is'' [in bold type], followed by all drug-drug and drug-food interaction warnings.

(vi) ''When using this product'' [in bold type], followed by the side effects that the consumer may experience, and the substances (e.g., alcohol) or activities (e.g., operating machinery, driving a car, warnings set forth in § 369.21 of this chapter for drugs in dispensers pressurized by gaseous propellants) to avoid while using the product.

(vii) ''Stop use and ask a doctor if'' [in bold type], followed by any signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product.

(viii) Any required warnings in an applicable OTC drug monograph, other OTC drug regulations, or approved drug application that do not fit within one of the categories listed in paragraphs (c)(5)(i) through (c)(5)(vii), (c)(5)(ix), and (c)(5)(x) of this section.

(ix) The pregnancy/breast-feeding warning set forth in § 201.63(a); the third trimester warning set forth in § 201.63(e) for products containing aspirin or carbaspirin calcium; the third trimester warning set forth in approved drug applications for products containing ketoprofen, naproxen sodium, and ibuprofen (not intended exclusively for use in children).

(x) The ''Keep out of reach of children'' warning and the accidental overdose/ingestion warning set forth in § 330.1(g) of this chapter.

(6) ''Directions'', followed by the directions for use described in an applicable OTC drug monograph or approved drug application.

(7) ''Other information'', followed by additional information that is not included under paragraphs (c)(2) through (c)(6), (c)(8), and (c)(9) of this section, but which is required by or is made optional under an applicable OTC drug monograph, other OTC drug regulation, or is included in the labeling of an approved drug application.

(i) Required information about certain ingredients in OTC drug products (e.g., sodium in § 201.64(c)) shall appear as follows: ''each (insert appropriate dosage unit) contains:'' [in bold type] (insert name(s) of ingredient(s) and the quantity of each ingredient). This information shall be the first statement under this heading.

(ii) The phenylalanine/aspartame content required by § 201.21(b), if applicable, shall appear as the next item of information.

(iii) Additional information that is authorized to appear under this heading shall appear as the next item(s) of information. There is no required order for this subsequent information.

(8) ''Inactive ingredients'', followed by a listing of the established name of each inactive ingredient. If the product is an OTC drug product that is not also a cosmetic product, then the inactive ingredients shall be listed in alphabetical order. If the product is an OTC drug product that is also a cosmetic product, then the inactive ingredients shall be listed as set forth in § 701.3(a) or (f) of this chapter, the names of cosmetic ingredients shall be determined in accordance with § 701.3(c) of this chapter, and the provisions in § 701.3(e), (g), (h), (l), (m), (n), and (o) of this chapter and § 720.8 of this chapter may also apply, as appropriate. If there is a difference in the labeling provisions in this § 201.66 and §§ 701.3 and 720.8 of this chapter, the labeling provisions in this § 201.66 shall be used.

(9) ''Questions?'' or ''Questions or comments?'', followed by the telephone number of a source to answer questions about the product. It is recommended that the days of the week and times of the day when a person is available to respond to questions also be included. A graphic of a telephone or telephone receiver may appear before the heading. The telephone number must appear in a minimum 6-point bold type.

(d) *Format requirements*. The title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(9) of this section shall be presented on OTC drug products in accordance with the following specifications. In the interest of uniformity of presentation, FDA strongly reccommends that the Drug Facts labeling be presented using the graphic specifications set forth in appendix A to part 201.

(1) The title ''Drug Facts'' or ''Drug Facts (continued)'' shall use uppercase letters for the first letter of the words ''Drug'' and ''Facts.'' All headings and subheadings in paragraphs (c)(2) through (c)(9) of this section shall use an uppercase letter for the first letter in the first word and lowercase letters for all other words. The title, headings, and subheadings in paragraphs (c)(1), (c)(2), and (c)(4) through (c)(9) of this section shall be left justified.

(2) The letter height or type size for the title ''Drug Facts'' shall appear in a type size larger than the largest type size used in the Drug Facts labeling. The letter height or type size for the title ''Drug Facts (continued)'' shall be no smaller than 8-point type. The letter height or type size for the headings in paragraphs (c)(2) through (c)(9) of this section shall be the larger of either 8-point or greater type, or 2-point sizes greater than the point size of the text. The letter height or type size for the subheadings and all other information described in paragraphs (c)(2) through (c)(9) of this section shall be no smaller than 6-point type.

(3) The title, headings, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section shall be legible and clearly presented, shall not appear in reverse type, shall have at least 0.5-point leading (i.e., space between two lines of text), and shall not have letters that touch. The type style for the title, headings, subheadings, and all other required information described in paragraphs (c)(2) through (c)(9) of this section shall be any single, clear, easy-to-read type style, with no more than 39 characters per inch. The title and headings shall be in bold italic, and the subheadings shall be in bold type, except that the word ''(continued)'' in the title ''Drug Facts (continued)'' shall be regular type. The type shall be all black or one dark color, printed on a white or other light, neutral color, contrasting background, except that the title and the headings may be presented in a single, alternative, contrasting dark color unless otherwise provided in an approved drug application, OTC drug monograph (e.g., current requirements for bold print in §§ 341.76 and 341.80 of this chapter), or other OTC drug regulation (e.g., the requirement for a box and red letters in § 201.308(c)(1)).

(4) When there is more than one statement, each individual statement listed under the headings and subheadings in paragraphs (c)(4) through (c)(7) of this section shall be preceded by a solid square or solid circle bullet of 5-point type size. Bullets shall be presented in the same shape and color throughout the labeling. The first bulleted statement on each horizontal line of text shall be either left justified or separated from an appropriate heading or subheading by at least two square ''ems'' (i.e., two squares of the size of the letter ''M''). If more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement shall be separated from the beginning of the next bulleted statement by at least two square ''ems'' and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line.

(5) The title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(9) of this section may appear on more than one panel on the outside container of the retail package, or the immediate container label if there is no outside container or wrapper. The continuation of the required content and format onto multiple panels must retain the required order and flow of headings, subheadings, and information. A visual graphic (e.g., an arrow) shall be used to signal the continuation of the Drug Facts labeling to the next adjacent panel.

(6) The heading and information required under paragraph (c)(2) of this section shall appear immediately adjacent and to the left of the heading and information required under paragraph (c)(3) of this section. The active ingredients and purposes shall be aligned under the appropriate headings such that the heading and information required under paragraph (c)(2) of this section shall be left justified and the heading and information required under paragraph (c)(3) of this section shall be right justified. If the OTC drug product contains more than one active ingredient, the active ingredients shall be listed in alphabetical order. If more than one active ingredient has the same purpose, the purpose need not be repeated for each active ingredient, provided the information is presented in a manner that readily associates each active ingredient with its purpose (i.e., through the use of brackets, dot leaders, or other graphical features). The information described in paragraphs (c)(4) and (c)(6) through (c)(9) of this section may start on the same line as the required headings. None of the information described in paragraph (c)(5) of this section shall appear on the same line as the ''Warning'' or ''Warnings'' heading.

(7) Graphical images (e.g., the UPC symbol) and information not described in paragraphs (c)(1) through (c)(9) of this section shall not appear in or in any way interrupt the required title, headings, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section. Hyphens shall not be used except to punctuate compound words.

(8) The information described in paragraphs (c)(1) through (c)(9) of this section shall be set off in a box or similar enclosure by the use of a barline. A distinctive horizontal barline extending to each end of the ''Drug Facts'' box or similar enclosure shall provide separation between each of the headings listed in paragraphs (c)(2) through (c)(9) of this section. When a heading listed in paragraphs (c)(2) through (c)(9) of this section appears on a subsequent panel immediately after the ''Drug Facts (continued)'' title, a horizontal hairline shall follow the title and immediately precede the heading. A horizontal hairline extending within two spaces on either side of the ''Drug

Facts'' box or similar enclosure shall immediately follow the title and shall immediately precede each of the subheadings set forth in paragraph (c)(5) of this section, except the subheadings in paragraphs (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section.

(9) The information set forth in paragraph (c)(6) of this section under the heading ''Directions'' shall appear in a table format when dosage directions are provided for three or more age groups or populations. The last line of the table may be the horizontal barline immediately preceding the heading of the next section of the labeling.

(10) If the title, headings, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section, printed in accordance with the specifications in paragraphs (d)(1) through (d)(9) of this section, and any other FDA required information for drug products, and, as appropriate, cosmetic products, other than information required to appear on a principle display panel, requires more than 60 percent of the total surface area available to bear labeling, then the Drug Facts labeling shall be printed in accordance with the specifications set forth in paragraphs (d)(10)(i) through (d)(10)(v) of this section. In determining whether more than 60 percent of the total surface area available to bear labeling is required, the indications for use listed under the ''Use(s)'' heading, as set forth in paragraph (c)(4) of this section, shall be limited to the minimum required uses reflected in the applicable monograph, as provided in § 330.1(c)(2) of this chapter.

(i) Paragraphs (d)(1), (d)(5), (d)(6), and (d)(7) of this section shall apply.

(ii) Paragraph (d)(2) of this section shall apply except that the letter height or type size for the title ''Drug Facts (continued)'' shall be no smaller than 7-point type and the headings in paragraphs (c)(2) through (c)(9) of this section shall be the larger of either 7-point or greater type, or 1-point size greater than the point size of the text.

(iii) Paragraph (d)(3) of this section shall apply except that less than 0.5-point leading may be used, provided the ascenders and descenders do not touch.

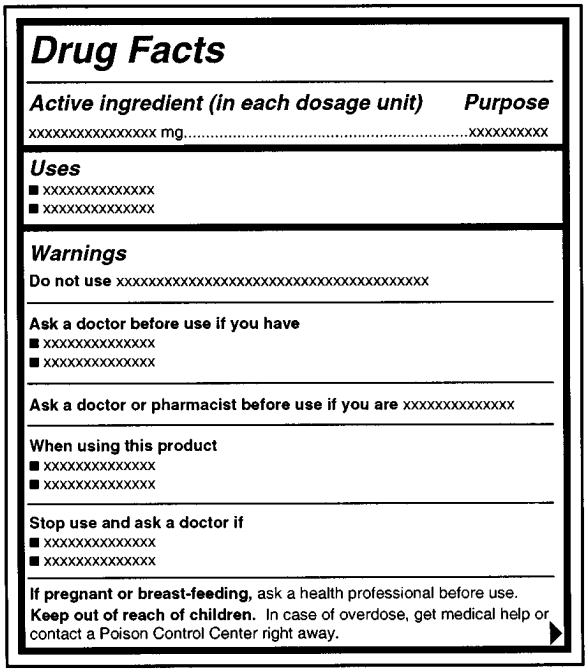
(iv) Paragraph (d)(4) of this section shall apply except that if more than one bulleted statement is placed on the same horizontal line, the additional bulleted statements may continue to the next line of text, and except that the bullets under each heading or subheading need not be vertically aligned.

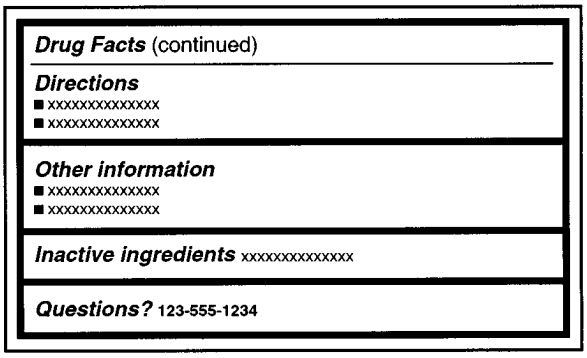
(v) Paragraph (d)(8) of this section shall apply except that the box or similar enclosure required in paragraph (d)(8) of this section may be omitted if the Drug Facts labeling is set off from the rest of the labeling by use of color contrast.

(11)(i) The following labeling outlines the various provisions in paragraphs (c) and (d) of this section:

BILLING CODE 4160–01–F

OTC Drug Product Labeling Outline





BILLING CODE 4160–01–C

(ii) The following sample label illustrates the provisions in paragraphs (c) and (d) of this section:

Drug Facts

Active ingredient (in each tablet) **Purpose**
Chlorpheniramine maleate 2 mg.....Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings
Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ you may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful 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 or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Drug Facts (continued)

Other information ■ store at 20-25°C (68-77°F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

(iii) The following sample label illustrates the provisions in paragraphs (c) and (d) of this section, including paragraph (d)(10) of this section, which permits modifications for small packages:

Drug Facts

Active ingredients (in each tablet) **Purpose**
Aluminum hydroxide gel 200 mg.....Antacid
Magnesium hydroxide 200 mg.....Antacid
Simethicone 25 mg.....Antigas

Uses
■ relieves symptoms referred to as gas
■ relieves: ■ heartburn ■ acid indigestion ■ sour stomach
■ upset stomach due to these symptoms

Warnings
Ask a doctor before use if you have kidney disease

Ask a doctor or pharmacist before use if you are taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if symptoms last for more than 2 weeks

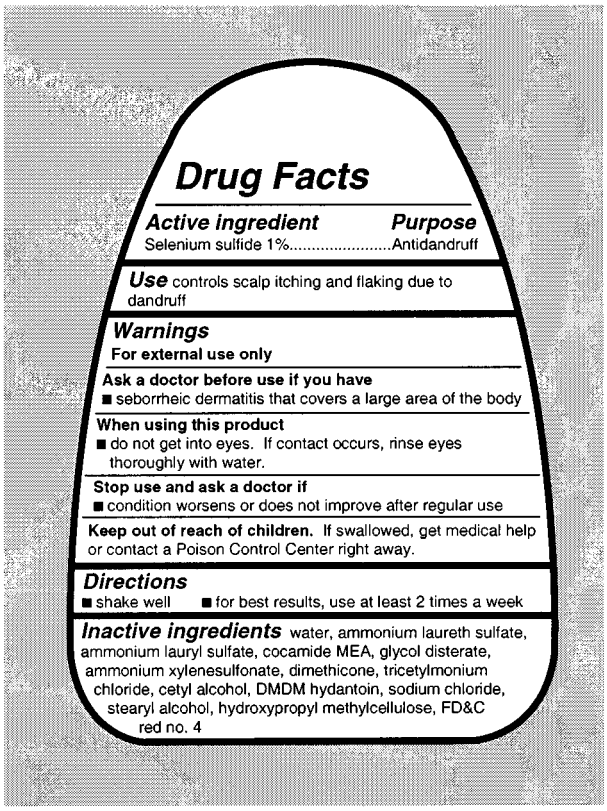
Keep out of reach of children.

Directions ■ chew 1 to 4 tablets 4 times daily
■ do not take more than 16 tablets in 24 hours or use the maximum dosage for more than 2 weeks

Inactive ingredients D&C red no. 30, D&C yellow no. 10, dextrose, FD&C blue no. 1, glycerin, magnesium stearate, mannitol, saccharin sodium, sorbitol, starch, sugar, talc

BILLING CODE 4160–01–C

(iv) The following sample label illustrates the provisions in paragraphs (c) and (d) of this section for a drug product marketed with cosmetic claims:



BILLING CODE 4160–01–C

(e) *Exemptions and deferrals.* FDA on its own initiative or in response to a written request from any manufacturer, packer, or distributor, may exempt or defer, based on the circumstances presented, one or more specific requirements set forth in this section on the basis that the requirement is inapplicable, impracticable, or contrary to public health or safety. Requests for exemptions shall be submitted in three copies in the form of an ''Application for Exemption'' to the Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The request shall be clearly identified on the envelope as a ''Request for Exemption from 21 CFR 201.66 (OTC Labeling Format)'' and shall be directed to Docket No. 98N–0337. A separate request shall be submitted for each OTC drug product. Sponsors of a product marketed under an approved drug application shall also submit a single copy of the exemption request to their application. Decisions on exemptions and deferrals will be maintained in a permanent file in this docket for public review. Exemption and deferral requests shall:

(1) Document why a particular requirement is inapplicable, impracticable, or is contrary to public health or safety; and

(2) Include a representation of the proposed labeling, including any outserts, panel extensions, or other graphical or packaging techniques intended to be used with the product.

(f) *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 OTC drug monograph or by regulation. The terms listed in § 330.1(j) 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 OTC drug monograph or by regulation. The terms listed in § 330.1(i) and (j) of this chapter shall not be used to change in any way the specific title, headings, and subheadings required under paragraphs (c)(1) through (c)(9) of this section.

(g) *Regulatory action.* An OTC drug product that is not in compliance with the format and content requirements in this section is subject to regulatory action.

5. Section 201.314 is amended by revising the first two sentences in paragraph (a) and by revising paragraphs (g)(1) and (h)(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 conspicuously bear, on a clearly contrasting background, the warning statement: ''Keep out of reach of children [highlighted in bold type]. In case of overdose, get medical help or contact a Poison Control Center right away,'' or ''Keep out of reach of children [highlighted in bold type],'' except that if the article is an aspirin preparation, it shall bear the first of these warning statements. * * *

* * * * *

(g)(1) The label of any drug containing more than 5 percent methyl salicylate

(wintergreen oil) should bear a conspicuous warning such as: ''Do not use otherwise than as directed.'' These drug products must also include the ''Keep out of reach of children'' warning and the accidental ingestion warning as required in § 330.1(g) of this chapter.

* * * * *

(h)(1) The labeling of orally or rectally administered over-the-counter aspirin and aspirin-containing drug products subject to this paragraph is required to prominently bear a warning. The warning shall be as follows: ''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.''

* * * * *

6. 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 (under the subheading ''Choking'') and directions:

'''Choking' [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 choking warning.''

* * * * *

7. Appendix A is added to part 201 to read as follows:

Appendix A to Part 201—Examples of Graphic Enhancements Used by FDA

I. Section 201.66 Standard Labeling Format

A. Overall

1. The ''Drug Facts'' labeling is set off in a box or similar enclosure by the use of a barline with all black type printed on a white, color contrasting background.

B. Typeface and size

1. ''Drug Facts'' is set in 14 point Helvetica Bold Italic, left justified.
2. ''Drug Facts (continued)'' is set in 8 point Helvetica Bold Italic for the words ''Drug Facts'' and 8 point Helvetica Regular for the word ''(continued)'' and is left justified.
3. The headings (e.g., ''Directions'') are set in 8 point Helvetica Bold Italic, left justified.
4. The subheadings (e.g., ''Ask a doctor or pharmacist before use if you are'') are set in 6 point Helvetica Bold, left justified.
5. The information is set in 6 point Helvetica Regular with 6.5 point leading, left justified.
6. The heading ''Purpose'' is right justified.
7. The bullet is a 5 point solid square.
8. Two em spacing separates bullets when more than one bullet is on the same line.
9. A table format is used for 3 or more dosage directions.
10. A graphic appears at the bottom of the first panel leading the reader to the next panel.

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the ''Drug Facts'' box (or similar enclosure), providing separation between each of the headings.
2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the ''Drug Facts'' box (or similar enclosure), immediately following the title and immediately preceding the subheadings.
3. A 0.5-point horizontal hairline follows the title, immediately preceding the heading, when a heading appears on a subsequent panel immediately after the ''Drug Facts (continued)'' title.

D. Box or Enclosure

1. All information is enclosed by a 2.5-point barline.

II. Section 201.66 Modified Labeling Format

A. Overall

1. The ''Drug Facts'' labeling is presented in all black type printed on a white color contrasting background.

B. Typeface and size

1. ''Drug Facts'' is set in 9 point Helvetica Bold Italic, left justified.
2. The headings (e.g., ''Directions'') are set in 8 point Helvetica Bold Italic, left justified.
3. The subheadings (e.g., ''Ask a doctor or pharmacist before use if you are'') are set in 6 point Helvetica Bold, left justified.
4. The information is set in 6 point Helvetica Regular with 6.5 point leading, left justified.
5. The heading ''Purpose'' is right justified.
6. The bullet is a 5 point solid square.
7. Bulleted information may start on same line as headings (except for the ''Warnings'' heading) and subheadings, with 2 em spacing separating bullets, and need not be vertically aligned.

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the ''Drug Facts'' box (or similar enclosure), providing separation between each of the headings.
2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the ''Drug Facts'' box (or similar enclosure), immediately following the title and immediately preceding the subheadings.

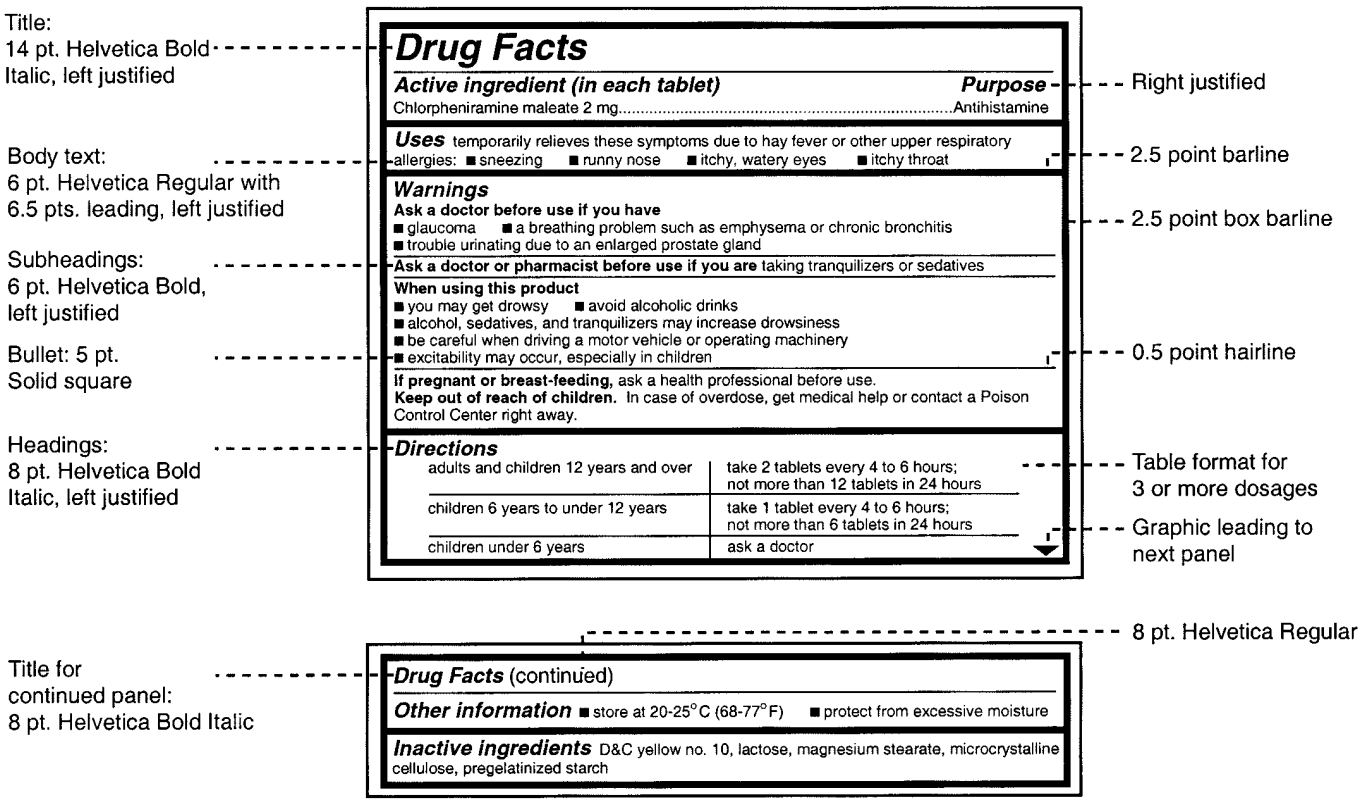
D. Box or Enclosure

1. All information is set off by color contrast. No barline is used.

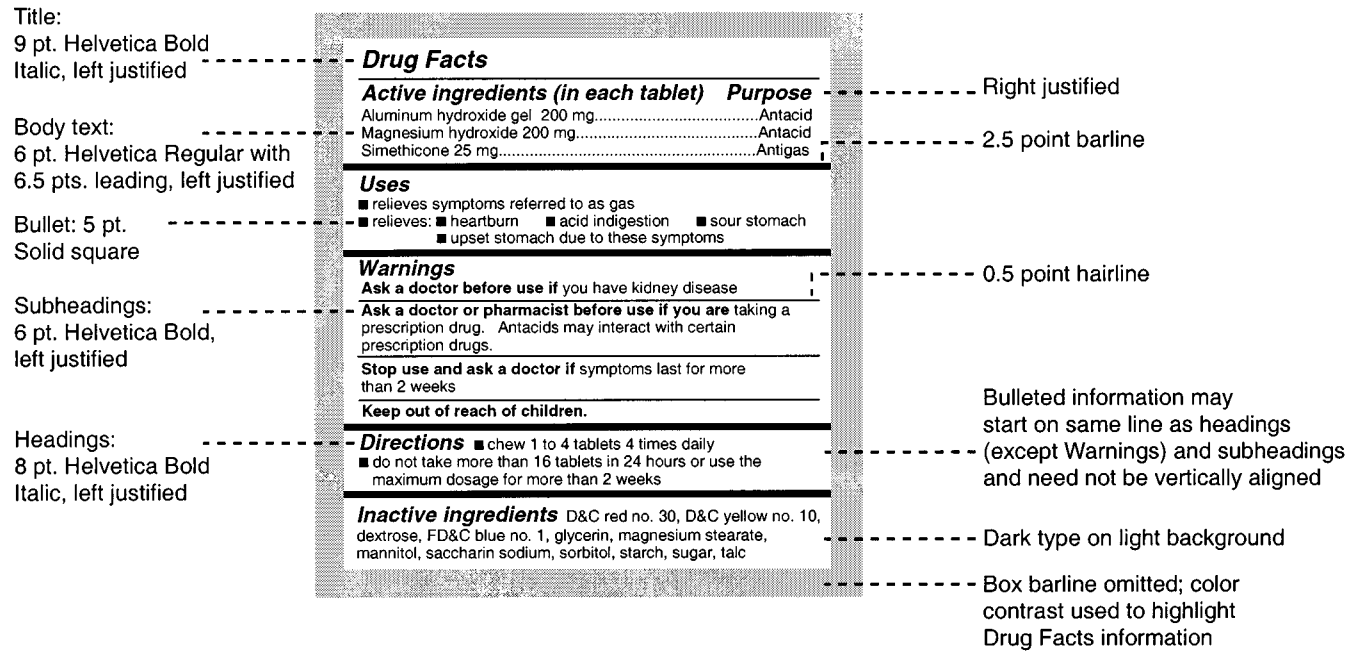
BILLING CODE 4160–01–F

III. Examples of § 201.66 Standard Labeling and Modified Labeling Formats

A. Section 201.66 Standard Labeling Format



B. Section 201.66 Modified Labeling Format



BILLING CODE 4160–01–C

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

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

9. Section 330.1 is amended by revising paragraphs (c)(1), (c)(2), (i), and (j), and by removing the first three sentences in paragraph (g) and adding two sentences in their place 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 in § 201.66 of this chapter. An OTC drug product that is not in compliance with chapter V and subchapter C, including § 201.66 of this chapter, is subject 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 OTC drug monograph established in this part.

(2) The ''Uses'' section of the label and labeling of the product shall contain the labeling describing the ''Indications'' that have been established in an applicable OTC drug monograph or alternative 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. Any other labeling under this subchapter and subchapter C *et seq.* of this chapter shall be stated in the exact language where exact language has been established and identified by quotation marks in an applicable OTC drug monograph or by regulation (e.g., § 201.63 of this chapter), except as provided in paragraphs (i) and (j) of this section.

* * * * *

(g) The labeling for all drugs contains the general warning: ''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 or contact a Poison Control Center right away''; for drugs used topically, rectally, or vaginally and not intended for oral ingestion, ''If swallowed, get medical help or contact a Poison Control Center right away''; and for drugs used topically and intended for oral use, ''If more than used for'' (insert intended use, e.g., pain) ''is accidentally swallowed, get medical help or contact a Poison Control Center right away.'' * * *

* * * * *

(i) The following terms 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 following terms shall not be used to change in any way the title, headings, and subheadings required under § 201.66(c)(1) through (c)(9) of this chapter:

(1) ''Abdominal'' or ''stomach'' (in context only).
(2) ''Administer'' or ''give''.
(3) ''Aggravate(s)'' or ''make(s) worse''.
(4) ''Application of this product'' or ''applying''.
(5) ''Are uncertain'' or ''do not know''.
(6) ''Ask'' or ''consult'' or ''contact''.
(7) ''Asking'' or ''consulting''.
(8) ''Assistance'' or ''help'' or ''aid''.
(9) ''Associated with'' or ''due to'' or ''caused by''.
(10) ''Avoid contact with eyes'' or ''do not get into eyes''.
(11) ''Avoid inhaling'' or ''do not inhale''.
(12) ''Before a doctor is consulted'' or ''without first consulting your doctor'' or ''consult your doctor before''.
(13) ''Beverages'' or ''drinks''.
(14) ''Clean'' or ''cleanse''.
(15) ''Consulting'' or ''advising''.
(16) ''Continue(s)'' or ''persist(s)'' or ''is persistent'' or ''do(es) not go away'' or ''last(s)''.
(17) ''Daily'' or ''every day''.
(18) ''Develop(s)'' or ''begin(s)'' or ''occur(s)''.
(19) ''Difficulty'' or ''trouble''.
(20) ''Difficulty in urination'' or ''trouble urinating''.
(21) ''Discard'' or ''throw away''.
(22) ''Discontinue'' or ''stop'' or ''quit''.
(23) ''Doctor'' or ''physician''.
(24) ''Drowsiness'' or ''the drowsiness effect''.
(25) ''Drowsiness may occur'' or ''you may get drowsy''.
(26) ''Enlargement of the'' or ''an enlarged''.
(27) ''Especially in children'' or especially children''.
(28) ''Exceed'' or ''use more than'' or ''go beyond''.
(29) ''Exceed recommended dosage'' or ''use more than directed''.
(30) ''Excessive'' or ''too much''.
(31) ''Excitability may occur'' or ''you may get excited''.
(32) ''Experience'' or ''feel''.
(33) ''For relief of'' or ''relieves''.
(34) ''For temporary reduction of'' or ''temporarily reduces''.
(35) ''For the temporary relief of'' or ''temporarily relieves''.
(36) ''For the treatment of'' or ''treats''.
(37) ''Frequently'' or ''often''.
(38) ''Give to'' or ''use in''.
(39) ''Immediately'' or ''right away'' or ''directly''.
(40) ''Immediately'' or ''as soon as''.
(41) ''Immediately following'' or ''right after''.
(42) ''Improve(s)'' or ''get(s) better'' or ''make(s) better''.
(43) ''Increased'' or ''more''.
(44) ''Increase your risk of'' or ''cause''.
(45) ''Indication(s)'' or ''Use(s)''.
(46) ''Inhalation'' or ''puff''.
(47) ''In persons who'' or ''if you'' or ''if the child''.
(48) ''Instill'' or ''put''.
(49) ''Is (are) accompanied by'' or ''you also have'' (in context only) or ''(optional: that) occur(s) with''.
(50) ''Longer'' or ''more''.
(51) ''Lung'' or ''pulmonary''.
(52) ''Medication(s)'' or ''medicine(s)'' or ''drug(s)''.
(53) ''Nervousness, dizziness, or sleeplessness occurs'' or ''you get nervous, dizzy, or sleepless''.
(54) ''Not to exceed'' or ''do not exceed'' or ''not more than''.
(55) ''Obtain(s)'' or ''get(s)''.
(56) ''Passages'' or ''passageways'' or ''tubes''.
(57) ''Perforation of'' or ''hole in''.
(58) ''Persistent'' or ''that does not go away'' or ''that continues'' or ''that lasts''.
(59) ''Per day'' or ''daily''.
(60) ''Presently'' or ''now''.
(61) ''Produce(s)'' or ''cause(s)''.
(62) ''Prompt(ly)'' or ''quick(ly)'' or ''right away''.
(63) ''Reduce'' or ''minimize''.
(64) ''Referred to as'' or ''of''.
(65) ''Sensation'' or ''feeling''.
(66) ''Solution'' or ''liquid''.
(67) ''Specifically'' or ''definitely''.
(68) ''Take'' or ''use'' or ''give''.
(69) ''Tend(s) to recur'' or ''reoccur(s)'' or ''return(s)'' or ''come(s) back''.
(70) ''To avoid contamination'' or ''avoid contamination'' or ''do not contaminate''.
(71) ''To help'' or ''helps''.
(72) ''Unless directed by a doctor'' or ''except under the advice of a doctor'' or ''unless told to do so by a doctor''.

(73) ''Use caution'' or ''be careful''.
(74) ''Usually'' or ''generally'' (in context only).
(75) ''You'' (''Your'') or ''the child'' (''the child's'').
(76) ''You also have'' or ''occurs with''.
(77) ''When practical'' or ''if possible''.
(78) ''Whether'' or ''if''.
(79) ''Worsen(s)'' or ''get(s) worse'' or ''make(s) worse''.

(j) 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. The following terms shall not be used to change in any way the specific title, headings, and subheadings required under § 201.66(c)(1) through (c)(9) of this chapter:
(l) ''And''.
(2) ''As may occur with''.
(3) ''Associated'' or ''to be associated''.
(4) ''Consult a doctor''.
(5) ''Discontinue use''.
(6) ''Drug Interaction Precaution''.
(7) ''Due to''.
(8) ''Except under the advice and supervision of a physician''.
(9) ''If this occurs''.
(10) ''In case of''.
(11) ''Notice''.
(12) ''Or''.
(13) ''Occurring with''.
(14) ''Or as directed by a doctor''.
(15) ''Such as''.
(16) ''Such as occurs with''.
(17) ''Tends to''.
(18) ''This product''.
(19) ''Unless directed by a doctor''.
(20) ''While taking this product'' or ''before taking this product''.
(21) ''Within''.

* * * * *

PART 331—ANTACID PRODUCTS FOR OVER–THE–COUNTER (OTC) HUMAN USE

10. The authority citation for 21 CFR part 331 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

11. Section 331.30 is amended by revising paragraph (d) to read as follows:

§ 331.30 Labeling of antacid products.

* * * * *

(d) *Drug interaction precaution*. The labeling of the product contains the following statement ''Ask a doctor or pharmacist before use if you are [bullet][1] presently taking a prescription drug. Antacids may interact with certain prescription drugs.''

* * * * *

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

12. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

13. Section 341.74 is amended by revising paragraphs (c)(4)(v) and (c)(4)(vi) to read as follows:

§ 341.74 Labeling of antitussive drug products.

* * * * *

(c) * * *
(4) * * *
(v) *For products containing dextromethorphan or dextromethorphan hydrobromide as identified in § 341.14(a)(3) and (a)(4) when labeled for adults or for adults and children under 12 years of age. Drug interaction precaution*. ''Do not use 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 do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.''
(vi) *For products containing dextromethorphan or dextromethorphan hydrobromide as identified in § 341.14(a)(3) and (a)(4) when labeled only for children under 12 years of age. Drug interaction precaution*. ''Do not give to a child who is 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 do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product.''

* * * * *

14. Section 341.76 is amended by revising paragraph (c)(4) to read as follows:

§ 341.76 Labeling of bronchodilator drug products.

* * * * *

(c) * * *
(4) *Drug interaction precaution*. ''Do not use 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 do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.''

* * * * *

15. Section 341.80 is amended by revising paragraphs (c)(1)(i)(D) and (c)(1)(ii)(D) to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

* * * * *

(c) * * *
(1) * * *
(i) * * *
(D) *Drug interaction precaution*. ''Do not use 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 do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.''
(ii) * * *
(D) *Drug interaction precaution*. ''Do not give to a child who is 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 do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product.''

* * * * *

PART 346—ANORECTAL DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

16. The authority citation for 21 CFR part 346 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

17. Section 346.50 is amended by revising paragraph (c)(7)(ii) to read as follows:

§ 346.50 Labeling of anorectal drug products.

* * * * *

(c) * * *
(7) * * *
(ii) ''Ask a doctor or pharmacist before use if you are [bullet][1] presently taking a prescription drug for high blood pressure or depression.''

* * * * *

[1] See § 201.66(b)(4) of this chapter.

[1] See § 201.66(b)(4) of this chapter.

PART 355—ANTICARIES DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

18. The authority citation for 21 CFR part 355 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

19. Section 355.50 is amended by revising paragraphs (c)(1) and (c)(2) to read as follows:

§ 355.50 Labeling of anticaries drug products.

* * * * *

(c) * * *

(1) *For all fluoride dentifrice (gel, paste, and powder) products.* ''Keep out of reach of children under 6 years of age. [highlighted in bold type] If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away.'' These warnings shall be used in place of the general warning statements required by § 330.1(g) of this chapter.

(2) *For all fluoride rinse and preventive treatment gel products.* ''Keep out of reach of children. [highlighted in bold type] If more than used for'' (select appropriate word: ''brushing'' or ''rinsing'') ''is accidentally swallowed, get medical help or contact a Poison Control Center right away.'' These warnings shall be used in place of the general warning statements required by § 330.1(g) of this chapter.

* * * * *

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

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

21. 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) * * * [statement in boldface type].

* * * * *

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER–THE–COUNTER SALE

22. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371.

23. Section 369.9 is revised to read as follows:

§ 369.9 General warnings re accidental ingestion by children.

Section 369.20 includes under certain items, but not all medicines, the statement: ''Keep this and all medicines out of children's reach. In case of overdose, get medical help or contact a Poison Control Center right away,'' or ''Keep out of reach of children.'' However, in view of the possibility of accidental ingestion of drugs, it is not only suggested but is recommended that one of these statements be used on the label of all drug products.

§ 369.20 Drugs; recommended warning and caution statements. [Amended]

24. Section 369.20 is amended as follows:

a. The entry ''NUX VOMICA AND STRYCHNINE PREPARATIONS.'' is revised to read as follows:

NUX VOMICA AND STRYCHNINE PREPARATIONS.

''Do not use more than the recommended dosage. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.''

b. The entry beginning ''SALICYLATES, INCLUDING ASPIRIN'' is revised to read as follows:

SALICYLATES, INCLUDING ASPIRIN AND SALICYLAMIDE (EXCEPT METHYL SALICYLATE, EFFERVESCENT SALICYLATE PREPARATIONS, AND PREPARATIONS OF AMINOSALICYLIC ACID AND ITS SALTS). (See also § 201.314 of this chapter.)

''Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away;'' or ''Keep out of reach of children.''

If the article is an aspirin preparation, it should bear the first of the above two warning statements. In either case, the above information should appear on the label.

Caution—For children under 3 years of age, consult your physician; or

Caution—For younger children, consult your physician.

One of the two immediately preceding caution statements is required on the label of all aspirin tablets, but such a statement is not required on the labels of other salicylates clearly offered for administration to adults only.

If offered for use in arthritis or rheumatism, in juxtaposition therewith, the statement:

Caution—If pain persists for more than 10 days, or redness is present, or in conditions affecting children under 12 years of age, consult a physician immediately.

c. The entry ''SALICYLATES: METHYL SALICYLATE (WINTERGREEN OIL).'' is revised to read as follows:

SALICYLATES: METHYL SALICYLATE (WINTERGREEN OIL). (See also §§ 201.303 and 201.314 of this chapter.)

''Do not use otherwise than as directed. Keep out of reach of children to avoid accidental poisoning. If swallowed, get medical help or contact a Poison Control Center right away.''

If the preparation is a counter-irritant or rubefacient the statement:

Caution—Discontinue use if excessive irritation of the skin develops. Avoid getting into the eyes or on mucous membranes.

If offered for use in arthritis or rheumatism, in juxtaposition therewith, the statement:

Caution—If pain persists for more than 10 days, or redness is present, or in conditions affecting children under 12 years of age consult a physician immediately.

d. The entry ''ZINC STEARATE DUSTING POWDERS.'' is revised to read as follows:

ZINC STEARATE DUSTING POWDERS.

''Keep out of reach of children; avoid inhaling. If swallowed, get medical help or contact a Poison Control Center right away.''

§ 369.21 Drugs; warning and caution statements required by regulations. [Amended]

25. Section 369.21 is amended as follows:

a. The entry '''COUGH–DUE–TO–COLD' PREPARATIONS (CARBETAPENTANE CITRATE).'' is revised to read as follows:

''COUGH–DUE–TO–COLD'' PREPARATIONS (CARBETAPENTANE CITRATE). (See § 310.201(a)(20) of this chapter.)

''Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.''

b. The entry ''SODIUM GENTISATE.'' is revised to read as follows:

SODIUM GENTISATE. (See §§ 201.314 and 310.301(a)(2) of this chapter.)

Warning—Do not give to children under 6 years of age or use for prolonged period unless directed by physician.

''Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.''

If offered for use in arthritis or rheumatism, in juxtaposition therewith, the statement:

Caution—If pain persists for more than 10 days, or redness is present, or

in conditions affecting children under 12 years of age, consult a physician immediately.

PART 701—COSMETIC LABELING

26. The authority citation for 21 CFR part 701 continues to read as follows:

Authority: 21 U.S.C. 321, 352, 361, 362, 363, 371, 374; 15 U.S.C. 1454, 1455.

27. Section 701.3 is amended by revising paragraph (d) to read as follows:

§ 701.3 Designation of ingredients.

* * * * *

(d) Where a cosmetic product is also an over-the-counter drug product, the declaration shall declare the active drug ingredients as set forth in § 201.66(c)(2) and (d) of this chapter, and the declaration shall declare the cosmetic ingredients as set forth in § 201.66(c)(8) and (d) of this chapter.

* * * * *

Dated: January 4, 1999.

Jane E. Henney

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

Note: The following Appendix A to the preamble will not appear in the Code of Federal Regulations.

BILLING CODE 4160–01–F

Appendix A to Preamble—Examples of Prototype OTC Drug Product Labeling

Example 1

Single Ingredient Product Using Standard Labeling Format*

Drug Facts

Active ingredient (in each tablet)	***Purpose***
Chlorpheniramine maleate 2 mg	Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings

Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ you may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful 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 or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Drug Facts (continued)

Other information ■ store at 20-25°C (68-77°F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

* Note: 14 point Helvetica Bold Italic Title
8 point Helvetica Bold Italic Headings
6 point Helvetica Bold Subheadings
6 point Helvetica Regular Text
6.5 point Leading

Example 2

Combination Product Using Standard Labeling Format*
[Outer Carton]

Drug Facts

Active ingredients (in each 5 mL) Purpose

Brompheniramine maleate 2 mg.....Antihistamine
Dextromethorphan HBr 10 mg.....Cough suppressant
Pseudoephedrine HCl 30 mg.....Nasal decongestant

Use temporarily relieves:
- sneezing
- runny nose
- nasal congestion
- cough

Warnings

Do not use 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 do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have
- heart disease
- glaucoma
- diabetes
- thyroid disease
- high blood pressure
- cough that occurs with too much phlegm (mucus)
- trouble urinating due to an enlarged prostate gland
- a breathing problem or chronic cough that lasts or as occurs with smoking, asthma, chronic bronchitis, or emphysema

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product
- **do not use more than directed**
- excitability may occur, especially in children
- drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery

Stop use and ask a doctor if
- you get nervous, dizzy, or sleepless
- cough lasts more than 7 days, comes back, or occurs with fever, rash, or headache that lasts. These could be signs of a serious condition.
- symptoms do not get better within 7 days or occur with a fever

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

Drug Facts (continued)

Directions
- take every 4 to 6 hours
- do not take more than 4 doses in 24 hours

adults and children 12 years and over	10 mL
children 6 years to under 12 years	5 mL
children under 6 years	ask a doctor

Inactive ingredients citric acid, FD&C blue #1, glycerin, propylene glycol, purified water, saccharin sodium, sodium benzoate, sorbitol

Questions? **123-555-1234**

* Note: 14 point Helvetica Bold Italic Title
8 point Helvetica Bold Italic Headings
6 point Helvetica Bold Subheadings
6 point Helvetica Regular Text
8 point Helvetica Bold Telephone Number
7 point Leading

Example 3

Combination Product Using Section 201.66(d)(10) Modified Format*
[Bottle with Wraparound Label, No Outer Carton]

PDP Space

Drug Facts

Active ingredients (in each 5 mL)	***Purpose***
Brompheniramine maleate 2 mg	Antihistamine
Dextromethorphan HBr 10 mg	Cough suppressant
Pseudoephedrine HCl 30 mg	Nasal decongestant

Use temporarily relieves:
■ sneezing ■ runny nose ■ nasal congestion ■ cough

Warnings

Do not use 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 do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have ■ diabetes ■ glaucoma
■ thyroid disease ■ cough that occurs with too much phlegm (mucus)
■ trouble urinating due to an enlarged prostate gland ■ heart disease
■ a breathing problem or chronic cough that lasts or as occurs with smoking, asthma, chronic bronchitis, or emphysema ■ high blood pressure

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product ■ **do not use more than directed**
■ drowsiness may occur ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

Stop use and ask a doctor if ■ you get nervous, dizzy, or sleepless
■ cough lasts more than 7 days, comes back, or occurs with fever, rash, or headache that lasts. These could be signs of a serious condition.
■ symptoms do not get better within 7 days or occur with a fever

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

Directions ■ take every 4 to 6 hours; not more than 4 doses in 24 hours

12 years and over	10 mL
6 to 12 years	5 mL
under 6 years	ask a doctor

Inactive ingredients citric acid, FD&C blue #1, glycerin, propylene glycol, purified water, saccharin sodium, sodium benzoate, sorbitol

* Note: 12 point Helvetica Bold Italic Title
8 point Helvetica Bold Italic Headings
6 point Helvetica Bold Subheadings
6 point Helvetica Regular Text
6.5 point Leading

Box barline omitted; color contrast used to highlight Drug Facts information

Example 4

Product Using Standard Labeling Format*
[Stand Alone Tube, No Outer Carton]

Drug Facts

Active ingredient	***Purpose***
Sodium fluoride 0.22%	Anticavity toothpaste

Use aids in the prevention of dental decay

Warning

Keep out of reach of children under 6 years of age. If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away.

Directions

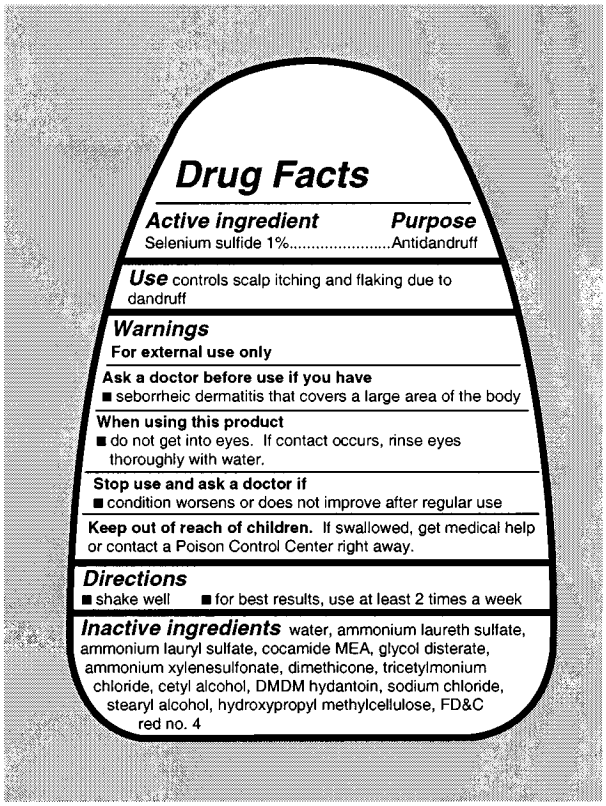
- do not swallow
- instruct children under 6 years in good rinsing habits (to reduce swallowing)
- supervise children as necessary until capable of using without supervision
- adults and children 2 years and over: brush teeth thoroughly after meals or at least twice a day or use as directed by a dentist or doctor
- children under 2 years: ask a dentist or doctor

Inactive ingredients carbomer 956, FD&C blue no.1, hydrated silica, sodium lauryl sulfate, sodium phosphate, sodium saccharin, sorbitol, titanium dioxide, trisodium phosphate, water, xanthan gum

* Note: 14 point Helvetica Bold Italic Title
8 point Helvetica Bold Italic Headings
6 point Helvetica Bold Italic Subheadings
6 point Helvetica Regular Text
7 point Leading

Example 5

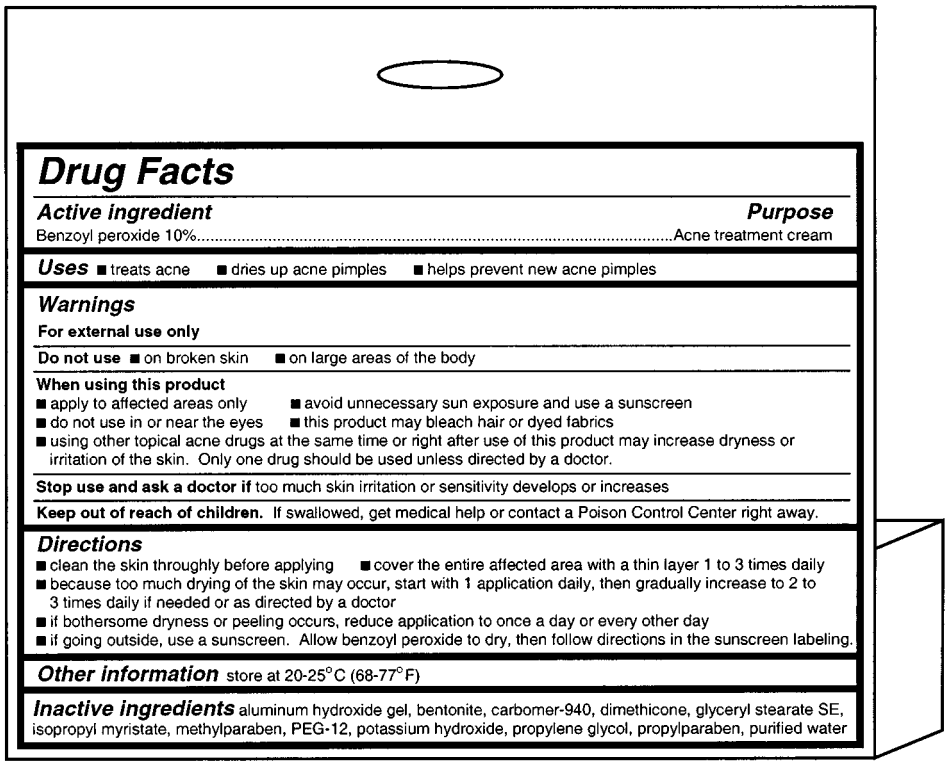
Drug-Cosmetic Product Using Standard Labeling Format*
[Irregular Shape Bottle Label, No Outer Carton]



* Note: 14 point Helvetica Bold Italic Title
8 point Helvetica Bold Italic Headings
6 point Helvetica Bold Subheadings
6 point Helvetica Regular Text
7 point Leading

Example 6

Product Marketed In A Tube Using Standard Labeling Format*
[Packaged In A Carton Riser]



Drug Facts

Active ingredient ***Purpose***

Benzoyl peroxide 10%.....Acne treatment cream

Uses ■ treats acne ■ dries up acne pimples ■ helps prevent new acne pimples

Warnings

For external use only

Do not use ■ on broken skin ■ on large areas of the body

When using this product

■ apply to affected areas only ■ avoid unnecessary sun exposure and use a sunscreen
■ do not use in or near the eyes ■ this product may bleach hair or dyed fabrics
■ using other topical acne drugs at the same time or right after use of this product may increase dryness or irritation of the skin. Only one drug should be used unless directed by a doctor.

Stop use and ask a doctor if too much skin irritation or sensitivity develops or increases

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

■ clean the skin throughly before applying ■ cover the entire affected area with a thin layer 1 to 3 times daily
■ because too much drying of the skin may occur, start with 1 application daily, then gradually increase to 2 to 3 times daily if needed or as directed by a doctor
■ if bothersome dryness or peeling occurs, reduce application to once a day or every other day
■ if going outside, use a sunscreen. Allow benzoyl peroxide to dry, then follow directions in the sunscreen labeling.

Other information store at 20-25°C (68-77°F)

Inactive ingredients aluminum hydroxide gel, bentonite, carbomer-940, dimethicone, glyceryl stearate SE, isopropyl myristate, methylparaben, PEG-12, potassium hydroxide, propylene glycol, propylparaben, purified water

* Note: 14 point Helvetica Bold Italic Title
8 point Helvetica Bold Italic Headings
6 point Helvetica Bold Subheadings
6 point Helvetica Regular Text
7 point Leading

Example 7

Product Using Section 201.66(d)(10) Modified Format*
[Tube With Wraparound Label]

Drug Facts

Active ingredient (in each tablet) ***Purpose***
Calcium carbonate 500 mg.....Antacid

Use relieves: ■ sour stomach ■ acid indigestion ■ heartburn ■ upset stomach due to these symptoms

Warnings

Ask a doctor or pharmacist before use if you are taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if symptoms last more than 2 weeks

Keep out of reach of children.

Directions ■ chew 2 to 4 tablets. Repeat hourly if symptoms return. ■ do not take more than 16 tablets in 24 hours or use the maximum dosage more than 2 weeks

Other information

■ **each tablet contains:** calcium 200 mg

Inactive ingredients cornstarch, mineral oil, sucrose, talc

* Note: 9 point Helvetica Narrow Bold Italic Title
8 point Helvetica Narrow Bold Italic Headings
6 point Helvetica Narrow Bold Subheadings
6 point Helvetica Narrow Text
6 point Leading

[FR Doc. 99–6296 Filed 3–11–99; 11:59 am]
BILLING CODE 4160–01–C