Guidance for Industry

Labeling OTC Human Drug Products

(Small Entity Compliance Guide)

DRAFT GUIDANCE

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document, contact Cazemiro R. Martin at 301-827-2222.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2004
OTC

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The Food and Drug Administration (FDA) has prepared this guidance in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act. It is intended to help small businesses better understand the new over-the-counter (OTC) labeling requirements set forth in 21 CFR 201.66 and prepare new labeling within the prescribed implementation compliance dates. To reduce the economic impact on small businesses, the new requirements provide an additional one-year extension to comply with 21 CFR 201.66 for OTC drug products with sales of less than $25,000 per year (see Table 3).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the *Federal Register* of March 17, 1999 (64 FR 13254), the Food and Drug Administration (FDA) published a final regulation (§ 201.66) establishing standardized content and format for the labeling of OTC drug products (Drugs Facts regulation). Standardized labeling for OTC drug products is intended to make it easier for consumers to read and understand OTC drug product labeling and use OTC drug products safely and effectively.

The new Drug Facts labeling regulation in § 201.66 covers all OTC drug and drug-cosmetic products,[2] whether marketed under a new drug marketing application (NDA), abbreviated new drug

[1] This guidance has been prepared by the Division of Over-the-Counter (OTC) Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

application (ANDA), or OTC drug monograph (or product not yet the subject of a final OTC drug monograph). A copy of § 201.66 can be found at the FDA Dockets Management Branch Web site.[3] The regulation in § 201.66 provides for standardized content and format requirements for the labeling of OTC drug and drug-cosmetic products. The regulation is divided into two main parts: (1) content requirements in paragraph (c) (i.e., headings, subheadings, and information in the order listed) and (2) format requirements in paragraph (d) (i.e., graphic specifications). This guidance document primarily discusses the requirements in paragraphs (c) and (d). The sections of the guidance track the sections of the rule and explain the rule's provisions.

III. SCOPE (21 CFR 201.66(a))

This section explains that the content and format requirements apply to the labeling of all OTC drug products. This scope includes products marketed under a final OTC drug monograph, an approved new drug application (NDA) or abbreviated new drug application (ANDA), and OTC products for which there is no final OTC drug monograph or approved drug application.

IV. DEFINITIONS (21 CFR 201.66(b))

This section contains definitions of terms, including an explanation of certain printing, typesetting, and graphics terms, applicable to this section of the regulation.

V. CONTENT REQUIREMENTS (21 CFR 201.66(c))[4]

This section requires that all OTC drug product labeling contain the following information about the product. The information must be organized according to the following headings and must be presented in this order:

(1) Title[5]	(4) Use(s)	(7) Other information
(2) Active ingredient(s)	(5) Warnings	(8) Inactive ingredients
(3) Purpose(s)	(6) Directions	(9) Questions? (optional)

This information must appear on the outside container or wrapper of the retail package, or on the immediate container label if there is no outside container or wrapper.

Product trade names and company names cannot appear within the Drug Facts box or similar enclosure. (§ 201.66(d)(7))

The following specific information must appear in the Drug Facts section.

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[2] Products with both drug and cosmetic attributes. For example, a sunscreen product intended for sunscreen (i.e., *drug*) uses and for moisturizing (i.e., *cosmetic)* uses.

[3] See http://www.fda.gov/cder/otc/label/label-fr-reg.htm.

[4]See Appendix A(I) to this draft guidance document for a general summary of content labeling requirements set forth in § 201.66(c).

[5] Title means the heading listed at the top of the required OTC drug product labeling, as set forth in § 201.66(c)(1).

(1) Title *(§ 201.66(c)(1))*

If the Drug Facts labeling appears on more than one panel or side of the labeling, the title **Drug Facts** (continued)[6] must appear at the top of each subsequent panel containing such information. See also the guidance for industry entitled *Labeling OTC Human Drug Products Using a Column Format* for guidance on the title, when a column format is used in the product's labeling.

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

An active ingredient is 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. 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. (§ 201.66(b)(2))

Depending on the type of product (oral or topical), the active ingredients can be stated in one of two ways: As the amount "in each":

- [for oral dosage forms] use the dosage unit stated in the directions for use (e.g., tablet, 5 mL teaspoonful), or
- [for topical dosage forms marketed with discrete dosage units] use gram, as stated in §§ 333.110 and 333.120, where the antibiotic active ingredients are stated as an amount in each gram of the product

Products marketed without discrete dosage units (e.g., topicals) must state the proportion (rather than the quantity) of each active ingredient (e.g., 1%), unless otherwise provided in an applicable OTC drug monograph or approved drug application. For example, the OTC anticaries final monograph (21 CFR part 355) lists fluoride active ingredients as a percent fluoride with an available fluoride ion concentration of a certain number of parts per million (ppm). Because the concentration expressed in ppm may be confusing to consumers, the available ion concentration must be expressed on the label in fluoride ion % (i.e., ppm converted to a "%" weight to volume notation of available fluoride ion). These anticaries products must list under this heading the ingredient %, followed by fluoride ion concentration in percent notation (e.g., Sodium fluoride 0.24% (0.14% W/V fluoride ion)).

For OTC drug products that contain both drug and cosmetic ingredients, the drug ingredients are considered the active ingredients, and the cosmetic ingredients are considered the inactive ingredients. (See §§ 201.66(b)(2), 201.66(b)(8))

(3) Purpose(s) (§ 201.66(c)(3))

Each active ingredient in the product is to be followed by a description of the ingredient's purpose, unless this information is specifically exempted in an OTC drug monograph. The statement of identity that appears in an applicable OTC drug monograph shall be stated as the purpose of the

[6] The word *(continued)* appears in regular type.

active ingredient. If there is no statement of identity or no applicable OTC drug monograph, then FDA recommends that the following criteria should be used in stating the ingredient's purpose:

- its general pharmacological category(ies), or
- the principal intended action(s) of the drug

If two active ingredients in a product have the same purpose (e.g., two sunscreen or skin protectant ingredients are present in the product), then the purpose can be stated only once as long as the purpose is clearly associated with both active ingredients. (See example in section VI of this guidance document.)

(4) Use(s) (§ 201.66(c)(4))

The uses are the specific indications or approved uses for the drug product. For drug-cosmetic products, only the drug-related indications can be included in the **Uses** section.

(5) Warning(s) (§ 201.66(c)(5))

With regard to subject specific warnings described in §§ 201.66(c)(5)(ii)(A) through (5)(ii)(G), except for the Reye's syndrome warning, which must appear first when required, there is no required order in which these specific warning statements must appear. The Agency suggests that manufacturers list the specific warning statements in the order of importance or impact.

When applicable, information that must appear under the following **Warning** subheadings includes:

(a) **Do not use** (§ 201.66(c)(5)(iii)):

Information appearing under this subheading includes situations in which consumers should not use the product unless a prior diagnosis has been established by a doctor or for situations in which consumers should not use the product under any circumstances regardless of whether a doctor or health professional is consulted.

In some instances, manufacturers need to convert existing warnings to the new Drug Facts labeling format (see 21 CFR 201.66(a)). For example, the current warning "Do not use this product on irritated skin, on any area that is infected or reddened, if you are a diabetic, or if you have poor blood circulation" would be formatted to appear after the **Do not use** subheading as follows:

- on irritated skin
- on any area that is infected or reddened
- if you are a diabetic
- if you have poor blood circulation

(b) **Ask a doctor before use if you have** (§ 201.66(c)(5)(iv))

Information under this subheading includes all warnings for persons with certain preexisting conditions (excluding pregnancy) and all warnings for persons experiencing certain symptoms. The warnings under this subheading are intended only for situations where consumers should not use the product until a doctor is consulted. Examples of such situations include: (1) high blood pressure,

heart disease, thyroid disease, glaucoma, diabetes, and other conditions listed in various OTC drug monographs or approved drug applications and (2) certain types of cough (i.e., persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm). For example, in the new Drug Facts format, these warnings would appear as follows:

Ask a doctor before use if you have

- heart disease
- cough that occurs with too much phlegm (mucus)
- chronic cough that lasts as occurs with smoking, asthma, chronic bronchitis, or emphysema

(c) **Ask a doctor or pharmacist before use if you are** (§ 201.66(c)(5)(v))

Information under this subheading includes all drug-drug and drug-food interaction warnings. Examples include: sedatives or tranquilizers with antihistamines and a prescription drug for asthma with an OTC bronchodilator.

(d) **When using this product** (§ 201.66(c)(5)(vi))

Information under this subheading includes all side effects that consumers may experience and identifies the substances (e.g., alcohol) that could cause the side effect and the activity (e.g., operating machinery, driving a car) that should be avoided while using the product. This subheading also includes warnings for drugs in dispensers pressurized by gaseous propellants. FDA recommends that such information appear in bulleted text format as follows:

- May cause drowsiness [or can appear as: drowsiness may occur]
- Alcohol, sedatives, and tranquilizers may increase the drowsiness effect [or can appear as: alcohol, sedatives, and tranquilizers may increase drowsiness]
- Do not puncture or incinerate. Contents under pressure.

(e) **Stop use and ask a doctor if** (§ 201.66(c)(vii))

Information under this subheading includes any signs of toxicity or other reactions that would require a patient to immediately stop using the product. For example, the bulleted statement "you get nervous, dizzy, or sleepless" would appear in this section.

(f) Any [other] required warnings (§ 201.66(c)(viii))

This location in the warnings section includes 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 above or below. There are a limited number of such warnings. One such warning is the CFC warning[7] required in certain approved drug applications, which states:

[7] Warning statements for drug products containing or manufactured with chlorofluorocarbons or other ozone-depleting substances (see § 201.320).

"Contains CFC-[insert number] and CFC-[insert number], substances, which harm public health and the environment by destroying ozone in the upper atmosphere."

(g) **Pregnancy and related warnings**

When applicable, these types of warnings must also be placed in the **Warnings** section. Warnings may include one or more of the following:

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

(h) **Keep out of reach of children** and the accidental overdose/ingestion warnings in § 330.1(g)

In a few very special instances, the Keep-out-of-reach-of-children warning can be omitted (see lipstick with a sunscreen in § 352.52(f)(1)(vi)). The accidental overdose/ingestion warning can also be omitted in some instances (see §§ 331.30(f), 332.30(c), 341.74(f) and 352.52(f)(1)(v)).

(6) <u>Directions</u> (§ 201.66(c)(6))

Depending on the product, the directions can appear completely in a table, as a number of bulleted statements, or as a combination of a table and bulleted statements. For example, a table format must be used when dosage directions are provided for three or more age groups or populations. Dosage directions provided for one or two age groups or populations can be presented using bulleted statements. (See §§ 201.66(d)(4)), 201.66(d)(9))

However, a table format can be used for two age groups or populations if it helps make the presentation of the information clearer and easier to read.

FDA recommends that when a combination of a table and bulleted statements is used, the bulleted statements (e.g., "do not use more than directed") appear before or after the table. FDA also recommends that statements such as "shake well" appear as a separate bulleted statement within the directions. For example:

- shake well
- drink a full glass (8 oz) of liquid with each dose
- do not use more than directed

adults and children 12 years and older	2 tablets every 6 hours
children 6 -12 years	1 tablet every 6 hours
children under 6 years	ask a doctor

(7) Other Information (§ 201.66(c)(7))

Information under this heading must contain information not included under the other headings or subheadings, but is required or is made optional under an OTC drug monograph, other OTC drug regulation, or approved drug application.

If present and required by the OTC drug regulation to be included in the OTC drug labeling, certain ingredients in OTC drug products (e.g., sodium in § 201.64(c)) must appear as follows: "each (insert appropriate dosage unit) contains: [in bold type] (insert name(s) of ingredient(s) and quantity of each ingredient)." This statement must be the first statement under this heading.

Under this heading, phenylalanine/aspartame content required by § 201.21(b), if applicable, must appear as the next bulleted statement as follows: "Phenylketonurics: Contains Phenylalanine (insert quantity) mg per (insert appropriate dosage unit)."

The tamper-evident statement must be prominently placed on the drug product package to alert consumers about the product's tamper-evident features (21 CFR 211.132). The tamper-evident statement describes the tamper-evident feature of the product package and advises consumers that, if the feature is breached or missing when the product is purchased, tampering may have occurred. Tamper-evident packaging with an appropriate labeling statement will be more likely to protect consumers because the consumer will be in a better position to detect tampering when he or she has knowledge that a tamper-evident feature has been incorporated into the product design. The Agency allows flexibility in the placement of this statement on the package and does not require that it be included within the Drug Facts section. However, if included in this section, the statement must appear under the heading "**Other information**" (see 21 CFR 201.66(c)(7)).

The Agency also noted in the final rule preamble for the Drug Facts regulation that many products are now marketed with "peel back" or "fold out" labels affixed to the product package and that these labels could be used to accommodate all of the FDA required information in the Drug Facts section (64 FR 13254 at 13268; March 17, 1999). These types of labels were not in use at the time the tamper-evident requirements became effective. Recently, interested parties have inquired whether the tamper-evident statement may be included in a Drug Facts section that appears in such "peel back" or "fold out" labels. We believe that the goals of the tamper evident statement would likely not be achieved if the statement only appears in a "peel back" or "fold out" label and is not clearly visible without peeling back or folding out the label.

It is important that the consumer view the tamper-evident statement before purchase and use of the product so that he or she will be better aware of the tamper-evident features and any signs of tampering. Once the consumer opens the tamper-evident package, the tamper-evident features have

been breached. If the consumer has failed to examine these features before opening, then the consumer will likely not know if there were any signs of tampering. A tamper-evident statement inside a "peel back" or "fold out" label that is not visible on the outside of the package is unlikely to be viewed before breach of the tamper evident feature. The consumer may not be aware to peel back or unfold this label to view the tamper-evident statement before opening the package. Thus, we recommend that the statement not appear within the Drug Facts box in a "peel back" or "fold out" label if the statement would not be clearly visible without peeling back or folding out the label. We recommend instead in these circumstances that the tamper evident statement be outside the Drug Facts box in another part of the label where the statement is clearly visible without further manipulation of that label.

For example, the above-mentioned statements would appear under this heading as follows:

Other information

- each tablet contains: calcium 10 mg, magnesium 10 mg, and sodium 15 mg
- Phenylketonurics: Contains phenylalanine 10 mg per tablet
- [insert storage information]
- [if applicable, insert tamper-evident statement]

(8) Inactive ingredients (§ 201.66(c)(8))

This section contains a list of inactive ingredients, using their established names. For OTC drug products (not cosmetic product), the established names of inactive ingredients must be listed in alphabetical order (§ 201.66(c)(8)). For example: **Inactive ingredients** colloidal silicon dioxide, FD&C blue #1 lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, povidone, propylene glycol, titanium dioxide.

For an OTC product that is a drug-cosmetic product, the inactive ingredients must be listed in order of predominance in the product formulation (§ 201.66(c)(8)). For example: **Inactive ingredients** water, sorbitan isostearate, sorbitol, triethanolamine, stearic acid, barium sulfate, benzyl alcohol, dimethicone, methylparaben, aloe extract, carbomer, disodium EDTA.

Note: For ingredients that may be contained in the product, see section VI(5) of this guidance document**.**

(9) Questions? or Questions or comments? (§ 201.66(c)(9))

If this heading is included in the Drug Facts box (see 21 CFR 201.66(c)(9)), the telephone number or a source to answer questions about the product must be included in this section. FDA recommends that the days of the week and times of the day when a person is available to respond to questions also be included. While this heading and subsequent information are not required, the Agency recommends all manufacturers, distributors, and repackers include this heading and subsequent information within the Drug Facts box.

Although not permitted to appear in or otherwise interrupt the required Drug Facts labeling information, brand names or product attributes can appear in the telephone number and/or in the

Web site address. However, if the telephone number appears as letters of the brand name or product attribute, FDA recommends that the manufacturer also include the numerical representation of the telephone number in this section.

VI. FORMAT LABELING REQUIREMENTS (21 CFR 201.66(d))[8]

This section addresses the manner in which the title, headings, subheadings, and other information set forth in § 201.66(c) must be presented in the labeling of OTC drug products. Sample annotated graphics appear in Appendix A to part 201.

(1) Use of bold type and mathematical notation

Where FDA regulations require bold print for specific information, FDA recommends that manufacturers not use bold print for other information in that immediate area (unless required by regulation to do so) because this practice might reduce the emphasis on the FDA bold print information.

For easier understanding, fractions (e.g., 1/2) may be expressed in text format (i.e., one-half) when used within the Drug Facts box or similar enclosure. The text must be in the same single, clear, easy-to-read type style and type size used for the other text included in the Drug Facts box. However, if fractions are expressed in mathematical notation, each component of the numerical notation must be no smaller than 6-point type.

(2) Bulleted Statements

Bullets are a visual cue adopted by the Agency to aid in the presentation of OTC drug or drug-cosmetic product labeling information. Bullets are a solid square or solid circle in a 5-point type size, presented in the same shape and color throughout the labeling. Under § 201.66(d)(4), bullets are required to be used in the following ways:

- When there is more than one statement listed under the headings **Uses**, **Warnings**, **Directions**, or **Other information**, or any subheadings under these headings, each individual statement is preceded by a bullet (see all examples below).
- The first bulleted statement on each horizontal line of text is either left justified or separated from an appropriate heading or subheading by at least 2 square *ems* (i.e., 2 squares the size of the capital letter M in the font being used).
- If more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement is separated from the beginning of the next bulleted statement by at least 2 square *ems* and the complete additional bulleted statements does not continue to the next line of text.

[8] See Appendix A(II) to this draft guidance document for a general summary of content labeling requirements set forth in § 201.66(c).

Note: If the modified format is used, additional bulleted statements can continue to the next line of text.

- Additional bulleted statements on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line (see example 2.b. below). This requirement does not apply when the modified labeling format (as described in section VII below) in § 201.66 (d)(10) is used (see example 2.c. below).

- If necessary, because of space constraints when using the standard labeling format, the Agency would allow a single bulleted statement to appear on the same line as a heading (except the heading **Warnings**) or a subheading (see example 2.e. below). If a bulleted statement is placed on the same line as a heading or subheading, additional bulleted statements that appear under the heading or subheading can either be left justified (see example 2.e below) or aligned with the first bulleted statement.

- If the size of the text is greater than 6-point type, FDA will allow in its discretion that bullets be greater than 5-point type.

The following examples show various arrangements of bulleted statements.

a. ***Uses***
- temporarily relieves pain and itching due to:
  - insect bites
  - minor skin irritations
  - rashes due to poison ivy, oak, and sumac
- dries the oozing and weeping of:
  - poison ivy
  - poison oak
  - poison sumac

Note: Align major bulleted statements and sub-bulleted statements.

b. **Ask a doctor before use if you have**
- heart disease
- glaucoma
- high blood pressure
- thyroid disease
- diabetes
- trouble urinating due to an enlarged prostate gland
- a breathing problem such as emphysema or chronic bronchitis

Note: Multiple bulleted statements on same line are aligned with the previous line of bulleted statements. Any bulleted statements not able to fit entirely on a multi-bulleted line must be left justified.

c. [Modified format] **Ask a doctor before use if you have** ● heart disease ● glaucoma ● high blood pressure ● thyroid disease ● diabetes ● trouble urinating due to an enlarged prostate gland ● a breathing problem such as emphysema or chronic bronchitis

Note: No bullet alignment is required in the modified format; bulleted statements can continue to the next line of text.

d. **Ask a doctor or pharmacist before use if you are** taking a prescription drug for:
- anticoagulation (blood thinning)
- gout
- diabetes
- arthritis

Note: Multiple bulleted statements are not required to appear on same line as subheading.

e. ***Directions*** ● shake well
● adults and children 2 years and over: apply to affected area not more than 3 to 4 times daily
● children under 2 years: ask a doctor

Note: Bullets can appear on same line as headings and subheadings. However, no bulleted statements or text can appear on the same line as the **Warning** heading.

(3) Number of Label Panels/Column Format/Graphic

See separate guidance for industry entitled *Labeling OTC Human Drug Products Using a Column Format*.

(4) Active ingredient(s) and Purpose(s)

When there is more than one active ingredient, they are listed in alphabetical order. Furthermore, when more than one active ingredient has the same purpose, the purpose does not need to be repeated for each ingredient if the information is presented in a manner that readily associates each active ingredient with its purpose (by using brackets, dot leaders, or other graphical features). Examples include:

Active ingredients (in each tablet) **Purpose**
Acetaminophen 500 mg .....Pain reliever/fever reducer
Pseudoephedrine HCl 30 mg .....Nasal decongestant
Triprolidine HCl 1.25 mg.....Antihistamine

Active ingredients **Purpose**
Homosalate 6% }
Oxybenzone 3% }…….....Sunscreen
Padimate O 2% }

Note: Active ingredients with the same pharmacological activity can be bracketed together to avoid repetitive listing of purpose.

(5) Inactive ingredients: "contains one or more of these ingredients" labeling

There may be circumstances when manufacturers, repackers, and distributors who market OTC drug products use multiple suppliers for some products to maintain an uninterrupted supply of the product to their customers. In such cases, the specific inactive ingredients in the products may vary slightly from supplier to supplier: some inactive ingredients may be present in products coming from all suppliers while other inactive ingredients may not be present. In order to have one label for all products, FDA recommends that the ingredients that may (or may not) be contained in each individual product be listed on the labeling in the following manner.

The Agency believes that this type of inactive ingredient labeling can be accomplished best by placing those ingredients that may (or may not) be contained in an OTC drug product in the inactive ingredient listing, as set forth in § 201.66(c)(8), with an asterisk placed next to those ingredients (e.g., acacia*, dextrose*, sucrose, xanthum gum*). The asterisk would then be reprinted at the bottom or end of the inactive ingredient section in the Drug Facts box, with the notation "* contains one or more of these ingredients" (if more than one ingredient may (or may not) be in the product), or "* may contain this ingredient" (if only one ingredient may (or may not) be in the product), whichever is appropriate.

FDA recommends that for product labeling using the standard labeling format set forth in § 201.66, the statement ("* contains one or more of these ingredients," or "* may contain this ingredient," whichever is appropriate) should be left justified at the end of the inactive ingredient section. For product labeling that uses the modified format set forth in § 201.66(d)(10), the appropriate statement should appear at the end of the inactive ingredient section with 2 square *ems* between the last inactive ingredient and the statement. The type size of these statements must be at least 6-point type (see 21 CFR 201.66(d)(2)).

Listing too many alternative ingredients could be misleading and could cause consumer confusion. To avoid such confusion, sponsors may wish to consider using a second set of labels for products with a lengthy list of different inactive ingredients. Additionally, to provide consumers with the opportunity to learn if an ingredient is in the lot number of the product, the Agency recommends that the optional information in § 201.66(c)(9) (**Questions?** or **Questions or comments?** followed by the telephone number of a source to answer questions about the product) be included in labeling.

Sponsors are also reminded to follow all applicable current good manufacturing practice regulations in 21 CFR part 211 for finished pharmaceuticals so that manufacturers maintain appropriate records showing which lot numbers of the product contain which inactive ingredients.

(6) HEADINGS: Uses, Warnings, Directions, Other Information, Inactive Ingredients, and Questions — Information on Same Line as Heading

- The information under any of these headings, except **Warning(s)**, may start on the same line as the heading.
- None of the information under the heading **Warning(s)** can appear on the same line as this heading (§ 201.66(d)(6)). However, information under any of the subheadings that appear under the heading **Warning(s)** can start on the same line as the subheading.

(7) Graphical Images/Pictograms

Graphical images (e.g., the American Dental Association seal, Good Housekeeping seal, the Universal Product Code (UPC) symbol) cannot appear in, or in any way interrupt, the information required in the Drug Facts labeling (§ 201.66(d)(7)). Below are examples of the possible placement of the UPC graphic image:

A pictogram is a pictorial representation of some object used to symbolize information. The use of pictograms is voluntary in product labeling. If used, pictograms must not appear within the Drug Facts labeling (see § 201.66(d)(7)). The only allowed exception is the use of a telephone or telephone receiver before the **Questions** heading (see§ 201.66(c)(9)). A pictogram that directs attention away from required information, that is ambiguous, or that can be misunderstood by consumers may render a product misbranded.
Note: product trade name and company name cannot appear in or in any way interrupt the information required in the Drug Facts labeling.

(8) Barlines/Hairlines[9]

- All of the Drug Facts information must be set off in a box or similar enclosure by the use of a barline (§ 201.66(d)(8)). FDA recommends size 2.5-point type.
- A distinctive horizontal barline (recommended size 2.5-point type) extending to each end of the Drug Facts box or similar enclosure must separate each of the headings in the Drug Facts labeling (§ 201.66(d)(8)).
- A horizontal hairline (recommended size 0.5-point type) extending within two spaces on either side of the **Drug Facts** box or similar enclosure must immediately follow the title Drug Facts (§201.66(d)(8)).
- When a heading appears on a subsequent panel after the **Drug Facts** (continued) title, a horizontal hairline (recommended size 0.5-point type), rather than a barline, must follow the title and immediately precede the heading (§ 201.66(d)(8)).
- A horizontal hairline (recommended size 0.5-point type) extending within two spaces on either side of the Drug Facts box or similar enclosure must immediately precede each of the

[9] A barline is a distinctive horizontal line that extends to each end of the Drug Facts box or similar enclosure and provides separation between each of the headings listed in § 201.66(c)(2) through (c)(9) (§ 201.66(d)(8)). A hairline is a distinctive horizontal line that extends within two spaces on either side of the Drug Facts box or similar enclosure (§ 201.66(d)(8)). This line immediately follows the title **Drug Facts** and the title **Drug Facts** (continued) on subsequent panels and immediately precedes each of the subheadings set forth in § 201.66(c)(5), except the subheadings in § 201.66(c)(5)(ii)(A) through (c)(5)(ii)(G).

subheadings in the **Warning(s)** section except for the subheadings in paragraphs (c)(5)(ii)(A) through (c)(5)(ii)(G). The specific subheadings in these paragraphs are not preceded by any horizontal hairlines.

- When a table is used as the last item of information in the **Directions** section, the last line of the table may be the horizontal barline that immediately precedes the heading of the next section of the labeling (§ 201.66(d)(9)).

Examples of the use of barlines and hairlines appear in Appendix A to part 201. See also the guidance for industry entitled *Labeling OTC Human Drug Products Using a Column Format* for additional information when a column format is used in the labeling.

VII. STANDARD AND MODIFIED LABELING FORMATS

The regulation contains a formula that allows use of a modified labeling format, which is described in § 201.66(d)(10). When the required Drug Facts content information in paragraph (c) printed as specified in paragraph (d), plus any other FDA required information for drug or drug-cosmetic products (other than information required to appear on the principle display panel), requires more than 60 percent of the total surface area available to bear labeling, the Drug Facts labeling must appear in the modified labeling format. In determining whether more than 60 percent available labeling space is required, the indications for use listed under the **Uses(s)** heading must be limited to the minimum required uses reflected in the applicable monograph (see § 330.1(c)(2)). Table 1 describes selected format requirements used in the standard and modified labeling formats.

Table 1. — Comparison of Standard and Modified Labeling Formats

Labeling Element	Standard Format	Modified Format
Drug Facts Box	Set off by barline	Barline may be omitted if color contrast used to set off from the rest of the labeling.
Drug Facts	Larger than largest type size used in Drug Facts box or similar enclosure	Larger than largest type size used in the Drug Facts box or similar enclosure
Drug Facts (continued)	No smaller than 8-point type	No smaller than 7-point type
Headings	≥ 8-point or 2-point type greater than point size of text	≥ 7-point or 1-point type greater than point size of text
Subheadings	No smaller than 6-point type	No smaller than 6-point type
Bulleted text	No smaller than 6-point type	No smaller than 6-point type
Leading	Minimum 0.5-point type	Less than 0.5-point type can be used, provided the ascenders and descenders do not touch
Bullets	Minimum 5-point type Vertical alignment	Minimum 5-point type No alignment required

If you need assistance in making content or format conversions of existing labeling to the new required labeling, you should contact the Division of OTC Drug Products for guidance (see Appendix for contact information).

VIII. TOPIC-SPECIFIC GUIDANCE DOCUMENTS

The Agency has developed several guidance documents to help manufacturers, packers, and distributors implement the final rule establishing standardized content and format requirements for the labeling of all OTC drug products. Currently available guidances include[10]:

- ANDA labeling: guidance for industry entitled *Labeling OTC Human Drug Products — Updating Labeling in ANDAs*
- Column format: guidance for industry entitled *Labeling OTC Human Drug Products —Using a Column Format*

IX. OTHER FDA LABELING REQUIREMENTS

In addition to the standardized content and format regulations, there are other labeling requirements that may be applicable to the product and that manufacturers, packers, and distributors are required to follow. The general labeling requirements in 21 CFR part 201 specify what information must be included on a drug product's labeling and how the information should be presented, among other things. The Federal Food, Drug, and Cosmetic Act (the Act) defines labeling in broad terms, such that labeling means all labels and "other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article" (see section 201(m) of the Act (21 U.S.C. 321(m)). This definition does not require labeling to be physically attached to a drug. For example, an outer carton, a brochure about the product, or a package insert is considered labeling. Table 2 summarizes some of the other labeling requirements that may be applicable in addition to the standardized content and format requirements in 21 CFR 201.66.

Table 2.— General Labeling Requirements in 21 CFR Parts 201 and 211

Paragraph	Description of Paragraph
201.1	Name and place of business of manufacturer, packer, or distributor
201.5	Adequate directions for use
201.17	Location of expiration dates
201.18	Control numbers
201.60	Principle Display Panel
201.61	Statement of Identity • Established name of drug • Statement of general pharmacological category(ies) or the principal intended actions • Bold type • Size related to the most prominent printed matter
201.62	Declaration of net quantity of contents
201.63	Pregnancy/breast feeding warnings
211.132(c)	Tamper-evident labeling

[10] A draft guidance has been issued on EXEMPTIONS AND DEFERRALS (§ 201.66(e)). Once finalized, this guidance will contain the Agency's recommendations on this topic.

X. IMPLEMENTATION OF THE OTC LABELING REQUIREMENTS

- Applicable implementation dates vary according to the regulatory status of the OTC drug product (see Table 3 below).

- FDA has granted a stay of compliance for implementation of the Drug Facts Rule until further notice (67 FR 16304) for OTC drug products that contain no more than two doses of an OTC drug product and, because of their limited surface area available to bear labeling, qualify for the labeling modifications set forth in § 201.66(d)(10).

605

606 **Table 3.— Implementation Chart**
607

Products	Time periods*
Subject to NDA/ANDA:	
Single entity products approved before May 16, 1999.	By May 2002 (or by May 16, 2003, if annual sales of the product are less than $25,000).
Single entity products approved on or after May 16, 1999.	Immediately upon approval of the application.
Combination products approved before May 16, 1999.	By May 2002 (or by May 16, 2003, if annual sales of the product are less than $25,000).
Combination products approved on or after May 16, 1999.	Immediately upon approval of the application.
Subject to OTC Drug Monograph(s):	
Single entity products finalized before May 16, 1999.	By May 16, 2002 (or by May 16, 2003, if annual sales of the product are less than $25,000).
Single entity products finalized on or after May 16, 1999.	Within the period specified in the final monograph. However, if a monograph has not been finalized as of May 16, 2002, then the product must comply as of the first major labeling revision after May 16, 2002, or May 16, 2005, whichever occurs first.
Combination products in which all applicable monographs were finalized before May 16, 1999.	By May 16, 2002 (or by May 16, 2003, if annual sales of the product are less than $25,000).
Combination products in which at least one applicable monograph was finalized before May 16, 1999, and at least one applicable monograph is finalized on or after May 16, 1999.	Within the period specified in the last applicable monograph to be finalized, or by May 16, 2002 (or by May 16, 2003, if annual sales of the product are less than $25,000), whichever occurs first, unless the last applicable monograph to be finalized specifies a later date.
Combination products in which all applicable monographs are finalized on or after May 16, 1999.	Within the period specified in the last applicable monograph to be finalized. However, if the last monograph is not finalized as of May 16, 2002, then the product must comply as of the first major labeling revision after May 16, 2002, or by May 16, 2005, 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 May 16, 2002, then the product must comply as of the first major labeling revision after May 16, 2002, or by May 16, 2005, whichever occurs first.

608 ***** Time delayed until further notice for OTC drug products that contain no more than two doses of an OTC drug product
609 and, because of their limited total surface area available to bear labeling, qualify for the labeling modifications set forth
610 in § 201.66(d)(10).
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615 The Appendix to this draft guidance document is provided for quick reference to certain content and
616 format requirements associated with key labeling elements. If you have questions on whether a
617 particular FDA requirement applies to your drug or drug-cosmetic product, please contact the
618 relevant office listed in the Appendix.
619

620 **APPENDIX: SUMMARY OF LABELING REQUIREMENTS AND RELEVANT**
621 **CONTACTS**
622
623 **Table I. Labeling Content: 21 CFR 201.66(c)(1) through (c)(9)**
624

Paragraph	Description of Paragraph	Comments
(c)(1)	**Drug Facts**, **Drug Facts** (continued)	Title to be used is **Drug Facts** (on subsequent panels use **Drug Facts** (continued)
(c)(2)	**Active ingredient,** established name, quantity	For drug-cosmetic products, the drug ingredients are considered the active ingredients, and the cosmetic ingredients are considered the inactive ingredients. See 21 CFR 201.66(b)(2), 21 CFR 201.66(b)(8), 21 CFR 201.66(c)(8), and 21 CFR 701.3(a) and (f).
(c)(3)	**Purpose(s)**	If there is no statement of identity or no applicable OTC drug monograph, the ingredient purpose is stated based on its general pharmacological category(ies), or the principal intended action(s) of the drug.
(c)(4)	**Use(s)**	The use(s) is/are the specific indication(s) or approved use(s) for the drug product. For drug-cosmetic products, the use in the Drug Facts labeling is attributed only to the drug component. See 21 CFR 201.66(c)(4).
(c)(5)	**Warning(s)**	Warning(s) information appears in a specific order, under the heading **Warnings**, as applicable. Most warnings follow specific subheadings, as described below in (c)(5)(i) through (c)(5)(x).
(c)(5)(i)	**For external/rectal/ vaginal use only**	Appears in bold type. In some instances, the **external-use-only** warning can be omitted. For example, OTC lip protectant drug products may omit this warning (21 CFR 347.50(e)(1)(iii)).
(c)(5)(ii)	All applicable warnings	Appear with subheadings highlighted in bold type.
(c)(5)(ii)(A)	**Reye's syndrome warning**	When this warning is required, it is the first warning of the warnings listed in paragraphs (c)(5)(ii)(A) through (c)(5)(ii)(G) to appear in this location in the **Warnings** labeling.
(c)(5)(ii)(B)	Allergic reaction warnings	Subheading **Allergy alert** is used.
(c)(5)(ii)(C)	**Flammability warning,** with appropriate signal word	The appropriate flammability signal word in an approved drug application or OTC drug monograph is used.

Paragraph	Description of Paragraph	Comments
(c)(5)(ii)(D)	Water soluble gum warning, **Choking**	The subheading **Choking** is used.
(c)(5)(ii)(E)	**Alcohol warning**	Subheading **Alcohol warning** is used.
(c)(5)(ii)(F)	**Sore throat warning**	Subheading **Sore throat warning** is used.
(c)(5)(ii)(G)	**Dosage warning**	The warnings in § 201.307(b)(2)(i) or (b)(2)(ii) for drug products containing sodium phosphates. The subheading **Dosage warning** is used.
(c)(5)(iii)	**Do not use** followed by all contraindications	Subheading used for all absolute contraindications and involve several different types of situations.
(c)(5)(iv)	**Ask a doctor before use if you have**	Subheading used for certain preexisting conditions or when experiencing certain symptoms.
(c)(5)(v)	**Ask a doctor or pharmacist before use if you are**	Subheading used for all drug-drug and drug-food interactions.
(c)(5)(vi)	**When using this product**	Subheading used for all side effects that the consumer may experience; identifies substances or activities that should be avoided while using the product.
(c)(5)(vii)	**Stop use and ask a doctor if**	Subheading used for any signs of toxicity or other reactions that would necessitate immediately discontinuing use of product.
(c)(5)(viii)	Any required warnings	Location used to include any other required warnings that do not fit within §§ 201.66(c)(5)(i) through (c)(5)(vii),(c)(5)(ix), and (e)(5)(x).
(c)(5)(ix)	**The pregnancy/breast feeding warning**	General warning and other related warnings.
(c)(5)(x)	**Keep out of reach of children**	General warning and accidental **overdose/ingestion** warning in § 330.1(g).
(c)(6)	**Directions**	Described in an applicable OTC drug monograph or approved drug application.
(c)(7)	**Other information** and additional information not included in (c)(2) – (c)(6), (c)(8), (c)(9) of this section.	Subheading used for additional information that is not included under the other subheadings, but which is required or is made optional under an OTC drug monograph(s), other OTC drug regulation(s), or approved drug application.
(c)(7)(i)	certain ingredients (e.g. Na)	For example, see § 201.64(b)
(c)(7)(ii)	Phenylalanine	See § CFR 201.21(b)
(c)(7)(iii)	additional information	For example: storage conditions, tamper-evident statement
(c)(8)	**Inactive ingredients**	List of each inactive ingredient, using its established name

Paragraph	Description of Paragraph	Comments
(c)(9)	**Questions?** (or **Questions or Comments?**)	Optional subheading used to provide a telephone number of a source to answer questions about the product.

625
626 **Table II. Labeling Format**: **21 CFR 201.66(d)(1) through (d)(9)**
627

Paragraph	Description of Paragraph
(d)(1)	Drug Facts: first letter of words uppercase
"	Headings, subheadings: first letter of first word uppercase
"	Left justification
(d)(2)	Drug Facts type size greater than largest type size used in Drug Facts labeling
"	Heading 8-pt or 2-pt type sizes greater than text point size
"	≥ 6-pt type size for information in Drug Facts
"	Subheadings ≥ 6-pt type size
"	**Drug Facts** (continued): type size no smaller than 8-pt type
(d)(3)	Letters do not touch
"	≥ 0.5 pt leading (space between lines)
"	No more than 39 characters per inch
"	Bold Italic headings and title
"	Bold subheading, except the phrase "(continued)"
"	Contrasting dark color for title and heading
(d)(4)	Bullet: solid circle or square 5-pt type, same shape and color, left justified or separated from heading or subheading by at least two square ems
"	Bullet on same lines: end of statement separated from bulleted statement by two em spaces
"	Bullet on same lines: additional bulleted statement does not continue on next line
"	Vertical alignment of bulleted statements
(d)(5)	Appear on more than one panel
"	Visual graphic signals continuation
(d)(6)	Left justification of information required by (c)(2)
"	Right justification of information required by (c)(3)
"	Alphabetical order of active ingredients
"	Information required by (c)(4), (c)(6) - (c)(9) may start on same line as required headings
"	None of information required in (c)(5) shall appear on same line as **Warnings**
(d)(7)	Graphical images should not interrupt the heading, subheading

Paragraph	Description of Paragraph
	and information. Hyphens should not be used except to punctuate compound words.
(d)(8)	Enclosed box using barline
"	Horizontal barline separates headings listed in (c)(2) - (c)(9)
"	Horizontal hairline immediately follows the title "Drug Facts (continued)", and immediately precedes a heading or subsequent text that follows after this title.
"	Horizontal hairline extending within 2 spaces on either side of the Drug Facts box shall immediately follow the title and precede the subheadings set forth in (c)(5) [except (c)(5) (ii) A – G]
(d)(9)	Directions in table format when dosage instructions are provided for three or more age groups or populations
"	Horizontal barline preceding the next heading may end the table

For additional information, contact the relevant office or division.

Office of Compliance (HFD-310)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
301-827-8958 or 301-827-8959

or

Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
301-827-2222

or

Office of Cosmetics and Colors (HFS-105)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW.
Washington, DC 20204
202-205-4061