Guidance for Industry

Labeling OTC Human Drug Products Questions and Answers

DRAFT GUIDANCE

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

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

OTC
January 2005

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Labeling OTC Human Drug Products — Questions and Answers

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist manufacturers, packers, and distributors of over-the-counter (OTC) drug products who have questions about the standardized labeling content and format requirements in § 201.66 (21 CFR 201.66). The examples in this guidance illustrate various format and content features of the labeling requirements and show how OTC drug monograph labeling information can be converted to the OTC "Drug Facts" format. This is one of a series of guidances intended to facilitate compliance with the labeling requirements in § 201.66.

II. BACKGROUND

In the *Federal Register* of March 17, 1999 (64 FR 13254), the Food and Drug Administration (FDA) published a final rule (21 CFR 201.66) establishing standardized content and format for the labeling of OTC drug products (Drug Facts labeling). The Drug Facts 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 Drug Facts labeling regulation in § 201.66 covers all OTC drug and drug-cosmetic products, whether marketed under a new drug marketing application (NDA), abbreviated new drug application (ANDA), or OTC drug monograph (or product not yet the subject of a final OTC drug monograph).[2]

The regulation is divided into two main parts: (1) Content requirements (i.e., headings, subheadings, and the order in which certain information must be listed) and (2) format

[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 (FDA).

[2] The text of § 201.66 can be found at the FDA Division of Dockets Management Internet site located at http://www.fda.gov/cder/otc/label/label-fr-reg.htm.

requirements (i.e., graphic specifications). This guidance primarily discusses questions received from manufacturers, packers, and distributors relating to these requirements, which are set forth in § 201.66 (c) and (d), respectively.

III. CONTENT LABELING REQUIREMENTS

The following questions and answers address the OTC labeling requirements in § 201.66. Tables in Appendix A of this draft guidance list the specific section-by-section requirements in § 201.66(c) and (d) as well as the expectations for implementing the requirements in the regulation. Please refer to these tables for details on specific requirements.

Question 1: What labeling information do the regulations require for all OTC drug products?

Answer 1: Section 201.66 requires that all OTC drug product labeling contain the following information about the product. This information must be organized according to the following headings and must be presented in the following order:

1. Title ("Drug Facts" or "Drug Facts (continued)")
2. Active ingredients
3. Purpose
4. Use(s)
5. Warnings
6. Directions
7. Other information
8. Inactive ingredients
9. Questions (optional) ("Questions?" or "Questions or comments?")

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. (If the Drug Facts information appears on the outside container or wrapper of the retail package, its use on the immediate container is optional. See Appendix A.)

Question 2: Why must the title "Drug Facts (continued)" appear on each subsequent panel in which the Drug Facts appear?

Answer 2: The title "Drug Facts" must appear on the first panel and the title "Drug Facts (continued)" must appear on each subsequent panel to ensure that the person reading the labeling can follow through to the end of the labeling (§ 201.66(c)(1)).

Question 3: What indications can be included in the* Use(s)*) section if the product is a drug and cosmetic product?

Answer 3: For drug-cosmetic products, only the drug-related indications can be included in the *Use(s)* section.

Question 4: Is there a required order for listing subject specific warnings?

Answer 4: Section 201.66(c) requires that warnings in paragraph (c)(5) appear in the order listed.

Question 5: ***What information must appear under the* Warnings *subheading "Do not use"? Can I convert the text of existing warnings in final OTC monographs or approved applications to the bulleted statement format under this subheading?***

Answer 5: The "Do not use" subheading (§ 201.66(c)(5)(iii)) is reserved for (1) products that should not be used unless a previous diagnosis has been made by a doctor or (2) products that should not be used under any circumstances by certain consumers, regardless of whether a doctor or health professional is consulted.

Manufacturers can convert existing formats to the Drug Facts labeling format. For example, the current warning "Do not use this product unless a diagnosis of asthma has been made by a doctor" can be placed under the subheading "Do not use" and shortened to read "unless a diagnosis of asthma has been made by a doctor." (i.e., "**Do not use** unless a diagnosis of asthma has been made by a doctor")

Question 6: ***How could I convert a lengthy warning under the subheading "Ask a doctor before use if you have" into the bulleted text format?***

Answer 6: Here is an example: The warning for oral and topical antitussives states: "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor." Under this subheading, this warning can be converted into bulleted statements as follows:

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

Question 7: ***How could I convert the OTC antihistamine drug product warning "Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor" into bulleted text ?***

Answer 7: This warning could appear as follows:

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

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

Question 8: ***What information must appear under the subheading "When using this product"? How could I convert text of existing required warnings to bulleted text format under this subheading?***

Answer 8: This subheading must be used for all side effects that consumers may experience. It identifies substances (e.g., alcohol) or activities (e.g., operating machinery, driving a car) that should be avoided while using the product. This subheading must also include warnings for drugs in dispensers pressurized by gaseous propellants. Such information whould appear in bulleted text format as follows:

- may cause drowsiness [or may appear as: ● drowsiness may occur]
- alcohol, sedatives, and tranquilizers may increase the drowsiness effect [or may appear as: ● alcohol, sedatives, and tranquilizers may increase drowsiness]
- do not puncture or incinerate; contents under pressure.

Question 9: What information must appear under the subheading "Stop use and ask a doctor if"?

Answer 9: You must include under the "Stop use…" subheading any signs of toxicity or other reactions that would require a consumer to immediately stop using the product. For example, the bulleted statement "you get nervous, dizzy, or sleepless" would appear in this section.

Question 10: Where must I put warnings required in an applicable OTC drug monograph, in other OTC drug regulations, or in an approved drug application that do not otherwise fit under the* Warning *heading or subheadings?

Answer 10: Such warnings must be placed in the Drug Facts *Warning* section. For example, chlorofluorocarbons (CFC) warnings, required in certain approved drug applications, must be put in the *Warnings* section. The warning would appear as follows: "Contains CFC-[insert number] and CFC-[insert number], substances that harm public health and the environment by destroying ozone in the upper atmosphere" (§ 201.320).

Question 11: Where must pregnancy information and related warnings be placed?

Answer 11: When applicable, these types of warnings must also be placed in the second to last subsection of the *Warnings* section. Warnings may include one or more of the following:

- The pregnancy/breast-feeding warning
- The third trimester warning 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).

Question 12: Should all OTC drug product labeling include the "Keep out of reach of children" and the accidental overdose/ingestion warnings?

Answer 12: In most cases, these warnings are required for OTC drug products and therefore must be included in the Drug Facts box. In a few very special instances, the "Keep out of reach of children" warning may be omitted. (See lipstick with a sunscreen in § 352.52(f)(1)(vi).) The accidental overdose/ingestion warning may also be omitted in some instances, as specified in an applicable OTC drug monograph or approved new drug application.

Question 13: Do I have to present information under* Directions *in a table format?

Answer 13: 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 (§ 201.66(d)(9)). Dosage directions provided for one or two age groups or populations can be presented using bulleted statements. 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.

Under this heading, information other than age groups should appear as bulleted statements. 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

Question 14: What information must be included under the heading* Other information*?

Answer 14: This section must include information that is 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 applicable, the first bulleted statement under this heading must include calcium, magnesium, potassium, and sodium to read as follows: "each (insert appropriate dosage unit) contains: [in bold type] (insert name(s) of ingredient(s) and quantity of each ingredient)" (§§ 201.70, 201.71, 201.72, 201.64, respectively. See also § 201.66(c)(7)(i)).

If applicable, phenylalanine/aspartame content shall appear as the next item as follows: "Phenylketonurics: Contains Phenylalanine (insert quantity) mg per (insert appropriate dosage unit)." This statement must be listed as the first bulleted

statement under this heading or the second bulleted statement if Ca, Mg, Na, or K is (are) present. For example:

Other information

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

Question 15: Where must the tamper-evident statement appear in my OTC product labeling?

Answer 15: 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.

Question 16: Do I have to list the inactive ingredients in my OTC drug product labeling in alphabetical order?

Answer 16: It depends.

For OTC drug products that are not also cosmetic products, the established name of each inactive ingredient must be listed in alphabetical order (§ 201.66(c)(8)). For example, the *Inactive ingredients* section would appear as follows:

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 descending order of predominance in the product formulation (§§ 201.66(c)(8) and 701.3(a)). For example, the *Inactive ingredients* section would appear as follows:

Inactive ingredients water, sorbitan isostearate, sorbitol, triethanolamine, stearic acid, barium sulfate, benzyl alcohol, dimethicone, methylparaben, aloe extract, carbomer, disodium EDTA

Question 17: Do I have to include a* Questions *section in the Drug Facts box or similar enclosure?

Answer 17: No. Although this heading and subsequent information is not required, the Agency encourages all manufacturers, distributors, and repackers to include a telephone number in this section. The telephone number of a source to answer questions about the product would be included in this section.

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

IV. FORMAT LABELING REQUIREMENTS[4]

Question 18: How must the content labeling requirements be presented within the Drug Facts box or similar enclosure?

Answer 18: All features of the Drug Facts box or similar enclosure and the required content information must be presented according to graphic specifications, which are listed in Appendix A (Table 2) of this draft guidance document (see also §§ 201.66(c) and (d)).

Question 19: Can I use bold type for any information I consider needs greater prominence?

Answer 19: FDA recommends that you avoid using bold type in the immediate area where existing regulations require specific text be in bold type.

Question 20: How should fractions be expressed within the Drug Facts box?

Answer 20: Fractions (e.g., 1/2) can be expressed in mathematical notation or text format (i.e., one-half). 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. If expressed in mathematical notation, each component of the numerical notation must be no smaller than 6-point type.

Question 21: How should I arrange additional text related to a single bulleted statement?

Answer 21: FDA recommends that additional text be formatted as indented subbulleted statements. For example:

Uses

- temporarily relieves pain and itching due to:
  - insect bites
  - minor skin irritations
- dries the oozing and weeping of:
  - poison ivy
  - poison oak
  - poison sumac

Question 22: Can I begin a bulleted statement on the same line as a heading or subheading?

Answer 22: Yes. However, no bulleted statement or text can appear on the same line as the *Warning* heading.

Question 23: Should bulleted statements be left justified when using the standard labeling format?

Answer 23: Yes. The first bulleted statement on each horizontal line of text must be left justified, except if the bulleted statement appears on the same line of an appropriate heading or subheading (§ 201.66(d)(4)). Any bulleted statements that do not fit entirely on a multi-bulleted line should begin left justified on the following line.

[4] See Appendix A (Table 2) of this draft guidance for specific format labeling requirements in § 201.66(d).

(Note: no bulleted statement or text can appear on the same line as the *Warning* heading.)

For example:

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

Question 24: Should bulleted statements be aligned with the bulleted statements on the previous line when using the modified labeling format?

Answer 24: No. Using this format, bulleted statements do not need to be aligned and can continue to the next line of text (§ 201.66(d)(10)(iv)). For example:

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

Question 25: Where can I find guidance on the use of a column format as part of the new OTC labeling requirements?

Answer 25: A guidance document entitled *Labeling OTC Human Drug Products Using a Column Format* is available on the CDER Internet site at http://www.fda.gov/cder/guidance/index.htm. A written request for a copy can be submitted to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Question 26: How can I obtain copies of other FDA labeling guidance relating to the new OTC labeling requirements?

Answer 26: Copies of the guidances are available on the Internet at http://www.fda.gov/cder/guidance/index.htm, or send a written request for single copies to the Division of Drug Information (see address above).

Question 27: How must I list ingredients under the heading* Active ingredients*?

Answer 27: The ingredients must be listed in alphabetical order.

Question 28: How should I list under the heading* Purpose *ingredients with the same pharmacological action?

Answer 28: When more than one active ingredient has the same purpose, the information can be presented in a manner that readily associates each active ingredient with its purpose (by using brackets, dot leaders, or other graphical features). For example:

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

Question 29: How should I list inactive ingredients that may or may not be contained in my product?

Answer 29: These ingredients should be listed in alphabetical order along with those ingredients that are contained in your product. FDA recommends that you place an asterisk next to those ingredients that, depending on the source, may or may not be contained in the product (e.g., acacia*, dextrose*, sucrose, xanthum gum*). The asterisk should be referenced 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 as described in §§ 201.66(d)(1) through (d)(9), 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. The type size of these statements must be at least 6-point type. For product labeling that uses the modified format as described in § 201.66(d)(10), the asterisk statement could appear on the same line as the last listed inactive ingredient if separated from the last listed ingredient by at least two square "ems"[3].

Listing too many alternative ingredients could be misleading and may 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 Part 211 for finished pharmaceuticals so that manufacturers

[3] Two square "ems" are two squares of the size of the letter "M." (See 21 CFR 201.66(d)(4).)

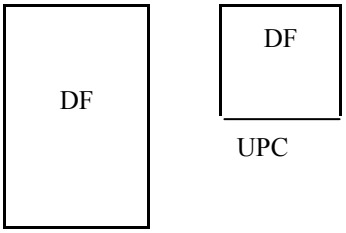
maintain appropriate records showing which lot numbers of the product contain which inactive ingredients.

Question 30: Can I use a pictogram or graphical image such as the Universal Product Code (UPC) symbol within the Drug Facts box?

Answer 30: No. The only pictogram that may be included within the Drug Facts information is a telephone or telephone receiver before the Questions heading. Pictograms and graphical images such as 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)). They can appear outside the Drug Facts box. The following examples illustrate how the UPC code can be placed in relation to the Drug Facts Box.

Illustration 1.

Illustration 2. (showing second panel)



Question 31: When can I use the modified labeling format?

Answer 31: When the required Drug Facts content information printed in the standardized format 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.

Question 32: What is the difference between the standard and modified labeling formats?

Answer 32: The following table illustrates the differences between the two labeling formats.

Table 1. Standard Versus Modified Labeling Format

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 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 greater type, or 2-point type greater than point size of text	≥7-point or greater type, 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	Less than 0.5 point may be used, provided the ascenders and descenders do not touch
Bullets	Minimum 5-point type Vertical alignment	Minimum 5-point type No alignment required

Question 33: What other labeling requirements may be applicable in addition to the standardized content and format requirements in § 201.66?

Answer 33: Additional labeling requirements in Part 201 that may be applicable are summarized as follows:

Table 2. Additional Labeling Requirements

Paragraph	Description of Paragraph
§ 201.1	Name and place of business of manufacturer, packer, or distributor
§ 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
§ 201.20	Declaration of the presence of FD&C Yellow No. 5 and/or FD&C Yellow No. 6
§ 201.132(c)	Tamper-evident labeling

Question 34: When must my product comply with the new OTC labeling requirements?

Answer 34: The date by which your product must comply with the new labeling requirements depends on its current marketing status. See Appendix A (Table 3) of this guidance to determine the date of implementation of the "Drug Facts" requirements.

V. EXEMPTION AND DEFERRALS

Question 35: Are there any exemptions or deferrals to the Drug Facts labeling requirements?

Answer 35: Section 201.66(e) provides that FDA on its own initiative or in response to 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 contrary to public health or safety. FDA points out that 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. FDA reviews each exemption and deferral request submitted and, based on the data submitted, makes a determination whether to grant or deny such requests.

If you have questions on whether a particular FDA requirement applies to your drug or drug-cosmetic product, please contact:

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

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

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

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526 **APPENDIX A: SUMMARY**
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528 **Table 1. Labeling Content: § 201.66(c)(1) Through (c)(9)**
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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, strength/concentration)	For drug-cosmetic products, the drug ingredients are considered the active ingredients, and the cosmetic ingredients are considered the inactive ingredients.
(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. See 21 CFR 201.66(b)(2), (b)(8), (c)(8); and 21 CFR 701.3(a) and (f).
(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.
(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 (e.g., lip protectant drug products), the **external use only** warning may be omitted.
(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.
(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 21 CFR 201.307(b)(2)(i) or (b)(2)(ii) for drug products containing sodium phosphates. The subheading **Dosage warning** is used to introduce this information.
(c)(5)(iii)	**Do not use**	Subheading used for all absolute contraindications and involve several different types of situations.

Paragraph	Description of Paragraph	Comments
(c)(5)(iv)	**Ask a doctor before use if you have**	Subheading is used for certain preexisting conditions.
(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 adverse 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 sections 201.66(c)(5)(i) through (c)(5)(vii), (c)(5)(ix), and (c)(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 21 CFR 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, e.g., storage conditions.	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)	See 21 CFR 201.64(b), 201.70(b), 201.71(b), and 201.72(b)
(c)(7)(ii)	Phenylalanine	See 21 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
(c)(9)	**Questions?** (or **Questions or Comments?**)	Optional heading used to provide a telephone number of a source to answer questions about the product.

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533 **Table 2 Labeling Format: 21 CFR 201.66(d)(1) through (d)(9)**
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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 point sizes greater than text point size

Paragraph	Description of Paragraph
"	Type size ≥6 pt size for information in Drug Facts
"	Subheadings ≥ 6 point type size
"	Drug Facts (continued) type size no smaller than 8-point type
(d)(3)	Letters do not touch
"	≥.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 "ems"
"	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 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 precedes heading immediately after the title "Drug Facts"
"	Horizontal hairline follows the title "Drug Facts (continued)"
"	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

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Table 3. Implementation Chart

Products	Time periods*
Subject to NDA/ANDA:	
Single entity products approved 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 approved on or after May 16, 1999.	Immediately upon approval of the application.
Combination products approved 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 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.

* Time delayed until further notice for OTC drug products that contain no more than two doses of an OTC drug product and, because of their limited total surface area available to bear labeling, qualify for the labeling modifications set forth in § 201.66(d)(10).