

associated with the product without indicating each active ingredient (the established name and quantity of each active ingredient are not required); the dosage form; and the price charged for a prescription for a specific quantity of the drug product.

(3) The reminder advertisement or reminder labeling may also include other written, printed, or graphic matter, e.g., identification of professional or convenience services provided by the pharmacy: *Provided*, That such information is neither false nor misleading and contains no representation or suggestion concerning the drug product's safety, effectiveness, or indications for use.

(4) The price stated in the reminder advertisement or reminder labeling as that charged for a prescription shall include all charges to the consumer including, but not limited to, the cost of the drug product, professional fees, and handling fees, if any. Mailing fees and delivery fees, if any, may be stated separately and without repetition.

(b) This exemption from §§ 201.100 and 202.1 of this chapter is applicable to all prescription drug reminder labeling and reminder advertisements solely intended to provide consumers with information regarding the price charged for prescriptions including price lists, catalogs, and other promotional material, whether mailed, posted in a pharmacy, placed in a newspaper, or aired on radio or television.

(c) Any reminder advertisement or reminder labeling intended to provide consumers with prescription price information which is not in compliance with this section shall be the subject of appropriate regulatory action. Such action may be taken against the product and/or the responsible person.

[40 FR 58799, Dec. 18, 1975]

## PART 201—LABELING

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### APPENDIX A TO PART 201—EXAMPLES OF GRAPHIC ENHANCEMENTS USED BY FDA

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.

SOURCE: 40 FR 13998, Mar. 27, 1975, unless otherwise noted.

EDITORIAL NOTE: Nomenclature changes to part 201 appear at 69 FR 13717, Mar. 24, 2004.

### Subpart A—General Labeling Provisions

#### § 201.1 Drugs; name and place of business of manufacturer, packer, or distributor.

- (a) A drug or drug product (as defined in § 320.1 of this chapter) in finished package form is misbranded under section 502 (a) and (b)(1) of the act if its label does not bear conspicuously the name and place of business of the manufacturer, packer, or distributor. This paragraph does not apply to any drug or drug product dispensed in accordance with section 503(b)(1) of the act.

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(b) As used in this section, and for purposes of section 502 (a) and (b)(1) of the act, the manufacturer of a drug product is the person who performs all of the following operations that are required to produce the product: (1) Mixing, (2) granulating, (3) milling, (4) molding, (5) lyophilizing, (6) tableting, (7) encapsulating, (8) coating, (9) sterilizing, and (10) filling sterile, aerosol, or gaseous drugs into dispensing containers.

(c) If no person performs all of the applicable operations listed in paragraph (b) of this section, no person may be represented as manufacturer except as follows:

(1) If the person performs more than one half of the applicable operations listed in paragraph (b) of this section and acknowledges the contribution of other persons who have performed the remaining applicable operations by stating on the product label that "Certain manufacturing operations have been performed by other firms."; or

(2) If the person performs at least one applicable operation listed in paragraph (b) of this section and identifies by appropriate designation all other persons who have performed the remaining applicable operations, e.g., "Made by (Person A), Filled by (Person B), Sterilized by (Person C)"; or

(3) If the person performs at least one applicable operation listed in paragraph (b) of this section and the person is listed along with all other persons who have performed the remaining applicable operations as "joint manufacturers." A list of joint manufacturers shall be qualified by the phrase "Jointly Manufactured By \_\_\_\_\_," and the names of all of the manufacturers shall be printed together in the same type size and style; or

(4) If the person performs all applicable operations listed in paragraph (b) of this section except for those operations listed in paragraph (d) of this section. For purposes of this paragraph, person, when it identifies a corporation, includes a parent, subsidiary, or affiliate company where the related companies are under common ownership and control.

(d) The Food and Drug Administration finds that it is the common prac-

tice in the drug industry to contract out the performance of certain manufacturing operations listed in paragraph (b) of this section. These operations include: (1) Soft-gelatin encapsulating, (2) aerosol filling, (3) sterilizing by irradiation, (4) lyophilizing, and (5) ethylene oxide sterilization.

(e) A person performs an operation listed in paragraph (b) of this section only if the operation is performed, including the performance of the appropriate in-process quality control operations, except laboratory testing of samples taken during processing, as follows:

(1) By individuals, a majority of whom are employees of the person and, throughout the performance of the operation, are subject to the person's direction and control;

(2) On premises that are continuously owned or leased by the person and subject to the person's direction and control; and

(3) On equipment that is continuously owned or leased by the person. As used in this paragraph, person, when it identifies a corporation, includes a parent, subsidiary, or affiliate company where the related companies are under common ownership and control.

(f) The name of the person represented as manufacturer under paragraph (b) or (c) of this section must be the same as either (1) the name of the establishment (as defined in §207.1 of this chapter) under which that person is registered at the time the labeled product is produced or (2) the registered establishment name of a parent, subsidiary, or affiliate company where the related companies are under common ownership and control. In addition, the name shall meet the requirements of paragraph (g) of this section.

(g) The requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied, in the case of a corporate person, only by the actual corporate name, except that the corporate name may be the name of a parent, subsidiary, or affiliate company where the related companies are under common ownership and control. The corporate name may be preceded or followed by the name of the particular division of

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the corporation. "Company," "Incorporated," etc., may be abbreviated or omitted and "The" may be omitted. In the case of an individual, partnership, or association, the name under which the business is conducted shall be used.

(h)(1) Except as provided in this section, no person other than the manufacturer, packer, or distributor may be identified on the label of a drug or drug product.

(2) The appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. That representation is false and misleading, and the drug product is misbranded under section 502(a) of the act, if the person is not the manufacturer of the product in accordance with this section.

(3) If the names of two or more persons appear on the label of a drug or drug product, the label may identify which of the persons is to be contacted for further information about the product.

(4) If a trademark appears on the drug or drug product label or appears as a mark directly on the drug product (e.g., tablet or capsule), the label may identify the holder or licensee of the trademark. The label may also state whether the person identified holds the trademark or is licensee of the trademark.

(5) If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for \_\_\_\_\_", "Distributed by \_\_\_\_\_", "Manufactured by \_\_\_\_\_ for \_\_\_\_\_", "Manufactured for \_\_\_\_\_ by \_\_\_\_\_", "Distributor: \_\_\_\_\_", "Marketed by \_\_\_\_\_". The qualifying phrases may be abbreviated.

(6) If the packer is identified on the label, the name shall be qualified by the phrase "Packed by \_\_\_\_\_" or "Packaged by \_\_\_\_\_". The qualifying phrases may be abbreviated.

(i) The statement of the place of business shall include the street address, city, State, and ZIP Code. For a foreign manufacturer, the statement of the place of business shall include the street address, city, country, and any applicable mailing code. The street address may be omitted if it is shown in

a current city directory or telephone directory. The requirement for inclusion of the ZIP Code shall apply to consumer commodity labels developed or revised after July 1, 1969. In the case of nonconsumer packages, the ZIP Code shall appear either on the label or the labeling (including the invoice).

(j) If a person manufactures, packs, or distributes a drug or drug product at a place other than the person's principal place of business, the label may state the principal place of business in lieu of the actual place where such drug or drug product was manufactured or packed or is to be distributed, unless such statement would be misleading.

(k) Paragraphs (b), (c), (d), (e), and (f) of this section, do not apply to the labeling of drug components.

(l) A drug product is misbranded under section 502(a) of the act if its labeling identifies a person as manufacturer, packer, or distributor, and that identification does not meet the requirements of this section.

(m) This section does not apply to biological drug products that are subject to the requirements of section 351 of the Public Health Service Act, 42 U.S.C. 262.

[45 FR 25775, Apr. 15, 1980; 45 FR 72118, Oct. 31, 1980, as amended at 48 FR 37620, Aug. 19, 1983; 81 FR 60212, Aug. 31, 2016]

### § 201.2 Drugs and devices; National Drug Code numbers.

The National Drug Code (NDC) number is requested but not required to appear on all drug labels and in all drug labeling, including the label of any prescription drug container furnished to a consumer.

[40 FR 52002, Nov. 7, 1975, as amended at 81 FR 60212, Aug. 31, 2016]

### § 201.5 Drugs; adequate directions for use.

*Adequate directions for use* means directions under which the layman can use a drug safely and for the purposes for which it is intended. (Section 201.128 defines "intended use.") Directions for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of:

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(a) Statements of all conditions, purposes, or uses for which such drug is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the drug is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.

(b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.

(c) Frequency of administration or application.

(d) Duration of administration or application.

(e) Time of administration or application (in relation to time of meals, time of onset of symptoms, or other time factors).

(f) Route or method of administration or application.

(g) Preparation for use, i.e., shaking, dilution, adjustment of temperature, or, other manipulation or process.

[41 FR 6908, Feb. 13, 1976]

### § 201.6 Drugs; misleading statements.

(a) Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug or a device or a food or cosmetic.

(b) The labeling of a drug which contains two or more ingredients may be misleading by reason, among other reasons, of the designation of such drug in such labeling by a name which includes or suggests the name of one or more but not all such ingredients, even though the names of all such ingredients are stated elsewhere in the labeling.

[41 FR 6908, Feb. 13, 1976]

### § 201.10 Drugs; statement of ingredients.

(a) The ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall ap-

pear together, without any intervening written, printed, or graphic matter, except the proprietary names of ingredients, which may be included with the listing of established names, and such statements that are specifically required for certain ingredients by the act or regulations in this chapter.

(b) The term *ingredient* applies to any substance in the drug, whether added to the formulation as a single substance or in admixture with other substances.

(c) The labeling of a drug may be misleading by reason (among other reasons) of:

(1) The order in which the names of the ingredients present in the drug appear in the labeling, or the relative prominence otherwise given such names.

(2) Failure to reveal the proportion of, or other fact with respect to, an ingredient present in such drug, when such proportion or other fact is material in the light of the representation that such ingredient is present in such drug.

(3) The employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.

(4) The featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.

(5) Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.

(d)(1) If the drug is in tablet or capsule form or other unit dosage form, any statement of the quantity of an ingredient contained therein shall express the quantity of such ingredient in each such unit. If the drug is not in unit dosage form, any statement of the quantity of an ingredient contained therein shall express the amount of such ingredient in a specified unit of

weight or measure of the drug, or the percentage of such ingredient in such drug. Such statements shall be in terms that are informative to licensed practitioners, in the case of a prescription drug, and to the layman, in the case of a nonprescription drug.

(2) A statement of the percentage of an ingredient in a drug shall, if the term *percent* is used without qualification, mean percent weight-in-weight, if the ingredient and the drug are both solids, or if the ingredient is a liquid and the drug is a solid; percent weight in volume at 68 °F. (20 °C.), if the ingredient is a solid and the drug is a liquid; and percent volume in volume at 68 °F. (20 °C.), if both the ingredient and the drug are liquids, except that alcohol shall be stated in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C.).

(e) A derivative or preparation of a substance named in section 502(e) of the act is an article derived or prepared from such substance by any method, including actual or theoretical chemical action.

(f) If an ingredient is a derivative or preparation of a substance specifically named in section 502(e) of the act and the established name of such ingredient does not indicate that it is a derivative or preparation of the parent substance named in section 502(e) of the act, the labeling shall, in conjunction with the listing of the established name of such ingredient, declare that such article is a derivative or preparation of such parent substance.

(g)(1) If the label or labeling of a prescription drug bears a proprietary name or designation for the drug or any ingredient thereof, the established name, if such there be, corresponding to such proprietary name or designation shall accompany such proprietary name or designation each time it is featured on the label or in the labeling for the drug; but, except as provided in this subparagraph, the established name need not be used with the proprietary name or designation in the running text of the label or labeling. On any label or page of labeling in which the proprietary name or designation is not featured but is used in the running text, the established name shall be used at least once in the running text

in association with such proprietary name or designation and in the same type size used in such running text: *Provided, however,* That if the proprietary name or designation is used in the running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such running text. If any labeling includes a column with running text containing detailed information as to composition, prescribing, side effects, or contraindications and the proprietary name or designation is used in such column but is not featured above or below the column, the established name shall be used at least once in such column of running text in association with such proprietary name or designation and in the same type size used in such column of running text: *Provided, however,* That if the proprietary name or designation is used in such column of running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such column of running text. Where the established name is required to accompany or to be used in association with the proprietary name or designation, the established name shall be placed in direct conjunction with the proprietary name or designation, and the relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as “brand of” preceding the established name, by brackets surrounding the established name, or by other suitable means.

(2) The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

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(h)(1) In the case of a prescription drug containing two or more active ingredients, if the label bears a proprietary name or designation for such mixture and there is no established name corresponding to such proprietary name or designation, the quantitative ingredient information required on the label by section 502(e) of the act shall be placed in direct conjunction with the most prominent display of the proprietary name or designation. The prominence of the quantitative ingredient information shall bear a reasonable relationship to the prominence of the proprietary name.

(2) If the drug is packaged in a container too small to bear the quantitative ingredient information on the main display panel, the quantitative ingredient information required by section 502(e) of the act may appear elsewhere on the label, even though the proprietary name or designation appears on the main display panel of the label; but side- or back-panel placement shall in this case be so arranged and printed as to provide size and prominence of display reasonably related to the size and prominence of the front-panel display.

(i) A drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1)(A)(ii) and (B) of the act shall be exempt from compliance with those clauses: *Provided*, That:

(1) The label bears:

- (i) The proprietary name of the drug;
- (ii) The established name, if such there be, of the drug;
- (iii) An identifying lot or control number; and
- (iv) The name of the manufacturer, packer, or distributor of the drug; and

(2) All the information required to appear on the label by the act and the regulations in this chapter appears on the carton or other outer container or wrapper if such carton, outer container, or wrapper has sufficient space to bear such information, or such complete label information appears on a leaflet with the package.

[40 FR 13998, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

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### § 201.15 Drugs; prominence of required label statements.

(a) A word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of:

(1) The failure of such word, statement, or information to appear on the part or panel of the label which is presented or displayed under customary conditions of purchase;

(2) The failure of such word, statement, or information to appear on two or more parts or panels of the label, each of which has sufficient space therefor, and each of which is so designed as to render it likely to be, under customary conditions of purchase, the part or panel displayed;

(3) The failure of the label to extend over the area of the container or package available for such extension, so as to provide sufficient label space for the prominent placing of such word, statement, or information;

(4) Insufficiency of label space for the prominent placing of such word, statement, or information, resulting from the use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;

(5) Insufficiency of label space for the prominent placing of such word, statement, or information, resulting from the use of label space to give materially greater conspicuousness to any other word, statement, or information, or to any design or device; or

(6) Smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.

(b) 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:

(1) The use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;

(2) The use of label space to give greater conspicuousness to any word,

statement, or other information than is required by section 502(c) of the act; or

(3) The use of label space for any representation in a foreign language.

(c)(1) All words, statements, and other information required by or under authority of the act to appear on the label or labeling shall appear thereon in the English language: *Provided, however*, That in the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English.

(2) If the label contains any representation in a foreign language, all words, statements, and other information required by or under authority of the act to appear on the label shall appear thereon in the foreign language.

(3) If the labeling contains any representation in a foreign language, all words, statements, and other information required by or under authority of the act to appear on the label or labeling shall appear on the labeling in the foreign language.

[41 FR 6908, Feb. 13, 1976]

**§ 201.16 Drugs; Spanish-language version of certain required statements.**

An increasing number of medications restricted to prescription use only are being labeled solely in Spanish for distribution in the Commonwealth of Puerto Rico where Spanish is the predominant language. Such labeling is authorized under § 201.15(c). One required warning, the wording of which is fixed by law in the English language, could be translated in various ways, from literal translation to loose interpretation. The statutory nature of this warning requires that the translation convey the meaning properly to avoid confusion and dilution of the purpose of the warning. Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act requires, at a minimum, that the label bear the statement “Rx only.” The Spanish-language version of this must be “Solamente Rx”.

[67 FR 4906, Feb. 1, 2002]

**§ 201.17 Drugs; location of expiration date.**

When an expiration date of a drug is required, e.g., expiration dating of drug products required by § 211.137 of this chapter, it shall appear on the immediate container and also the outer package, if any, unless it is easily legible through such outer package. However, when single-dose containers are packed in individual cartons, the expiration date may properly appear on the individual carton instead of the immediate product container.

[43 FR 45076, Sept. 29, 1978]

**§ 201.18 Drugs; significance of control numbers.**

The lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. An incorrect lot number may be regarded as causing the article to be misbranded.

**§ 201.19 Drugs; use of term “infant”.**

The regulations affecting special dietary foods (§ 105.3(e) of this chapter) define an infant as a child not more than 12 months old. Apart from this, the Food and Drug Administration has not established any definition of the term *infant*. Some question has arisen whether, for the purposes of drug labeling, an infant means a child up to 1 year of age or a child up to 2 years of age. Until the term is more precisely defined by legislation or formal regulation, where the exact meaning of the term is significant, manufacturers should qualify any reference to “infant” to indicate whether it refers to a child who is not more than 1 year of age, or a child not more than 2 years of age.

[40 FR 13998, Mar. 27, 1975, as amended at 42 FR 14091, Mar. 15, 1977; 44 FR 16006, Mar. 16, 1979]

**§ 201.20 Declaration of presence of FD&C Yellow No. 5 and/or FD&C Yellow No. 6 in certain drugs for human use.**

(a) The label for over-the-counter and prescription drug products intended for human use administered orally, nasally, rectally, or vaginally, or for use in the area of the eye, containing



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FD&C Yellow No. 5 as a color additive using the names FD&C Yellow No. 5 and tartrazine. The labeling for over-the-counter and prescription drug products shall bear a statement such as “Contains FD&C Yellow No. 5 (tartrazine) as a color additive” or “Contains color additives including FD&C Yellow No. 5 (tartrazine)”. The labels of certain drug products subject to this labeling requirement that are also cosmetics, such as antibacterial mouthwashes and fluoride toothpastes, need not comply with this requirement provided they comply with the requirements of § 701.3 of this chapter.

(b) For prescription drugs for human use containing FD&C Yellow No. 5 that are administered orally, nasally, vaginally, or rectally, or for use in the area of the eye, the labeling required by § 201.100(d) shall bear the warning statement “This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.” This warning statement shall appear in the “Precautions” section of the labeling.

(c) The label for over-the-counter drug products intended for human use administered orally, nasally, rectally, or vaginally containing FD&C Yellow No. 6 shall specifically declare the presence of FD&C Yellow No. 6 by listing the color additive using the name FD&C Yellow No. 6. The labeling for over-the-counter and prescription drug products containing FD&C Yellow No. 6 shall declare the presence of FD&C Yellow No. 6. The labels of certain drug products subject to this labeling requirement that are also cosmetics, such as antibacterial mouthwashes and fluoride toothpastes, need not comply with this requirement provided they comply with the requirements of § 701.3 of this chapter.

[45 FR 60422, Sept. 12, 1980, as amended at 51 FR 41783, Nov. 19, 1986; 52 FR 21509, June 8, 1987; 59 FR 60898, Nov. 29, 1994]

EFFECTIVE DATE NOTE: At 53 FR 49138, Dec. 6, 1988, § 201.20(c) was suspended pending further agency action.

### § 201.21 Declaration of presence of phenylalanine as a component of aspartame in over-the-counter and prescription drugs for human use.

(a) Aspartame is the methylester of a dipeptide composed of two amino acids, phenylalanine and aspartic acid. When these two amino acids are so combined to form aspartame (1-methyl *N*-L- $\alpha$ -aspartyl-L-phenylalanine), they produce an intensely sweet-tasting substance, approximately 180 times as sweet as sucrose. The Food and Drug Administration has determined that aspartame when used at a level no higher than reasonably required to perform its intended technical function is safe for use as an inactive ingredient in human drug products, provided persons with phenylketonuria, who must restrict carefully their phenylalanine intake, are alerted to the presence of phenylalanine in the drug product and the amount of the ingredient in each dosage unit.

(b) The label and labeling of all over-the-counter human drug products containing aspartame as an inactive ingredient shall bear a statement to the following effect: Phenylketonurics: Contains Phenylalanine ( )mg Per (Dosage Unit).

(c) The package labeling and other labeling providing professional use information concerning prescription drugs for human use containing aspartame as an inactive ingredient shall bear a statement to the following effect under the “Precautions” section of the labeling, as required in § 201.57(f)(2): Phenylketonurics: Contains Phenylalanine ( )mg Per (Dosage Unit).

(d) Holders of approved new drug applications who reformulate their drug products under the provisions of this section shall submit supplements under § 314.70 of this chapter to provide for the new composition and the labeling changes.

(Approved by the Office of Management and Budget under control number 0910–0242)

[52 FR 2111, Jan. 20, 1987; 52 FR 12152, Apr. 15, 1987; 53 FR 4135, Feb. 12, 1988]

**§ 201.22 Prescription drugs containing sulfites; required warning statements.**

(a) Sulfites are chemical substances that are added to certain drug products to inhibit the oxidation of the active drug ingredient. Oxidation of the active drug ingredient may result in instability and a loss of potency of the drug product. Examples of specific sulfites used to inhibit this oxidation process include sodium bisulfite, sodium metabisulfite, sodium sulfite, potassium bisulfite, and potassium metabisulfite. Recent studies have demonstrated that sulfites may cause allergic-type reactions in certain susceptible persons, especially asthmatics. The labeling for any prescription drug product to which sulfites have been added as an inactive ingredient, regardless of the amount added, must bear the warning specified in paragraph (b) or (c) of this section.

(b) The labeling required by §§ 201.57 and 201.100(d) for prescription drugs for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations, shall bear the warning statement "Contains (*insert the name of the sulfite, e.g., sodium metabisulfite*), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people." This statement shall appear in the "Warnings" section of the labeling.

(c) The labeling required by §§ 201.57 and 201.100(d) for sulfite-containing epinephrine for injection for use in allergic emergency situations shall bear the warning statement "Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains (*insert the name of the sulfite, e.g., sodium metabisulfite*), a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using

epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations." This statement shall appear in the "Warnings" section of the labeling.

[51 FR 43904, Dec. 5, 1986]

**§ 201.23 Required pediatric studies.**

(a) A manufacturer of a marketed drug product, including a biological drug product, that is used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients, as defined in §§ 314.55(c)(5) and 601.27(c)(5) of this chapter, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the approved indications may be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the known or appropriate use of the drug product in such subpopulations. The applicant may also be required to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing therapies for pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.

(b) The Food and Drug Administration (FDA) may by order, in the form of a letter, after notifying the manufacturer of its intent to require an assessment of pediatric safety and effectiveness of a pediatric formulation, and after offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within a

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time specified in the order, if FDA finds that:

(1) The drug product is used in a substantial number of pediatric patients for the labeled indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

(2) There is reason to believe that the drug product would represent a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients.

(c)(1) An applicant may request a full waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed, or

(ii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(2) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and

(B) Is not likely to be used in a substantial number of patients in that age group, and

(C) The absence of adequate labeling could not pose significant risks to pediatric patients; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed, or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group, or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(3) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more

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of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(d) If a manufacturer fails to submit a supplemental application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within the time specified by FDA, the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic.

[63 FR 66668, Dec. 2, 1998]

### § 201.24 Labeling for systemic antibacterial drug products.

The labeling of all systemic drug products intended for human use indicated to treat a bacterial infection, except a mycobacterial infection, must bear the following statements:

(a) At the beginning of the label, under the product name, the labeling must state:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of *(insert name of antibacterial drug product)* and other antibacterial drugs, *(insert name of antibacterial drug product)* should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

(b) In the "Indications and Usage" section, the labeling must state:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of *(insert name of antibacterial drug product)* and other antibacterial drugs, *(insert name of antibacterial drug product)* should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

(c) In the “Precautions” section, under the “General” subsection, the labeling must state:

Prescribing (*insert name of antibacterial drug product*) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

(d) In the “Precautions” section, under the “Information for Patients” subsection, the labeling must state:

Patients should be counseled that antibacterial drugs including (*insert name of antibacterial drug product*) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When (*insert name of antibacterial drug product*) is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by (*insert name of antibacterial drug product*) or other antibacterial drugs in the future.

[68 FR 6081, Feb. 6, 2003]

#### § 201.25 Bar code label requirements.

(a) *Who is subject to these bar code requirements?* Manufacturers, repackers, relabelers, and private label distributors of a human prescription drug product or an over-the-counter (OTC) drug product that is regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act are subject to these bar code requirements unless they are exempt from the registration and drug listing requirements in section 510 of the Federal Food, Drug, and Cosmetic Act.

(b) *What drugs are subject to these bar code requirements?* The following drug products are subject to the bar code label requirements:

(1) Prescription drug products, however:

(i) The bar code requirement does not apply to the following entities:

- (A) Prescription drug samples;
- (B) Allergenic extracts;
- (C) Intrauterine contraceptive devices regulated as drugs;
- (D) Medical gases;

(E) Radiopharmaceuticals; and

(F) Low-density polyethylene form fill and seal containers that are not packaged with an overwrap.

(ii) The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

(2) Biological products; and

(3) OTC drug products that are dispensed pursuant to an order and are commonly used in hospitals. For purposes of this section, an OTC drug product is “commonly used in hospitals” if it is packaged for hospital use, labeled for hospital use (or uses similar terms), or marketed, promoted, or sold to hospitals.

(c) *What does the bar code look like? Where does the bar code go?* (1) Each drug product described in paragraph (b) of this section must have a bar code that contains, at a minimum, the appropriate National Drug Code (NDC) number in a linear bar code that meets European Article Number/Uniform Code Council (EAN/UCC) or Health Industry Business Communications Council (HIBCC) standards or another standard or format that has been approved by the relevant Food and Drug Administration Center Director. Additionally, the bar code must:

(i) Be surrounded by sufficient blank space so that the bar code can be scanned correctly; and

(ii) Remain intact under normal conditions of use.

(2) The bar code must appear on the drug’s label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act.

(d) *Can a drug be exempted from the bar code requirement?* (1) On our own initiative, or in response to a written request from a manufacturer, repacker, relabeler or private label distributor, we may exempt a drug product from the bar code label requirements set forth in this section. The exemption request must document why:

(i) compliance with the bar code requirement would adversely affect the safety, effectiveness, purity or potency of the drug or not be technologically

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feasible, and the concerns underlying the request could not reasonably be addressed by measures such as package redesign or use of overwraps; or

(ii) an alternative regulatory program or method of product use renders the bar code unnecessary for patient safety.

(2) Requests for an exemption should be sent to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993-0002 (requests involving a drug product or biological product regulated by the Center for Drug Evaluation and Research) or to the Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002 (requests involving a biological product regulated by the Center for Biologics Evaluation and Research).

[69 FR 9170, Feb. 26, 2004, as amended at 76 FR 12847, Mar. 9, 2011; 80 FR 18090, Apr. 3, 2015; 81 FR 60212, Aug. 31, 2016]

### **§ 201.26 Exceptions or alternatives to labeling requirements for human drug products held by the Strategic National Stockpile.**

(a) The appropriate FDA Center Director may grant an exception or alternative to any provision listed in paragraph (f) of this section and not explicitly required by statute, for specified lots, batches, or other units of a human drug product, if the Center Director determines that compliance with such labeling requirement could adversely affect the safety, effectiveness, or availability of such product that is or will be included in the Strategic National Stockpile.

(b)(1)(i) A Strategic National Stockpile official or any entity that manufactures (including labeling, packing, relabeling, or repackaging), distributes, or stores a human drug product that is or will be included in the Strategic National Stockpile may submit, with written concurrence from a Strategic National Stockpile official, a written request for an exception or alternative described in paragraph (a) of this section to the Center Director.

(ii) The Center Director may grant an exception or alternative described in paragraph (a) of this section on his or her own initiative.

(2) A written request for an exception or alternative described in paragraph (a) of this section must:

(i) Identify the specified lots, batches, or other units of the human drug product that would be subject to the exception or alternative;

(ii) Identify the labeling provision(s) listed in paragraph (f) of this section that are the subject of the exception or alternative request;

(iii) Explain why compliance with such labeling provision(s) could adversely affect the safety, effectiveness, or availability of the specified lots, batches, or other units of a human drug product that are or will be held in the Strategic National Stockpile;

(iv) Describe any proposed safeguards or conditions that will be implemented so that the labeling of the product includes appropriate information necessary for the safe and effective use of the product, given the anticipated circumstances of use of the product;

(v) Provide a draft of the proposed labeling of the specified lots, batches, or other units of the human drug product subject to the exception or alternative; and

(vi) Provide any other information requested by the Center Director in support of the request.

(c) The Center Director must respond in writing to all requests under this section.

(d) A grant of an exception or alternative under this section will include any safeguards or conditions deemed appropriate by the Center Director so that the labeling of product subject to the exception or alternative includes the information necessary for the safe and effective use of the product, given the anticipated circumstances of use.

(e) If you are a sponsor receiving a grant of a request for an exception or alternative to the labeling requirements under this section:

(1) You need not submit a supplement under § 314.70(a) through (c) or § 601.12(f)(1) through (f)(2) of this chapter; however,

(2) You must report any grant of a request for an exception or alternative

under this section as part of your annual report under §§314.70(d) or 601.12(f)(3) of this chapter.

(f) The Center Director may grant an exception or alternative under this section to the following provisions of this chapter, to the extent that the requirements in these provisions are not explicitly required by statute:

(1) §201.1(h)(1) through (h)(2), (h)(5) through (h)(6), and (i);

(2) §201.10(a), (d)(2), (f), (g)(1), and (h)(1);

(3) §201.17;

(4) §201.18;

(5) §201.19;

(6) §201.20;

(7) §201.21;

(8) §201.22;

(9) §201.24; and

(10) §312.6.

[72 FR 73599, Dec. 28, 2007]

### Subpart B—Labeling Requirements for Prescription Drugs and/or Insulin

#### § 201.50 Statement of identity.

(a) The label of prescription and insulin-containing drugs in package form shall bear as one of its principal features a statement of the identity of the drug.

(b) Such statement of identity shall be in terms of the established name of the drug. In the case of a prescription drug that is a mixture and that has no established name, the requirement for statement of identity shall be deemed to be satisfied by a listing of the quantitative ingredient information as prescribed by §201.10.

(c) The statement of identity of a prescription drug shall also comply with the placement, size and prominence requirements of §201.10.

[40 FR 13998, Mar. 27, 1975, as amended at 63 FR 26698, May 13, 1998]

#### § 201.51 Declaration of net quantity of contents.

(a) The label of a prescription or insulin-containing drug in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination of numerical count and weight or

measure. The statement of quantity of drugs in tablet, capsule, ampule, or other unit dosage form shall be expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semi-solid, or viscous, or in terms of fluid measure if the drug is liquid. When the drug quantity statement is in terms of the numerical count of the drug units, it shall be augmented to give the weight or measure of the drug units or the quantity of each active ingredient in each drug unit or, when quantity does not accurately reflect drug potency, a statement of the drug potency.

(b) Statements of weight of the contents shall in the case of prescription drugs be expressed in terms of avoirdupois pound, ounce, and grain or of kilogram, gram, and subdivisions thereof. A statement of liquid measure of the contents shall in the case of prescription drugs be expressed in terms of the U.S. gallon of 231 cubic inches and quart, pint, fluid-ounce, and fluid-dram subdivisions thereof, or of the liter and milliliter, or cubic centimeter, and shall express the volume at 68 °F. (20 °C.). A statement of the liquid measure of the contents in the case of insulin-containing drugs shall be expressed in terms of the liter and milliliter, or cubic centimeter, and shall express the volume at 68 °F. (20 °C.).

(c) The declaration shall contain only such fractions as are generally used in expressing the quantity of the drug. A common fraction shall be reduced to its lowest terms; a decimal fraction shall not be carried out to more than three places, except in the case of a statement of the quantity of an active ingredient in a unit of a drug.

(d) The declaration shall appear as a distinct item on the label and, in the case of large volume parenterals, may be embossed on the glass.

(e) The declaration shall accurately reveal the quantity of drug in the package exclusive of wrappers and other material packed therewith.

(f) A statement of the quantity of a prescription or insulin-containing drug in terms of weight or measure applicable to such drug, under the provisions of paragraph (a) of this section, shall

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express with prominence and conspicuousness the number of the largest whole unit, as specified in paragraph (b) of this section, that are contained in the package. Any remainder shall be expressed in terms of common or decimal fractions of such unit or in terms of the next smaller whole unit and common or decimal fractions thereof.

(g) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large. In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.

(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

## § 201.55 Statement of dosage.

Section 201.100(b)(2) requires that labels for prescription drugs bear a statement of the recommended or usual dosage. Since the dosage for some prescription drugs varies within extremely wide limits, depending upon the conditions being treated, it may not be possible in all cases to present an informative or useful statement of the recommended or usual dosage in the space available on the label or carton of the package. It is the view of the Food and Drug Administration that when such a situation prevails, compliance with this requirement would be met by a statement such as "See package insert

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for dosage information", where the detailed information is contained in such insert. However, if an informative, realistic, recommended or usual dosage can readily be set forth on the label, it should appear thereon.

## § 201.56 Requirements on content and format of labeling for human prescription drug and biological products.

(a) *General requirements.* Prescription drug labeling described in § 201.100(d) must meet the following general requirements:

(1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.

(b) *Categories of prescription drugs subject to the labeling content and format requirements in §§ 201.56(d) and 201.57.* (1) The following categories of prescription drug products are subject to the labeling requirements in paragraph (d) of this section and § 201.57 in accordance with the implementation schedule in paragraph (c) of this section:

(i) Prescription drug products for which a new drug application (NDA), biologics license application (BLA), or efficacy supplement was approved by the Food and Drug Administration (FDA) between June 30, 2001 and June 30, 2006;

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after June 30, 2006.

(2) Prescription drug products not described in paragraph (b)(1) of this section are subject to the labeling requirements in paragraph (e) of this section and § 201.80.

(c) *Schedule for implementing the labeling content and format requirements in §§ 201.56(d) and 201.57.* For products described in paragraph (b)(1) of this section, labeling conforming to the requirements in paragraph (d) of this section and § 201.57 must be submitted according to the following schedule:

(1) For products for which an NDA, BLA, or efficacy supplement is submitted for approval on or after June 30, 2006, proposed conforming labeling must be submitted as part of the application.

(2) For products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006, or that has been approved any time from June 30, 2005, up to and including June 30, 2006, a supplement with proposed conforming labeling must be submitted no later than June 30, 2009.

(3) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2004, up to and including June 29, 2005, a supplement with proposed conforming labeling must be submitted no later than June 30, 2010.

(4) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2003, up to and including June 29, 2004, a supplement with proposed conforming labeling must be submitted no later than June 30, 2011.

(5) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2002, up to and including June 29, 2003, a supplement with proposed conforming labeling must be submitted no later than June 30, 2012.

(6) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2001, up to and including June 29, 2002, a supplement with proposed conforming labeling must be submitted no later than June 30, 2013.

(d) *Labeling requirements for new and more recently approved prescription drug products.* This paragraph applies only to prescription drug products described in paragraph (b)(1) of this section and must be implemented according to the schedule specified in paragraph (c) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.57(a), (b), and (c) under the following headings and subheadings and in the following order:

- Highlights of Prescribing Information
  - Product Names, Other Required Information
  - Boxed Warning
  - Recent Major Changes
  - Indications and Usage
  - Dosage and Administration
  - Dosage Forms and Strengths
  - Contraindications
  - Warnings and Precautions
  - Adverse Reactions
  - Drug Interactions
  - Use in Specific Populations
- Full Prescribing Information: Contents
- Full Prescribing Information
  - Boxed Warning
  - 1 Indications and Usage
  - 2 Dosage and Administration
  - 3 Dosage Forms and Strengths
  - 4 Contraindications
  - 5 Warnings and Precautions
  - 6 Adverse Reactions
  - 7 Drug Interactions
  - 8 Use in Specific Populations
    - 8.1 Pregnancy
    - 8.2 Lactation
    - 8.3 Females and Males of Reproductive Potential
  - 8.4 Pediatric use
  - 8.5 Geriatric use
  - 9 Drug Abuse and Dependence
    - 9.1 Controlled substance
    - 9.2 Abuse
    - 9.3 Dependence
  - 10 Overdosage
  - 11 Description
  - 12 Clinical Pharmacology
    - 12.1 Mechanism of action
    - 12.2 Pharmacodynamics
    - 12.3 Pharmacokinetics
  - 13 Nonclinical Toxicology
    - 13.1 Carcinogenesis, mutagenesis, impairment of fertility
    - 13.2 Animal toxicology and/or pharmacology
  - 14 Clinical Studies
  - 15 References
  - 16 How Supplied/Storage and Handling
  - 17 Patient Counseling Information



(2) Additional nonstandard subheadings that are used to enhance labeling organization, presentation, or ease of use (e.g., for individual warnings or precautions, or for each drug interaction) must be assigned a decimal number that corresponds to their placement in labeling. The decimal numbers must be consistent with the standardized identifying numbers listed in paragraph (d)(1) of this section (e.g., subheadings added to the “Warnings and Precautions” section must be numbered 5.1, 5.2, and so on).

(3) Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the full prescribing information.

(4) Omit clearly inapplicable sections, subsections, or specific information. If sections or subsections required under paragraph (d)(1) of this section are omitted from the full prescribing information, the heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of Contents: “\* Sections or subsections omitted from the full prescribing information are not listed.”

(5) Any risk information that is required under § 201.57(c)(9)(iv) is considered “appropriate pediatric contraindications, warnings, or precautions” within the meaning of section 505A(1)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355A(1)(2)), whether such information appears in the “Contraindications,” “Warnings and Precautions,” or “Use in Specific Populations” section of labeling.

(e) *Labeling requirements for older prescription drug products.* This paragraph applies only to approved prescription drug products not described in paragraph (b)(1) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.80 under the following section headings and in the following order:

- Description
- Clinical Pharmacology
- Indications and Usage
- Contraindications

- Warnings
- Precautions
- Adverse Reactions
- Drug Abuse and Dependence
- Overdosage
- Dosage and Administration
- How Supplied

(2) The labeling may contain the following additional section headings if appropriate and if in compliance with § 201.80(l) and (m):

- Animal Pharmacology and/or Animal Toxicology
- Clinical Studies
- References

(3) Omit clearly inapplicable sections, subsections, or specific information.

(4) The labeling may contain a “Product Title” section preceding the “Description” section and containing only the information required by § 201.80(a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(1)(iv) and § 201.100(e). The information required by § 201.80(a)(1)(i) through (a)(1)(iv) must appear in the “Description” section of the labeling, whether or not it also appears in a “Product Title.”

(5) The labeling must contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.

(6) The requirement in § 201.80(f)(2) to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling must be implemented no later than June 30, 2007.

[71 FR 3986, Jan. 24, 2006, as amended at 79 FR 72101, Dec. 4, 2014]

**§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).**

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling,

which must be implemented no later than June 30, 2007.

(a) *Highlights of prescribing information.* The following information must appear in all prescription drug labeling:

(1) *Highlights limitation statement.* The verbatim statement “These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”

(2) *Drug names, dosage form, route of administration, and controlled substance symbol.* The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in §600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug’s dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by §1302.04 of this chapter.

(3) *Initial U.S. approval.* The verbatim statement “Initial U.S. Approval” followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the line immediately beneath the established name or, for biological products, proper name of the product.

(4) *Boxed warning.* A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word “WARNING” and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: “See full prescribing information for complete boxed warning.”

(5) *Recent major changes.* A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1),

(c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under §314.70(c)(6) or (d)(2), or §601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section’s identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) *Indications and usage.* A concise statement of each of the product’s indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: “(Drug) is a (name of class) indicated for (indication(s)).”

(7) *Dosage and administration.* A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

(8) *Dosage forms and strengths.* A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets) and whether the product is scored.

(9) *Contraindications.* A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) *Warnings and precautions.* A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) *Adverse reactions.* (i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and Web address for voluntary reporting of adverse reactions).”

(iii) For vaccines, the verbatim statement “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions).”

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) *Drug interactions.* A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(13) *Use in specific populations.* A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) *Patient counseling information statement.* The verbatim statement “See 17 for Patient Counseling Information” or, if the product has FDA-approved patient labeling, the verbatim statement “See 17 for Patient Counseling Information and (insert either FDA-approved patient labeling or Medication Guide).”

(15) *Revision date.* The date of the most recent revision of the labeling, identified as such, placed at the end of Highlights.

(b) *Full prescribing information: Contents.* Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) *Full prescribing information.* The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) *Boxed warning.* Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word “WARNING” and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the “Contraindications” or “Warnings and Precautions” section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) *1 Indications and usage.* This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under §314.510 or §601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the “Clinical Studies” section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the “Dosage and Administration” section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the

drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in §314.126(b) of this chapter unless this requirement is waived under §201.58 or §314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in §314.126(b) of this chapter unless the requirement is waived under §201.58 or §314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) *2 Dosage and administration.* (i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

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(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to adminis-

tration, whenever solution and container permit.")

(4) *3 Dosage forms and strengths.* This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) *4 Contraindications.* This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state "None."

(6) *5 Warnings and precautions.* (i) *General.* This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate

mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) *Other special care precautions.* This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

(iii) *Monitoring: Laboratory tests.* This section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) *Interference with laboratory tests.* This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

(7) *6 Adverse reactions.* This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse

events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) *Listing of adverse reactions.* This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) *Categorization of adverse reactions.* Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) *Clinical trials experience.* This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified,

if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) *Postmarketing experience.* This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) *Comparisons of adverse reactions between drugs.* For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

(8) *7 Drug interactions.* (i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the “Contraindications” or “Warnings and Precautions” sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the “Clinical Pharmacology” section that are pertinent to clinical use of the drug must not be repeated in this section.

(ii) This section must also contain practical guidance on known interference of the drug with laboratory tests.

(9) *8 Use in specific populations.* This section must contain the following subsections:

(i) *8.1 Pregnancy.* This subsection of the labeling must contain the following information in the following order under the subheadings “Pregnancy Exposure Registry,” “Risk Summary,” “Clinical Considerations,” and “Data”:

(A) *Pregnancy exposure registry.* If there is a scientifically acceptable pregnancy exposure registry for the drug, contact information needed to enroll in the registry or to obtain information about the registry must be provided following the statement: “There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (*name of drug*) during pregnancy.”

(B) *Risk summary.* The Risk Summary must contain risk statement(s) based on data from all relevant sources (human, animal, and/or pharmacologic) that describe, for the drug, the risk of adverse developmental outcomes (*i.e.*, structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth). When multiple data sources are available, the statements must be presented in the following order: Human, animal, pharmacologic. The source(s) of the data must be stated. The labeling must state the percentage range of live births in the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure. If such information is available for the population(s) for which the drug is labeled, it must also be included. When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary. When applicable, risk statements as described in paragraphs (c)(9)(i)(B)(1) and (2) of this section must include a cross-reference to additional details in the relevant portion of the “Data” subheading in the “Pregnancy” subsection of the labeling. If data demonstrate that a drug is not systemically absorbed following a particular route of administration, the Risk Summary must contain only the following statement: “(*Name of drug*) is not absorbed systemically following (route of administration), and maternal use is not expected to result in fetal exposure to the drug.”

(1) *Risk statement based on human data.* When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the Risk Summary must summarize the specific developmental outcome(s); their incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, this risk must be quantitatively compared to the risk for the same outcome in infants born to women who were not exposed to the drug but who have the disease or condition for which the drug is indicated to be used. When risk information is not available for women with the disease or condition for which the drug is indicated, the risk for the specific outcome must be compared to the rate at which the outcome occurs in the general population. The Risk Summary must state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.

(2) *Risk statement based on animal data.* When animal data are available, the Risk Summary must summarize the findings in animals and based on these findings, describe, for the drug, the potential risk of any adverse developmental outcome(s) in humans. This statement must include: The number and type(s) of species affected, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents, and outcomes for pregnant animals and offspring. When animal studies do not meet current standards for nonclinical developmental toxicity studies, the Risk Summary must so state. When there are no animal data, the Risk Summary must so state.

(3) *Risk statement based on pharmacology.* When the drug has a well-understood mechanism of action that may result in adverse developmental outcome(s), the Risk Summary must explain the mechanism of action and the potential associated risks.

(C) *Clinical considerations.* Under the subheading "Clinical Considerations," the labeling must provide relevant in-

formation, to the extent it is available, under the headings "Disease-associated maternal and/or embryo/fetal risk," "Dose adjustments during pregnancy and the postpartum period," "Maternal adverse reactions," "Fetal/Neonatal adverse reactions," and "Labor or delivery":

(1) *Disease-associated maternal and/or embryo/fetal risk.* If there is a serious known or potential risk to the pregnant woman and/or the embryo/fetus associated with the disease or condition for which the drug is indicated to be used, the labeling must describe the risk.

(2) *Dose adjustments during pregnancy and the postpartum period.* If there are pharmacokinetic data that support dose adjustment(s) during pregnancy and the postpartum period, a summary of this information must be provided.

(3) *Maternal adverse reactions.* If use of the drug is associated with a maternal adverse reaction that is unique to pregnancy or if a known adverse reaction occurs with increased frequency or severity in pregnant women, the labeling must describe the adverse reaction and available intervention(s) for monitoring or mitigating the reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk to the pregnant woman of experiencing the adverse reaction.

(4) *Fetal/Neonatal adverse reactions.* If it is known or anticipated that treatment of the pregnant woman increases or may increase the risk of an adverse reaction in the fetus or neonate, the labeling must describe the adverse reaction, the potential severity and reversibility of the adverse reaction, and available intervention(s) for monitoring or mitigating the reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk.

(5) *Labor or delivery.* If the drug is expected to affect labor or delivery, the labeling must provide information about the effect of the drug on the pregnant woman and the fetus or neonate; the effect of the drug on the



duration of labor and delivery; any increased risk of adverse reactions, including their potential severity and reversibility; and must provide information about available intervention(s) that can mitigate these effects and/or adverse reactions. The information described under this heading is not required for drugs approved for use only during labor and delivery.

(D) *Data*—(1) “Data” subheading. Under the subheading “Data,” the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

(2) *Human and animal data headings*. Human and animal data must be presented separately, beneath the headings “Human Data” and “Animal Data,” and human data must be presented first.

(3) *Description of human data*. For human data, the labeling must describe adverse developmental outcomes, adverse reactions, and other adverse effects. To the extent applicable, the labeling must describe the types of studies or reports, number of subjects and the duration of each study, exposure information, and limitations of the data. Both positive and negative study findings must be included.

(4) *Description of animal data*. For animal data, the labeling must describe the following: Types of studies, animal species, dose, duration and timing of exposure, study findings, presence or absence of maternal toxicity, and limitations of the data. Description of maternal and offspring findings must include dose-response and severity of adverse developmental outcomes. Animal doses or exposures must be described in terms of human dose or exposure equivalents and the basis for those calculations must be included.

(ii) *8.2 Lactation*. This subsection of the labeling must contain the following information in the following order under the subheadings “Risk Summary,” “Clinical Considerations,” and “Data”:

(A) *Risk summary*. When relevant human and/or animal lactation data are available, the Risk Summary must include a cross-reference to the “Data” subheading in the “Lactation” subsection of the labeling. When human data are available, animal data must

not be included unless the animal model is specifically known to be predictive for humans. When use of a drug is contraindicated during breastfeeding, this information must be stated first in the Risk Summary.

(1) *Drug not absorbed systemically*. If data demonstrate that the drug is not systemically absorbed by the mother, the Risk Summary must contain only the following statement: “(Name of drug) is not absorbed systemically by the mother following (route of administration), and breastfeeding is not expected to result in exposure of the child to (name of drug).”

(2) *Drug absorbed systemically*. If the drug is absorbed systemically, the Risk Summary must describe the following to the extent relevant information is available:

(i) *Presence of drug in human milk*. The Risk Summary must state whether the drug and/or its active metabolite(s) are present in human milk. If there are no data to assess this, the Risk Summary must so state. If studies demonstrate that the drug and/or its active metabolite(s) are not detectable in human milk, the Risk Summary must state the limits of the assay used. If studies demonstrate the presence of the drug and/or its active metabolite(s) in human milk, the Risk Summary must state the concentration of the drug and/or its active metabolite(s) in human milk and the actual or estimated daily dose for an infant fed exclusively with human milk. The actual or estimated amount of the drug and/or its active metabolite(s) ingested by the infant must be compared to the labeled infant or pediatric dose, if available, or to the maternal dose. If studies demonstrate the presence of the drug and/or its active metabolite(s) in human milk but the drug and/or its active metabolite(s) are not expected to be systemically bioavailable to the breast-fed child, the Risk Summary must describe the disposition of the drug and/or its active metabolite(s). If only animal lactation data are available, the Risk Summary must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk and specify the animal species.

(ii) *Effects of drug on the breast-fed child*. The Risk Summary must include

information, on the known or predicted effects on the child from exposure to the drug and/or its active metabolite(s) through human milk or from contact with breast or nipple skin (for topical products). The Risk Summary also must include information on systemic and/or local adverse reactions. If there are no data to assess the effects of the drug and/or its active metabolite(s) on the breast-fed child, the Risk Summary must so state.

(iii) *Effects of drug on milk production.* The Risk Summary must describe the effects of the drug and/or its active metabolite(s) on milk production. If there are no data to assess the effects of the drug and/or its active metabolite(s) on milk production, the Risk Summary must so state.

(3) *Risk and benefit statement.* For drugs absorbed systemically, unless breastfeeding is contraindicated during drug therapy, the following risk and benefit statement must appear at the end of the Risk Summary: “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for (*name of drug*) and any potential adverse effects on the breast-fed child from (*name of drug*) or from the underlying maternal condition.”

(B) *Clinical considerations.* Under “Clinical Considerations,” the following information must be provided to the extent it is available and relevant:

(1) *Minimizing exposure.* The labeling must describe ways to minimize exposure in the breast-fed child if: The drug and/or its active metabolite(s) are present in human milk in clinically relevant concentrations; the drug does not have an established safety profile in infants; and the drug is used either intermittently, in single doses, or for short courses of therapy. When applicable, the labeling must also describe ways to minimize a breast-fed child’s oral intake of topical drugs applied to the breast or nipple skin.

(2) *Monitoring for adverse reactions.* The labeling must describe available intervention(s) for monitoring or mitigating the adverse reaction(s) presented in the Risk Summary.

(C) *Data.* Under the subheading “Data,” the labeling must describe the

data that are the basis for the Risk Summary and Clinical Considerations.

(iii) *8.3 Females and males of reproductive potential.* When pregnancy testing and/or contraception are required or recommended before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects, this subsection of labeling must contain this information under the subheadings “Pregnancy Testing,” “Contraception,” and “Infertility,” in that order.

(iv) *8.4 Pediatric use.* (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H) of this section, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the “Indications and Usage” section, and appropriate pediatric dosage information must be given under the “Dosage and Administration” section. The “Pediatric use” subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection should be discussed in more detail, if appropriate, under the “Clinical Pharmacology” or “Clinical Studies” section. As appropriate, this information must also be contained in the “Contraindications” and/or “Warnings and Precautions” section(s).

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the “Pediatric use” subsection and discussed in more detail, if appropriate, under the “Clinical Pharmacology” and

“Clinical Studies” sections. Appropriate pediatric dosage must be given under the “Dosage and Administration” section. The “Pediatric use” subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the “Contraindications” and/or “Warnings and Precautions” section(s).

(D)(1) When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the “Pediatric use” subsection of the labeling must contain either the following statement or a reasonable alternative:

The safety and effectiveness of (*drug name*) have been established in the age groups \_\_\_\_\_ to \_\_\_\_\_ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (*insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population*).

(2) Data summarized in the preceding prescribed statement in this subsection must be discussed in more detail, if appropriate, under the “Clinical Pharmacology” or the “Clinical Studies” section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose response information should be described in the “Clinical Pharmacology” section. Pediatric dosing instructions must be included in the “Dosage and Administration” section. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the “Pediatric use” subsection and, as appropriate, in the “Contraindications,” “Warnings and Precautions,” and “Dosage and Administration” sections.

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the “Pediatric use” subsection must contain an appropriate statement such as “Safety and effectiveness in pediatric patients below the age of (\_\_\_\_) have not been established.” If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the “Contraindications” or “Warnings and Precautions” section and this subsection must refer to it.

(F) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection must contain the following statement: “Safety and effectiveness in pediatric patients have not been established.” If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the “Contraindications” or “Warnings and Precautions” section and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug’s labeling and that the alternative statement is accurate and appropriate.

(H) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the “Contraindications” or “Warnings and Precautions” section.

(v) *8.5 Geriatric use.* (A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the “Indications and Usage” section, and appropriate geriatric dosage must be stated under the “Dosage and Administration” section. The “Geriatric use” subsection must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the “Geriatric use” subsection must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection must be discussed in more detail, if appropriate, under “Clinical Pharmacology” or the “Clinical Studies” section. As appropriate, this information must also be contained in the “Warnings and Precautions” and/or “Contraindications” section(s).

(B) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the “Geriatric use” subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The “Geriatric use” subsection must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(1) If clinical studies did not include sufficient numbers of subjects aged 65

and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the “Geriatric use” subsection must include the following statement:

Clinical studies of (*name of drug*) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(2) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor’s applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the “Geriatric use” subsection must contain the following statement:

Of the total number of subjects in clinical studies of (*name of drug*), \_\_\_ percent were 65 and over, while \_\_\_ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(3) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the

“Geriatric use” subsection must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, must refer to more detailed discussions in the “Contraindications,” “Warnings and Precautions,” “Dosage and Administration,” or other sections.

(C)(1) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the “Geriatric use” subsection and in detail under the “Clinical Pharmacology” section. The “Clinical Pharmacology” and “Drug Interactions” sections ordinarily contain information on drug/disease and drug/drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

(2) If a drug is known to be substantially excreted by the kidney, the “Geriatric use” subsection must include the statement:

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

(D) If use of the drug in the elderly appears to cause a specific hazard, the hazard must be described in the “Geriatric use” subsection, or, if appropriate, the hazard must be stated in the “Contraindications” or “Warnings and Precautions” section, and the “Geriatric use” subsection must refer to those sections.

(E) Labeling under paragraphs (c)(9)(v)(A) through (c)(9)(v)(C) of this section may include statements, if they are necessary for safe and effective use of the drug, and reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (*name of drug*) and observed closely.

(F) If the sponsor believes that none of the requirements described in paragraphs (c)(9)(v)(A) through (c)(9)(v)(E) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons

for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug’s labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(vi) *Additional subsections.* Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment).

(10) *9 Drug abuse and dependence.* This section must contain the following information, as appropriate:

(i) *9.1 Controlled substance.* If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

(ii) *9.2 Abuse.* This subsection must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used.

(iii) *9.3 Dependence.* This subsection must describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and must identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details must be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state and the principles of treating the effects of abrupt withdrawal must be described.

(11) *10 Overdosage.* This section must be based on human data. If human data are unavailable, appropriate animal and in vitro data may be used. The following specific information must be provided:

(i) Signs, symptoms, and laboratory findings associated with an overdosage of the drug;

(ii) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis);

(iii) Concentrations of the drug in biologic fluids associated with toxicity or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses;

(iv) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdose and the amount of the drug in a single dose that is likely to be life threatening;

(v) Whether the drug is dialyzable; and

(vi) Recommended general treatment procedures and specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be based on data available for the specific drug or experience with pharmacologically related drugs. Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated.

(12) *11 Description.* (i) This section must contain:

(A) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug or, for biological products, the proper name (as defined in § 600.3 of this chapter) and any appropriate descriptors;

(B) The type of dosage form(s) and the route(s) of administration to which the labeling applies;

(C) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for drug labels or §§ 610.60 and 610.61 of this chapter for biological product labels;

(D) If the product is sterile, a statement of that fact;

(E) The pharmacological or therapeutic class of the drug;

(F) For drug products other than biological products, the chemical name and structural formula of the drug; and

(G) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(ii) If appropriate, other important chemical or physical information, such as physical constants or pH, must be stated.

(13) *12 Clinical pharmacology.* (i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

(A) *12.1 Mechanism of action.* This subsection must summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (e.g., receptor, membrane, tissue, organ, whole body). If the mechanism of action is not known, this subsection must contain a statement about the lack of information.

(B) *12.2 Pharmacodynamics.* This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity. Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., "Warnings and Precautions" or "Dosage and Administration") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(C) *12.3 Pharmacokinetics.* This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism,

and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration ( $C_{\min}$ ), maximum concentration ( $C_{\max}$ ), time to maximum concentration ( $T_{\max}$ ), area under the curve (AUC), pertinent half-lives ( $t_{1/2}$ ), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution ( $V_d$ ) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and *in vitro* data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration" or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(ii) Data that demonstrate activity or effectiveness in *in vitro* or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section only under the following circumstances:

(A) *In vitro* data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following *in vitro* data are available but their clinical significance is unknown."

(B) For other classes of drugs, in *in vitro* and animal data that have not been shown by adequate and well-controlled studies, as defined in § 314.126(b) of this chapter, to be necessary for the

safe and effective use may be included in this section only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

(14) *13 Nonclinical toxicology*. This section must contain the following subsections as appropriate:

(i) *13.1 Carcinogenesis, mutagenesis, impairment of fertility*. This subsection must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the "Warnings and Precautions" section, must not be included in this subsection of the labeling.

(ii) *13.2 Animal toxicology and/or pharmacology*. Significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling must be included in this section (e.g., specifics about studies used to support approval under § 314.600 or § 601.90 of this chapter, the absence of chronic animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

(15) *14 Clinical studies*. This section must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required under §§ 201.56 and 201.57 because the study is essential to an understandable presentation of the

information in that section of the labeling, any detailed discussion of the study must appear in this section.

(i) For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in §314.126(b) of this chapter and must not imply or suggest indications or uses or dosing regimens not stated in the “Indications and Usage” or “Dosage and Administration” section. For biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the “Indications and Usage” or “Dosage and Administration” section.

(ii) Any discussion of a clinical study that relates to a risk from the use of the drug must also refer to the other sections of the labeling where the risk is identified or discussed.

(16) *15 References.* When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(17) *16 How supplied/storage and handling.* This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must include, as appropriate:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets) and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation;

(ii) The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100);

(iii) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number; and

(iv) Special handling and storage conditions.

(18) *17 Patient counseling information.* This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling. Any FDA-approved patient labeling printed immediately following this section or accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be detached and distributed to patients in compliance with §208.24 of this chapter. Medication Guides for distribution to patients are subject to the type size requirements set forth in §208.20 of this chapter.

(d) *Format requirements.* All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a



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minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8½ by 11 inches), single spaced, in 8 point type with ½-inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

[71 FR 3988, Jan. 24, 2006, as amended at 79 FR 72101, Dec. 4, 2014]

### § 201.58 Waiver of labeling requirements.

An applicant may ask the Food and Drug Administration to waive any requirement under §§ 201.56, 201.57, and 201.80. A waiver request must be submitted in writing to the Director (or the Director's designee), Center for Drug Evaluation and Research, Food and Drug Administration, Central Document Room, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or, if applicable, the Director (or the Director's designee), Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002. The waiver must be granted or denied

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in writing by the Director or the Director's designee.

[71 FR 3996, Jan. 24, 2006, as amended at 74 FR 13112, Mar. 26, 2009; 80 FR 18090, Apr. 3, 2015]

### Subpart C—Labeling Requirements for Over-the-Counter Drugs

SOURCE: 41 FR 6908, Feb. 13, 1976, unless otherwise noted.

#### § 201.60 Principal display panel.

The term *principal display panel*, as it applies to over-the-counter drugs in package form and as used in this part, means the part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale. The principal display panel shall be large enough to accommodate all the mandatory label information required to be placed thereon by this part with clarity and conspicuousness and without obscuring designs, vignettes, or crowding. Where packages bear alternate principal display panels, information required to be placed on the principal display panel shall be duplicated on each principal display panel. For the purpose of obtaining uniform type size in declaring the quantity of contents for all packages of substantially the same size, the term *area of the principal display panel* means the area of the side or surface that bears the principal display panel, which area shall be:

(a) In the case of a rectangular package where one entire side properly can be considered to be the principal display panel side, the product of the height times the width of that side;

(b) In the case of a cylindrical or nearly cylindrical container, 40 percent of the product of the height of the container times the circumference; and

(c) In the case of any other shape of container, 40 percent of the total surface of the container: *Provided, however*, That where such container presents an obvious "principal display panel" such as the top of a triangular or circular package, the area shall consist of the entire top surface.

In determining the area of the principal display panel, exclude tops, bottoms, flanges at the tops and bottoms of cans, and shoulders and necks of bottles or jars. In the case of cylindrical or nearly cylindrical containers, information required by this part to appear on the principal display panel shall appear within that 40 percent of the circumference which is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.

**§ 201.61 Statement of identity.**

(a) The principal display panel of an over-the-counter drug in package form shall bear as one of its principal features a statement of the identity of the commodity.

(b) Such statement of identity shall be in terms of the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. In the case of an over-the-counter drug that is a mixture and that has no established name, this requirement shall be deemed to be satisfied by a prominent and conspicuous statement of the general pharmacological action(s) of the mixture or of its principal intended action(s) in terms that are meaningful to the layman. Such statements shall be placed in direct conjunction with the most prominent display of the proprietary name or designation and shall employ terms descriptive of general pharmacological category(ies) or principal intended action(s); for example, "antacid," "analgesic," "decongestant," "antihistaminic," etc. The indications for use shall be included in the directions for use of the drug, as required by section 502(f)(1) of the act and by the regulations in this part.

(c) The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed.

**§ 201.62 Declaration of net quantity of contents.**

(a) The label of an over-the-counter drug in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination or numerical count and weight, measure, or size. The statement of quantity of drugs in tablet, capsule, ampule, or other unit form and the quantity of devices shall be expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semisolid, or viscous, or in terms of fluid measure if the drug is liquid. The drug quantity statement shall be augmented when necessary to give accurate information as to the strength of such drug in the package; for example, to differentiate between several strengths of the same drug "100 tablets, 5 grains each" or "100 capsules, 125 milligrams each" or "100 capsules, 250 milligrams each":  
*Provided, That:*

(1) In the case of a firmly established, general consumer usage and trade custom of declaring the quantity of a drug in terms of linear measure or measure of area, such respective term may be used. Such term shall be augmented when necessary for accuracy of information by a statement of the weight, measure, or size of the individual units or of the entire drug; for example, the net quantity of adhesive tape in package form shall be expressed in terms of linear measure augmented by a statement of its width.

(2) Whenever the Commissioner determines for a specific packaged drug that an existing practice of declaring net quantity of contents by weight, measure, numerical count, or a combination of these does not facilitate value comparisons by consumers, he shall by regulation designate the appropriate term or terms to be used for such article.

(b) Statements of weight of the contents shall be expressed in terms of avoirdupois pound and ounce. A statement of liquid measure of the contents shall be expressed in terms of the U.S. gallon of 231 cubic inches and quart, pint, and fluid-ounce subdivisions thereof, and shall express the volume

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at 68 °F (20 °C). See also paragraph (p) of this section.

(c) The declaration may contain common or decimal fractions. A common fraction shall be in terms of halves, quarters, eights, sixteenths, or thirty-seconds; except that if there exists a firmly established, general consumer usage and trade custom of employing different common fractions in the net quantity declaration of a particular commodity, they may be employed. A common fraction shall be reduced to its lowest terms; a decimal fraction shall not be carried out to more than two places. A statement that includes small fractions of an ounce shall be deemed to permit smaller variations than one which does not include such fractions.

(d) The declaration shall be located on the principal display panel of the label, and with respect to packages bearing alternate principal panels it shall be duplicated on each principal display panel.

(e) The declaration shall appear as a distinct item on the principal display panel, shall be separated, by at least a space equal to the height of the lettering used in the declaration, from other printed label information appearing above or below the declaration and, by at least a space equal to twice the width of the letter "N" of the style of type used in the quantity of contents statement, from other printed label information appearing to the left or right of the declaration. It shall not include any term qualifying a unit of weight, measure, or count, such as "giant pint" and "full quart", that tends to exaggerate the amount of the drug in the container. It shall be placed on the principal display panel within the bottom 30 percent of the area of the label panel in lines generally parallel to the base on which the package rests as it is designed to be displayed: *Provided*, That:

(1) On packages having a principal display panel of 5 square inches or less the requirement for placement within the bottom 30 percent of the area of the label panel shall not apply when the declaration of net quantity of contents meets the other requirements of this part; and

(2) In the case of a drug that is marketed with both outer and inner retail containers bearing the mandatory label information required by this part and the inner container is not intended to be sold separately, the net quantity of contents placement requirement of this section applicable to such inner container is waived.

(3) The principal display panel of a drug marketed on a display card to which the immediate container is affixed may be considered to be the display panel of the card, and the type size of the net quantity of contents statement is governed by the dimensions of the display card.

(f) The declaration shall accurately reveal the quantity of drug or device in the package exclusive of wrappers and other material packed therewith: *Provided*, That in the case of drugs packed in containers designed to deliver the drug under pressure, the declaration shall state the net quantity of the contents that will be expelled when the instructions for use as shown on the container are followed. The propellant is included in the net quantity declaration.

(g) The declaration shall appear in conspicuous and easily legible boldface print or type in distinct contrast (by typography, layout, color, embossing, or molding) to other matter on the package; except that a declaration of net quantity blown, embossed, or molded on a glass or plastic surface is permissible when all label information is so formed on the surface. Requirements of conspicuousness and legibility shall include the specifications that:

(1) The ratio of height to width of the letter shall not exceed a differential of 3 units to 1 unit, i.e., no more than 3 times as high as it is wide.

(2) Letter heights pertain to upper case or capital letters. When upper and lower case or all lower case letters are used, it is the lower case letter "o" or its equivalent that shall meet the minimum standards.

(3) When fractions are used, each component numeral shall meet one-half the minimum height standards.

(h) The declaration shall be in letters and numerals in a type size established in relationship to the area of the principal display panel of the package and

shall be uniform for all packages of substantially the same size by complying with the following type specifications:

(1) Not less than one-sixteenth inch in height on packages the principal display panel of which has an area of 5 square inches or less.

(2) Not less than one-eighth inch in height on packages the principal display panel of which has an area of more than five but not more than 25 square inches.

(3) Not less than three-sixteenths inch in height on packages the principal display panel of which has an area of more than 25 but not more than 100 square inches.

(4) Not less than one-fourth inch in height on packages the principal display panel of which has an area of more than 100 square inches, except not less than one-half inch in height if the area is more than 400 square inches.

Where the declaration is blown, embossed, or molded on a glass or plastic surface rather than by printing, typing, or coloring, the lettering sizes specified in paragraphs (h) (1) through (4) of this section shall be increased by one-sixteenth of an inch.

(i) On packages containing less than 4 pounds or 1 gallon and labeled in terms of weight or fluid measure:

(1) The declaration shall be expressed both in ounces, with identification by weight or by liquid measure and, if applicable (1 pound or 1 pint or more) followed in parentheses by a declaration in pounds for weight units, with any remainder in terms of ounces or common or decimal fractions of the pound (see examples set forth in paragraphs (k) (1) and (2) of this section), or in the case of liquid measure, in the largest whole units (quarts, quarts and pints, or pints, as appropriate) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart (see examples set forth in paragraphs (k) (3) and (4) of this section). If the net weight of the package is less than 1 ounce avoirdupois or the net fluid measure is less than 1 fluid ounce, the declaration shall be in terms of common or decimal fractions of the respective ounce and not in terms of drams.

(2) The declaration may appear in more than one line. The term *net weight* shall be used when stating the net quantity of contents in terms of weight. Use of the terms *net* or *net contents* in terms of fluid measure or numerical count is optional. It is sufficient to distinguish avoirdupois ounce from fluid ounce through association of terms; for example, "Net wt. 6 oz" or "6 oz net wt.," and "6 fl oz" or "net contents 6 fl oz".

(j) On packages containing 4 pounds or 1 gallon or more and labeled in terms of weight or fluid measure, the declaration shall be expressed in pounds for weight units with any remainder in terms of ounces or common or decimal fractions of the pound; in the case of fluid measure, it shall be expressed in the largest whole unit (gallons, followed by common or decimal fractions of a gallon or by the next smaller whole unit or units (quarts or quarts and pints)) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart; see paragraph (k)(5) of this section.

(k) Examples:

(1) A declaration of 1½ pounds weight shall be expressed as "Net wt. 24 oz (1 lb 8 oz)," or "Net wt. 24 oz (1½ lb)" or "Net wt. 24 oz (1.5 lb)".

(2) A declaration of three-fourths pound avoirdupois weight shall be expressed as "Net wt. 12 oz".

(3) A declaration of 1 quart liquid measure shall be expressed as "Net contents 32 fl oz (1 qt)" or "32 fl oz (1 qt)".

(4) A declaration of 1¾ quarts liquid measure shall be expressed as "Net contents 56 fl oz (1 qt 1 pt 8 oz)" or "Net contents 56 fl oz (1 qt 1.5 pt)," but not in terms of quart and ounce such as "Net 56 fl oz (1 qt 24 oz)."

(5) A declaration of 2½ gallons liquid measure shall be expressed as "Net contents 2 gal 2 qt," "Net contents 2.5 gallons," or "Net contents 2½ gal" but not as "2 gal 4 pt".

(1) For quantities, the following abbreviations and none other may be employed. Periods and plural forms are optional:

Gallon gal	pint pt
quart qt	ounce oz

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pound lb	yard yd
grain gr	feet or foot ft
kilogram kg	inch in
gram g	meter m
milligram mg	centimeter cm
microgram mcg	millimeter mm
liter l	fluid fl
milliliter ml	square sq
cubic centimeter cc	weight wt

(m) On packages labeled in terms of linear measure, the declaration shall be expressed both in terms of inches and, if applicable (1 foot or more), the largest whole units (yards, yards and feet, feet). The declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of inches and any remainder shall be in terms of inches or common or decimal fractions of the foot or yard; if applicable, as in the case of adhesive tape, the initial declaration in linear inches shall be preceded by a statement of the width. Examples of linear measure are “86 inches (2 yd 1 ft 2 in),” “90 inches (2½ yd),” “30 inches (2.5 ft),” “¾ inch by 36 in (1 yd),” etc.

(n) On packages labeled in terms of area measure, the declaration shall be expressed both in terms of square inches and, if applicable (1 square foot or more), the largest whole square unit (square yards, square yards and square feet, square feet). The declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of square inches and any remainder shall be in terms of square inches or common or decimal fractions of the square foot or square yard; for example, “158 sq inches (1 sq ft 14 sq in).”

(o) Nothing in this section shall prohibit supplemental statements at locations other than the principal display panel(s) describing in nondeceptive terms the net quantity of contents, provided that such supplemental statements of net quantity of contents shall not include any term qualifying a unit of weight, measure, or count that tends to exaggerate the amount of the drug contained in the package; for example, “giant pint” and “full quart.” Dual or combination declarations of net quantity of contents as provided for in paragraphs (a) and (i) of this section are not regarded as supplemental net quantity statements and shall be located on the principal display panel.

(p) A separate statement of net quantity of contents in terms of the metric system of weight or measure is not regarded as a supplemental statement and an accurate statement of the net quantity of contents in terms of the metric system of weight or measure may also appear on the principal display panel or on other panels.

(q) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large.

(r) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample,” “physician’s sample,” or a substantially similar statement and the contents of the package do not exceed 8 grams.

§ 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] In addition to the written warning, a symbol that conveys the intent of the warning may be used in labeling.

(b) Where a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in a new drug application (NDA) or for a product covered by an OTC drug final monograph in part 330 of this chapter, the specific warning shall be used in place of the warning in paragraph (a) of this section, unless otherwise stated in the NDA or in the final OTC drug monograph.

(c) The following OTC drugs are exempt from the provisions of paragraph (a) of this section:

(1) Drugs that are intended to benefit the fetus or nursing infant during the period of pregnancy or nursing.

(2) Drugs that are labeled exclusively for pediatric use.

(d) The Food and Drug Administration will grant an exemption from paragraph (a) of this section where appropriate upon petition under the provisions of §10.30 of this chapter. Decisions with respect to requests for exemptions shall be maintained in a permanent file for public review by the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(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.”

[47 FR 54757, Dec. 3, 1982, as amended at 55 FR 27784, July 5, 1990; 59 FR 14364, Mar. 28, 1994; 64 FR 13286, Mar. 17, 1999; 68 FR 24879, May 9, 2003]

#### § 201.64 Sodium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the sodium content per dosage unit (e.g., tablet, teaspoonful) if the sodium content of a single maximum recommended dose of the product (which may be one or more dosage units) is 5 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

(b) The sodium content shall be expressed in milligrams per dosage unit and shall include the total amount of sodium regardless of the source, i.e., from both active and inactive ingredients. The sodium content shall be rounded-off to the nearest whole number. The sodium content per dosage unit shall follow the heading “Other information” as stated in §201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading “Warning” (or “Warnings” if it appears with additional warning statements) if the amount of sodium present in the labeled maximum daily dose of the product is more than 140 milligrams: “Ask a doctor before use if you have [in bold type] [bullet]<sup>1</sup> a sodium-restricted diet”. The warnings in §§201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e.g., a calcium or sodium restricted diet.

(d) The term *sodium free* may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is 5 milligrams or less and the amount of sodium per dosage unit is 0 milligram (when rounded-off in accord with paragraph (b) of this section).

(e) The term *very low sodium* may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is 35 milligrams or less.

(f) The term *low sodium* may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is 140 milligrams or less.

(g) The term *salt* is not synonymous with the term sodium and shall not be used interchangeably or substituted for the term *sodium*.

(h) The terms *sodium free*, *very low sodium*, and *low sodium* shall be in print size and style no larger than the product’s statement of identity and shall not be unduly prominent in print size or style compared to the statement of identity.

(i) Any product subject to this paragraph that contains sodium bicarbonate, sodium phosphate, or sodium biphosphate as an active ingredient for oral ingestion and that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate

<sup>1</sup>See §201.66(b)(4) of this chapter for definition of bullet symbol.

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commerce after April 22, 1997, is misbranded under sections 201(n) and 502 (a) and (f) of the Federal Food, Drug, and Cosmetic Act (the act).

(j) Any product subject to paragraphs (a) through (h) of this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after April 23, 2004.

(2) September 24, 2005, for all OTC drug products subject to any OTC drug monograph, not yet the subject of any OTC drug monograph, or subject to drug marketing applications approved before April 23, 2004.

(k) The labeling of OTC drug products intended for rectal administration containing dibasic sodium phosphate and/or monobasic sodium phosphate shall contain the sodium content per delivered dose if the sodium content is 5 milligrams or more. The sodium content shall be expressed in milligrams or grams. If less than 1 gram, milligrams should be used. The sodium content shall be rounded-off to the nearest whole number if expressed in milligrams (or nearest tenth of a gram if expressed in grams). The sodium content per delivered dose shall follow the heading “Other information” as stated in § 201.66(c)(7). Any product subject to this paragraph that contains dibasic sodium phosphate and/or monobasic sodium phosphate as an active ingredient intended for rectal administration and that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after November 29, 2005, is misbranded under sections 201(n) and 502(a) and (f) of the act.

[61 FR 17806, Apr. 22, 1996, as amended at 62 FR 19925, Apr. 24, 1997; 64 FR 13286, Mar. 17, 1999; 69 FR 13724, Mar. 24, 2004; 69 FR 69280, Nov. 29, 2004]

**§ 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) 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:”

(B) *Allergic reaction and asthma alert warnings.* 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:” The asthma alert warning set forth in §§341.76(c)(5) and 341.76(c)(6) of this chapter. This warning shall follow the subheading “Asthma alert:”

(C) Flammability warning, with appropriate flammability signal word(s) (e.g., §§341.74(c)(5)(iii), 344.52(c), 358.150(c), and 358.550(c) of this chapter). This warning shall follow a subheading containing the appropriate flammability signal word(s) 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) Liver warning set forth in § 201.326(a)(1)(iii) and/or stomach bleeding warning set forth in § 201.326(a)(2)(iii). The liver warning shall follow the subheading “Liver warning:” and the stomach bleeding warning shall follow the subheading “Stomach bleeding 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:”

(H) Sexually transmitted diseases (STDs) warning for vaginal contraceptive and spermicide drug products containing nonoxynol 9 set forth in § 201.325(b)(2). This warning shall follow the subheading “Sexually transmitted diseases (STDs) alert:”

(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. For all OTC drug products under an approved drug application whose packaging does not include a toll-free number through which consumers can report complaints to the manufacturer or distributor of the drug product, the following text shall immediately follow the subheading: “[Bullet] side effects occur. You may report side effects to FDA at 1-800-FDA-1088.” The telephone number must appear in a minimum 6-point bold letter height or type size.

(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(b), calcium in §201.70(b), magnesium in §201.71(b), and potassium in §201.72(b)) shall appear as follows: “each (insert appropriate dosage unit) contains:” [in bold type (insert name(s) of ingredient(s) (in alphabetical order) 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 recommends 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, heading, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section shall be legible and clearly presented, 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 color printed on a white or other contrasting background, except that the

title and the headings may be presented in a single, alternative, contrasting 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 re-

quired 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:



<b>Drug Facts</b>	
<b>Active ingredient (in each tablet)</b>	<b>Purpose</b>
Chlorpheniramine maleate 2 mg.....	Antihistamine
<b>Uses</b> temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat	
<b>Warnings</b>	
<b>Ask a doctor before use if you have</b>	
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis	
■ trouble urinating due to an enlarged prostate gland	
<b>Ask a doctor or pharmacist before use if you are</b> taking tranquilizers or sedatives	
<b>When using this product</b>	
■ 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	
<b>If pregnant or breast-feeding</b> , ask a health professional before use.	
<b>Keep out of reach of children.</b> In case of overdose, get medical help or contact a Poison Control Center right away.	
<b>Directions</b>	
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

<b>Drug Facts (continued)</b>	
<b>Other information</b> ■ store at 20-25°C (68-77°F) ■ protect from excessive moisture	
<b>Inactive ingredients</b> 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 para-

graph (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.**

---

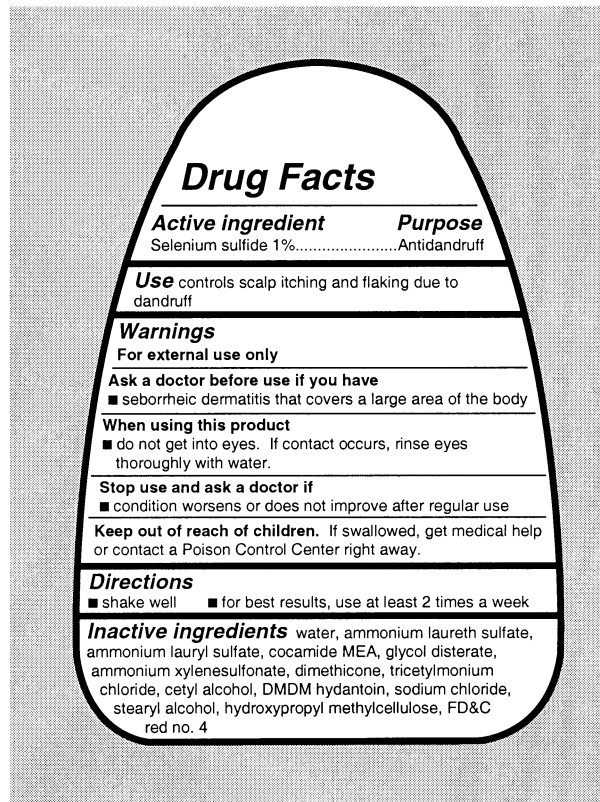
**Directions** ■ chew 1 to 4 tablets 4 times daily

- 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

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



(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



## § 201.70

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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.

[64 FR 13286, Mar. 17, 1999, as amended at 65 FR 8, Jan. 3, 2000; 65 FR 48904, Aug. 10, 2000; 69 FR 13733, Mar. 24, 2004; 72 FR 71785, Dec. 19, 2007; 73 FR 403, Jan. 3, 2008; 74 FR 19407, Apr. 29, 2009; 76 FR 44487, July 26, 2011]

### § 201.70 Calcium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the calcium content per dosage unit (e.g., tablet, teaspoonful) if the calcium content of a single maximum recommended dose of the product (which may be one or more dosage units) is 20 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

(b) The calcium content shall be expressed in milligrams or grams per dosage unit and shall include the total amount of calcium regardless of the source, i.e., from both active and inactive ingredients. If the dosage unit contains less than 1 gram of calcium, milligrams should be used. The calcium content per dosage unit shall be rounded-off to the nearest 5 milligrams (or nearest tenth of a gram if over 1 gram). The calcium content per dosage unit shall follow the heading “Other information” as stated in § 201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading “Warning” (or “Warnings” if it appears with additional warning statements) if the amount of calcium present in the labeled maximum daily dose of the product is more than 3.2 grams: “Ask a doctor before use if you have [in bold type] [bullet]<sup>1</sup> kidney stones [bullet] a calcium-restricted diet”. The warnings in §§ 201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e.g., a calcium or sodium restricted diet.

(d) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after April 23, 2004.

(2) September 24, 2005, for all OTC drug products subject to any OTC drug monograph, not yet the subject of any OTC drug monograph, or subject to drug marketing applications approved before April 23, 2004.

[69 FR 13733, Mar. 24, 2004]

### § 201.71 Magnesium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the magnesium content per dosage unit (e.g., tablet, teaspoonful) if the magnesium content of a single maximum recommended dose of the product (which may be one or more dosage units) is 8 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

(b) The magnesium content shall be expressed in milligrams or grams per dosage unit and shall include the total

<sup>1</sup>See § 201.66(b)(4) of this chapter for definition of bullet symbol.

amount of magnesium regardless of the source, i.e., from both active and inactive ingredients. If the dosage unit contains less than 1 gram of magnesium, milligrams should be used. The magnesium content shall be rounded-off to the nearest 5 milligrams (or nearest tenth of a gram if over 1 gram). The magnesium content per dosage unit shall follow the heading "Other information" as stated in § 201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading "Warning" (or "Warnings" if it appears with additional warning statements) if the amount of magnesium present in the labeled maximum daily dose of the product is more than 600 milligrams: "Ask a doctor before use if you have [in bold type] [bullet]<sup>1</sup> kidney disease [bullet] a magnesium-restricted diet". The warnings in §§ 201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e.g., a magnesium or potassium-restricted diet.

(d) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after April 23, 2004.

(2) September 24, 2005, for all OTC drug products subject to any OTC drug monograph, not yet the subject of any OTC drug monograph, or subject to drug marketing applications approved before April 23, 2004.

[69 FR 13734, Mar. 24, 2004]

#### § 201.72 Potassium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the potassium content per dosage unit (e.g., tablet, teaspoonful) if the potassium content

of a single maximum recommended dose of the product (which may be one or more dosage units) is 5 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

(b) The potassium content shall be expressed in milligrams or grams per dosage unit and shall include the total amount of potassium regardless of the source, i.e., from both active and inactive ingredients. If the dosage unit contains less than 1 gram of potassium, milligrams should be used. The potassium content shall be rounded-off to the nearest 5 milligrams (or nearest tenth of a gram if over 1 gram). The potassium content per dosage unit shall follow the heading "Other information" as stated in § 201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading "Warning" (or "Warnings" if it appears with additional warning statements) if the amount of potassium present in the labeled maximum daily dose of the product is more than 975 milligrams: "Ask a doctor before use if you have [in bold type] [bullet]<sup>1</sup> kidney disease [bullet] a potassium-restricted diet". The warnings in §§ 201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e.g., a magnesium or potassium-restricted diet.

(d) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after April 23, 2004.

(2) September 24, 2005, for all OTC drug products subject to any OTC drug monograph, not yet the subject of any

<sup>1</sup>See § 201.66(b)(4) of this chapter for definition of bullet symbol.

<sup>1</sup>See § 201.66(b)(4) of this chapter for definition of bullet symbol.

## § 201.80

OTC drug monograph, or subject to drug marketing applications approved before April 23, 2004.

[69 FR 13734, Mar. 24, 2004]

### **§ 201.80 Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1).**

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) *Description.* (1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

(ii) The type of dosage form and the route of administration to which the labeling applies;

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

(iv) If the product is sterile, a statement of that fact;

(v) The pharmacological or therapeutic class of the drug;

(vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) *Clinical Pharmacology.* (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabo-

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lites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

(2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement “The following in vitro data are available but their clinical significance is unknown.”

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

(c) *Indications and Usage.* (1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion

in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2)(i) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in §314.126(b) of this chapter unless the requirement is waived under §201.58 or §314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section.

(ii) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in §314.126(b) of this chapter unless the requirement is waived under §201.58 or §314.126(c) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in §314.126(b) of this chapter unless this requirement is waived under §201.58 or §314.126(c) of this chapter.

(d) *Contraindications.* Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) *Warnings.* Under this section heading, the labeling shall describe serious

adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the “Indications and Usage” section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the “Adverse Reactions” section of the labeling.

(f) *Precautions.* Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) *General.* This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.

(2) *Information for patients.* This subsection must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text

of such patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling. The type size requirement for the Medication Guide set forth in § 208.20 of this chapter does not apply to the Medication Guide that is reprinted in or accompanying the prescription drug labeling unless such Medication Guide is to be detached and distributed to patients in compliance with § 208.24 of this chapter.

(3) *Laboratory tests.* This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient’s response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) *Drug interactions.* This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the “Dosage and Administration” section of the labeling rather than under this subsection of the labeling.

(ii) *Drug/laboratory test interactions.* This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) *Carcinogenesis, mutagenesis, impairment of fertility.* This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

(6) *Pregnancy.* This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) *Teratogenic effects.* Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(a) If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to

demonstrate a risk to the fetus, the labeling shall also state: "Reproduction studies have been performed in (*kinds of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*)." The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(b) If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: "Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Reproduction studies in (*kind(s) of animal(s)*) have shown (*describe findings*) at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(c) If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: “(Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.” The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: “Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed.” The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(d) If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: “See ‘Warnings’ section.” Under the “Warnings” section, the labeling states: “(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.”

(e) If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal

risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: “See ‘Contraindications’ section.” Under “Contraindications,” the labeling shall state: “(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.”

(ii) *Nonteratogenic effects.* Under this heading the labeling shall contain other information on the drug’s effects on reproduction and the drug’s use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman’s chronic use of the drug for a preexisting condition or disease.

(7) *Labor and delivery.* If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) *Nursing mothers.* (i) If a drug is absorbed systemically, this subsection of

the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: "Because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, "Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "Caution should be exercised when (*name of drug*) is administered to a nursing woman."

(iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, "Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exer-

cised when (*name of drug*) is administered to a nursing woman."

(9) *Pediatric use.* (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this section, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage information shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug



in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the “Contraindications,” “Warnings,” and elsewhere in the “Precautions” sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the “Pediatric use” subsection of the labeling shall contain either the following statement, or a reasonable alternative: “The safety and effectiveness of (*drug name*) have been established in the age groups      to      (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).” Data summarized in the preceding prescribed statement in this subsection of the labeling shall

be discussed in more detail, if appropriate, under the “Clinical Pharmacology” or the “Clinical Studies” section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the “Clinical Pharmacology” section. Pediatric dosing instructions shall be included in the “Dosage and Administration” section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the “Pediatric use” subsection and, as appropriate, in the “Contraindications,” “Warnings,” “Precautions,” and “Dosage and Administration” sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the “Pediatric use” subsection of the labeling shall contain an appropriate statement such as “Safety and effectiveness in pediatric patients below the age of (      ) have not been established.” If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the “Contraindications” or “Warnings” section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: “Safety and effectiveness in pediatric patients have not been established.” If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the “Contraindications” or “Warnings” section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this

section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the "Contraindications," "Warnings," or "Precautions" section.

(10) *Geriatric use.* (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage shall be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use" subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information shall also be contained in "Contraindications," "Warnings," and elsewhere in "Precautions."

(ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the "Geriatric use" subsection and shall reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies

that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall include the following statement:

"Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), \_\_\_ percent were 65 and over, while \_\_\_ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the

studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the “Geriatric use” subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the “Contraindications,” “Warnings,” “Dosage and Administration,” or other sections of the labeling.

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the “Geriatric use” subsection of the labeling and in detail under the “Clinical Pharmacology” section. The “Clinical Pharmacology” section and “Drug interactions” subsection of the “Precautions” section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

(B) If a drug is known to be substantially excreted by the kidney, the “Geriatric use” subsection shall include the statement:

“This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.”

(iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the “Geriatric use” subsection of the labeling, or, if appropriate, the hazard shall be stated in the “Contraindications,” “Warnings,” or “Precautions” section

of the labeling, and the “Geriatric use” subsection shall refer to those sections.

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

“Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely.”

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug’s labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) *Adverse Reactions.* An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories

and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (*name of drug*) is (are) (*list reactions*). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (*list reactions*), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (*list reactions*)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in §314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in §314.126(b) of this chapter unless this requirement is waived under §201.58 or §314.126(c) of this chapter.

(h) *Drug Abuse and Dependence*. Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) *Controlled Substance*. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) *Abuse*. This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) *Dependence*. This subsection of the labeling shall describe characteristic effects resulting from both psycho-

logical and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) *Overdosage*. Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

(2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD<sub>50</sub> of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless

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specific data or scientific rationale exists to support safe and effective use.

(j) *Dosage and Administration.* This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. Dosing regimens must not be implied or suggested in other sections of labeling if not included in this section. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) *How Supplied.* This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

(1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system

is used, a statement of the strength is placed in parentheses after the metric designation;

(2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;

(3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and

(4) Special handling and storage conditions.

(1) *Animal Pharmacology and/or Animal Toxicology.* In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "*Clinical Studies*" and "*References*". These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1)(i) If the clinical study is cited in the labeling in place of a detailed discussion of data and information concerning an indication for use of the drug, the clinical study must constitute an adequate and well-controlled study as described in § 314.126(b) of this

chapter, except for biological products, and must not imply or suggest indications or uses or dosing regimens not stated in the “Indications and Usage” or “Dosage and Administration” section.

(ii) When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

[44 FR 37462, June 26, 1979, as amended at 55 FR 11576, Mar. 29, 1990; 59 FR 64249, Dec. 13, 1994; 62 FR 45325, Aug. 27, 1997; 63 FR 66396, Dec. 1, 1998. Redesignated and amended at 71 FR 3988, 3996, Jan. 24, 2006; 79 FR 72103, Dec. 4, 2014]

### Subpart D—Exemptions From Adequate Directions for Use

#### § 201.100 Prescription drugs for human use.

A drug subject to the requirements of section 503(b)(1) of the act shall be exempt from section 502(f)(1) if all the following conditions are met:

(a) The drug is:

(1)(i) In the possession of a person (or his agents or employees) regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of prescription drugs; or

(ii) In the possession of a retail, hospital, or clinic pharmacy, or a public health agency, regularly and lawfully engaged in dispensing prescription drugs; or

(iii) In the possession of a practitioner licensed by law to administer or prescribe such drugs; and

(2) It is to be dispensed in accordance with section 503(b)

(b) The label of the drug bears:

(1) The statement “Rx only” and

(2) The recommended or usual dosage and

(3) The route of administration, if it is not for oral use; and

(4) The quantity or proportion of each active ingredient, as well as the information required by section 502 (d) and (e); and

(5) If it is for other than oral use, the names of all inactive ingredients, except that:

(i) Flavorings and perfumes may be designated as such without naming their components.

(ii) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in subchapter A of this chapter.

(iii) Trace amounts of harmless substances added solely for individual product identification need not be named. If it is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection it need not be named.

(6) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug.

(7) A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity. Where there are standards and test procedures for determining that the container meets the requirements for specified types of containers as defined in an official compendium, such terms may be used. For example, “Dispense in tight, light-resistant container as defined in the National Formulary”. Where standards and test procedures for determining the types of containers to be used in dispensing the drug product are not included in an official compendium, the specific container or types of containers known to be adequate to maintain the identity, strength, quality, and purity of the drug products shall be described. For example, “Dispense

in containers which (statement of specifications which clearly enable the dispensing pharmacist to select an adequate container)”: *Provided, however,* That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraph (b) (2), (3), (5), and (7) of this section may be contained in other labeling on or within the package from which it is to be dispensed; the information referred to in paragraph (b)(1) of this section may be placed on such outer container only; and the information required by paragraph (b)(6) of this section may be on the crimp of the dispensing tube. The information required by this paragraph (b)(7) is not required for prescription drug products packaged in unit-dose, unit-of-use, on other packaging format in which the manufacturer’s original package is designed and intended to be dispensed to patients without repackaging.

(c)(1) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and

(2) If the article is subject to section 505 of the act, the labeling bearing such information is the labeling authorized by the approved new drug application or required as a condition for the certification or the exemption from certification requirements applicable to preparations of insulin or antibiotic drugs.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, rec-

ommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and §201.105(b)(2) contains:

(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 505 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved or permitted, under the provisions of section 505, and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling; and

(2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed.

(3) The information required, and in the format specified, by §§201.56, 201.57, and 201.80.

(e) All labeling described in paragraph (d) of this section bears conspicuously the name and place of business of the manufacturer, packer, or distributor, as required for the label of the drug under §201.1.

(f) Reminder labeling which calls attention to the name of the drug product but does not include indications or dosage recommendations for use of the drug product is exempted from the provisions of paragraph (d) of this section. This reminder labeling shall contain only the proprietary name of the drug product, if any; the established name of the drug product, if any; the established name of each active ingredient in the drug product; and, optionally, information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, the name and address of the manufacturer, packer, or distributor or other written, printed, or graphic matter containing no representation or suggestion relating to the drug product. If

the Commissioner finds that there is evidence of significant incidence of fatalities or serious injury associated with the use of a particular prescription drug, he may withdraw this exemption by so notifying the manufacturer, packer, or distributor of the drug by letter. Reminder labeling, other than price lists and catalogs solely intended to convey price information including, but not limited to, those subject to the requirements of § 200.200 of this chapter, is not permitted for a prescription drug product whose labeling contains a boxed warning relating to a serious hazard associated with the use of the drug product. Reminder labeling which is intended to provide consumers with information concerning the price charged for a prescription for a particular drug product shall meet all of the conditions contained in § 200.200 of this chapter. Reminder labeling, other than that subject to the requirements of § 200.200 of this chapter, is not permitted for a drug for which an announcement has been published pursuant to a review of the labeling claims for the drug by the National Academy of Sciences/National Research Council (NAS/NRC), Drug Efficacy Study Group, and for which no claim has been evaluated as higher than "possibly effective." If the Commissioner finds the circumstances are such that reminder labeling may be misleading to prescribers of drugs subject to NAS/NRC evaluation, such reminder labeling will not be allowed and the manufacturer, packer, or distributor will be notified either in the publication of the conclusions on the effectiveness of the drug or by letter.

[40 FR 13998, Mar. 27, 1975, as amended at 40 FR 58799, Dec. 18, 1975; 42 FR 15674, Mar. 22, 1977; 43 FR 37989, Aug. 25, 1978; 44 FR 20659, Apr. 6, 1979; 44 FR 37467, June 26, 1979; 45 FR 25777, Apr. 15, 1980; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999; 67 FR 4906, Feb. 1, 2002; 71 FR 3996, Jan. 24, 2006]

#### § 201.105 Veterinary drugs.

A drug subject to the requirements of section 503(f)(1) of the act shall be exempt from section 502(f)(1) of the act if all the following conditions are met:

(a) The drug is:

(1)(i) In the possession of a person (or his agents or employees) regularly and

lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of drugs that are to be used only by or on the prescription or other order of a licensed veterinarian; or

(ii) In the possession of a retail, hospital, or clinic pharmacy, or other person authorized under State law to dispense veterinary prescription drugs, who is regularly and lawfully engaged in dispensing drugs that are to be used only by or on the prescription or other order of a licensed veterinarian; or

(iii) In the possession of a licensed veterinarian for use in the course of his professional practice; and

(2) To be dispensed in accordance with section 503(f) of the act.

(b) The label of the drug bears:

(1) The statement "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian"; and

(2) The recommended or usual dosage; and

(3) The route of administration, if it is not for oral use; and

(4) The quantity or proportion of each active ingredient as well as the information required by section 502(e) of the act; and

(5) If it is for other than oral use, the names of all inactive ingredients, except that:

(i) Flavorings and perfumes may be designated as such without naming their components.

(ii) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in subchapter A of this chapter.

(iii) Trace amounts of harmless substances added solely for individual product identification need not be named.

If it is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection, it need not be named.



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(6) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug;

*Provided, however,* That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraphs (b) (2), (3), and (5) of this section may be contained in other labeling on or within the package from which it is to be so dispensed, and the information referred to in paragraph (b)(1) of this section may be placed on such outer container only, and the information required by paragraph (b)(6) of this section may be on the crimp of the dispensing tube.

(c)(1) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and

(2) If the article is subject to section 512 or 572 of the act, the labeling bearing such information is the labeling authorized by the approved new animal drug application or contained in the index listing: *Provided, however,* That the information required by paragraph (c)(1) of this section may be omitted from the dispensing package if, but only if, the article is a drug for which directions, hazards, warnings, and use information are commonly known to veterinarians licensed by law to administer the drug. Upon written request, stating reasonable grounds therefore, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, pack-

er, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and § 201.100(b)(2)) contains:

(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant warnings, hazards, contraindications, side effects, and precautions, and including information relevant to compliance with the new animal drug provisions of the act, under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 512 or 572 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved, permitted, or indexed under the provisions of section 512 or 572, and any other parts of the labeling are consistent with and not contrary to such approved, permitted, or indexed labeling; and

(2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed;

*Provided, however,* That the information required by paragraphs (d) (1) and (2) of this section is not required on the so-called reminder-piece labeling which calls attention to the name of the drug but does not include indications or dosage recommendations for use of the drug.

(e) All labeling, except labels and cartons, bearing information for use of the drug also bears the date of the issuance or the date of the latest revision of such labeling.

(f) A prescription drug intended for both human and veterinary use shall comply with paragraphs (e) and (f) of this section and § 201.100.

[40 FR 13998, Mar. 27, 1975, as amended at 42 FR 15674, Mar. 22, 1977; 57 FR 54300, Nov. 18, 1992; 72 FR 69119, Dec. 6, 2007]

**§ 201.115 New drugs or new animal drugs.**

A new drug shall be exempt from section 502(f)(1) of the act:

(a) To the extent to which such exemption is claimed in an approved application with respect to such drug under section 505 or 512 of the act or an index listing with respect to such drug under section 572 of the act; or

(b) If no application under section 505 or 512 of the act is approved and no request for addition to the index is granted under section 572 with respect to such drug but it complies with section 505(i), 512(j), or 572(g) of the act and regulations thereunder.

No exemption shall apply to any other drug which would be a new drug if its labeling bore representations for its intended uses.

[40 FR 13998, Mar. 27, 1975, as amended at 72 FR 69119, Dec. 6, 2007]

**§ 201.116 Drugs having commonly known directions.**

A drug shall be exempt from section 502(f)(1) of the act insofar as adequate directions for common uses thereof are known to the ordinary individual.

[41 FR 6910, Feb. 13, 1976]

**§ 201.117 Inactive ingredients.**

A harmless drug that is ordinarily used as an inactive ingredient, such as a coloring, emulsifier, excipient, flavoring, lubricant, preservative, or solvent, in the preparation of other drugs shall be exempt from section 502(f)(1) of the act. This exemption shall not apply to any substance intended for a use which results in the preparation of a new drug, unless an approved new-drug application provides for such use.

**§ 201.119 In vitro diagnostic products.**

(a) "In vitro diagnostic products" are those reagents, instruments and systems intended for use in the diagnosis of disease or in the determination of the state of health in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation and examination of specimens taken from the human body. These products are drugs or devices as defined in section 201(g) and 201(h), respec-

tively, of the Federal Food, Drug, and Cosmetic Act (the act) or are a combination of drugs and devices, and may also be a biological product subject to section 351 of the Public Health Service Act.

(b) A product intended for use in the diagnosis of disease and which is an in vitro diagnostic product as defined in paragraph (a) of this section shall be deemed to be in compliance with the requirements of this section and section 502(f)(1) of the act if it meets the requirements of § 809.10 of this chapter.

[41 FR 6910, Feb. 13, 1976]

**§ 201.120 Prescription chemicals and other prescription components.**

A drug prepared, packaged, and primarily sold as a prescription chemical or other component for use by registered pharmacists in compounding prescriptions or for dispensing in dosage unit form upon prescriptions shall be exempt from section 502(f)(1) of the act if all the following conditions are met:

(a) The drug is an official liquid acid or official liquid alkali, or is not a liquid solution, emulsion, suspension, tablet, capsule, or other dosage unit form; and

(b) The label of the drug bears:

(1) The statement "For prescription compounding"; and

(2) If in substantially all dosage forms in which it may be dispensed it is subject to section 503(b)(1) of the act, the statement "Rx only"; or

(3) If it is not subject to section 503(b)(1) of the act and is by custom among retail pharmacists sold in or from the interstate package for use by consumers, "adequate directions for use" in the conditions for which it is so sold.

*Provided, however,* That the information referred to in paragraph (b)(3) of this section may be contained in the labeling on or within the package from which it is to be dispensed.

(c) This exemption shall not apply to any substance intended for use in compounding which results in a new

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drug, unless an approved new-drug application covers such use of the drug in compounding prescriptions.

[40 FR 13998, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

### § 201.122 Drugs for processing, repackaging, or manufacturing.

A drug in a bulk package, except tablets, capsules, or other dosage unit forms, intended for processing, repackaging, or use in the manufacture of another drug shall be exempt from section 502(f)(1) of the act if its label bears the statement "Caution: For manufacturing, processing, or repackaging"; and if in substantially all dosage forms in which it may be dispensed it is subject to section 503(b)(1) of the act, the statement "Rx only", or if in substantially all dosage forms in which it may be dispensed it is subject to section 503(f)(1) of the act, the statement "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian". This exemption and the exemption under § 201.120 may be claimed for the same article. However, the exemption shall not apply to a substance intended for a use in manufacture, processing, or repackaging which causes the finished article to be a new drug or new animal drug, unless:

(a) An approved new drug application or new animal drug application or a new animal drug index listing covers the production and delivery of the drug substance to the application or index listing holder by persons named in the application or in the request for determination of eligibility for indexing, and, for a new drug substance, the export of it by such persons under § 314.410 of this chapter; or

(b) If no application is approved with respect to such new drug or new animal drug, and it is not listed in the index, the label statement "Caution: For manufacturing, processing, or repackaging" is immediately supplemented by the words "in the preparation of a new drug or new animal drug limited by Federal law to investigational use", and the delivery is made for use only in the manufacture of such new drug or new animal drug limited to investigational use as provided in part 312 or § 511.1 or § 516.125 of this chapter; or

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(c) A new drug application or new animal drug application or a request for addition to the index covering the use of the drug substance in the production and marketing of a finished drug product has been submitted but not yet approved, disapproved, granted, or denied, the bulk drug is not exported, and the finished drug product is not further distributed after it is manufactured until after the new drug application or new animal drug application is approved or the request for addition to the index is granted.

[41 FR 6911, Feb. 13, 1976, as amended at 41 FR 15844, Apr. 15, 1976; 50 FR 7492, Feb. 22, 1985; 55 FR 11576, Mar. 29, 1990; 57 FR 54301, Nov. 18, 1992; 67 FR 4906, Feb. 1, 2002; 72 FR 69119, Dec. 6, 2007]

### § 201.125 Drugs for use in teaching, law enforcement, research, and analysis.

A drug subject to § 201.100 or § 201.105, shall be exempt from section 502(f)(1) of the act if shipped or sold to, or in the possession of, persons regularly and lawfully engaged in instruction in pharmacy, chemistry, or medicine not involving clinical use, or engaged in law enforcement, or in research not involving clinical use, or in chemical analysis, or physical testing, and is to be used only for such instruction, law enforcement, research, analysis, or testing.

[41 FR 6911, Feb. 13, 1976]

### § 201.127 Drugs; expiration of exemptions.

(a) If a shipment or delivery, or any part thereof, of a drug which is exempt under the regulations in this section is made to a person in whose possession the article is not exempt, or is made for any purpose other than those specified, such exemption shall expire, with respect to such shipment or delivery or part thereof, at the beginning of that shipment or delivery. The causing of an exemption to expire shall be considered an act which results in such drug being misbranded unless it is disposed of under circumstances in which it ceases to be a drug or device.

(b) The exemptions conferred by §§ 201.117, 201.119, 201.120, 201.122, and 201.125 shall continue until the drugs are used for the purposes for which

they are exempted, or until they are relabeled to comply with section 502(f)(1) of the act. If, however, the drug is converted, compounded, or manufactured into a dosage form limited to prescription dispensing, no exemption shall thereafter apply to the article unless the dosage form is labeled as required by section 503(b) and §§ 201.100 or 201.105.

[41 FR 6911, Feb. 13, 1976]

**§ 201.128 Meaning of “intended uses”.**

The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122 refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.

[41 FR 6911, Feb. 13, 1976]

EFFECTIVE DATE NOTE: At 82 FR 2217, Jan. 9, 2017, § 201.128 was revised, effective Feb. 8, 2017. This effective date was delayed to Mar. 21, 2017, at 82 FR 9501, Feb. 7, 2017, and was then further delayed to Mar. 19, 2018 at 82 FR

14319, Mar. 20, 2017. At 83 FR 11639, Mar. 16, 2018, the effective date for this revision was delayed indefinitely. For the convenience of the user, the revised text is set forth as follows:

**§ 201.128 Meaning of “intended uses”.**

The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, 201.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. And if the totality of the evidence establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it is approved (if any), he is required, in accordance with section 502(f) of the Federal Food, Drug, and Cosmetic Act, or, as applicable, duly promulgated regulations exempting the drug from the requirements of section 502(f)(1), to provide for such drug adequate labeling that accords with such other intended uses.

**§ 201.129 Drugs; exemption for radioactive drugs for research use.**

A radioactive drug intended for administration to human research subjects during the course of a research project intended to obtain basic research information regarding metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry (but not intended for immediate therapeutic, diagnostic, or similar purposes), under the conditions set forth in § 361.1 of this chapter, shall be exempt from section 502(f)(1) of the act if the packaging, label, and labeling

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are in compliance with § 361.1(f) of this chapter.

[41 FR 6911, Feb. 13, 1976]

### Subpart E—Other Exemptions

#### § 201.150 Drugs; processing, labeling, or repacking.

(a) Except as provided by paragraphs (b) and (c) of this section, a shipment or other delivery of a drug which is, in accordance with the practice of the trade, to be processed, labeled, or repacked in substantial quantity at an establishment other than that where originally processed or packed, shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment, from compliance with the labeling and packaging requirements of sections 501(b) and 502 (b), (d), (e), (f), and (g) of the act if:

(1) The person who introduced such shipment or delivery into interstate commerce is the operator of the establishment where such drug is to be processed, labeled, or repacked; or

(2) In case such person is not such operator, such shipment or delivery is made to such establishment under a written agreement, signed by and containing the post-office addresses of such person and such operator, and containing such specifications for the processing, labeling, or repacking, as the case may be, of such drug in such establishment as will insure, if such specifications are followed, that such drug will not be adulterated or misbranded within the meaning of the act upon completion of such processing, labeling, or repacking. Such person and such operator shall each keep a copy of such agreement until 2 years after the final shipment or delivery of such drug from such establishment, and shall make such copies available for inspection at any reasonable hour to any officer or employee of the Department who requests them.

(b) An exemption of a shipment or other delivery of a drug under paragraph (a)(1) of this section shall, at the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment, become void ab initio if the drug comprising such shipment, delivery, or part

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is adulterated or misbranded within the meaning of the act when so removed.

(c) An exemption of a shipment or other delivery of a drug under paragraph (a)(2) of this section shall become void ab initio with respect to the person who introduced such shipment or delivery into interstate commerce upon refusal by such person to make available for inspection a copy of the agreement, as required by such paragraph (a)(2) of this section.

(d) An exemption of a shipment or other delivery of a drug under paragraph (a)(2) of this section shall expire:

(1) At the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment if the drug comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed; or

(2) Upon refusal by the operator of the establishment where such drug is to be processed, labeled, or repacked, to make available for inspection a copy of the agreement, as required by such clause.

[41 FR 6911, Feb. 13, 1976, as amended at 64 FR 400, Jan. 5, 1999]

#### § 201.161 Medical gases.

(a) Oxygen, nitrogen, carbon dioxide, helium, and nitrous oxide gases intended for drug use, and medically appropriate combinations of any of these gases intended for drug use, are exempted from the requirements of § 201.100(b)(2) and (3), and (c)(1), provided that, where applicable, the requirements of §§ 201.328 and 211.94(e)(2) of this chapter are met and the labeling bears, in addition to any other information required by the Federal Food, Drug, and Cosmetic Act, the following:

(1)(i) In the case of oxygen, a warning statement providing that uninterrupted use of high concentrations of oxygen over a long duration, without monitoring its effect on oxygen content of arterial blood, may be harmful; that oxygen should not be used on patients who have stopped breathing unless used in conjunction with resuscitative equipment; and, in the case of oxygen that may be provided without a prescription for use in the

event of depressurization or other environmental oxygen deficiency, or for oxygen deficiency or for use in emergency resuscitation when administered by properly trained personnel, a warning statement providing that oxygen may be used for emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation, and that for all other medical applications a prescription is required.

(ii) In the case of nitrogen, carbon dioxide, helium, nitrous oxide, and medically appropriate combinations of any of the gases listed in paragraph (a) of this section, a warning statement providing that the administration of the gas or gas combination (as applicable) may be hazardous or contraindicated; and that the gas or gas combination (as applicable) should be used only by or under the supervision of a licensed practitioner who is experienced in the use and administration of the gas or gas combination (as applicable) and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken.

(2) Any needed directions concerning the conditions for storage and warnings against the inherent dangers in the handling of the specific compressed gas.

(b) [Reserved]

[81 FR 81696, Nov. 18, 2016]

### Subpart F—Labeling Claims for Drugs in Drug Efficacy Study

#### § 201.200 Disclosure of drug efficacy study evaluations in labeling and advertising.

(a)(1) The National Academy of Sciences—National Research Council, Drug Efficacy Study Group, has completed an exhaustive review of labeling claims made for drugs marketed under new-drug and antibiotic drug procedures between 1938 and 1962. The results are compiled in “Drug Efficacy Study, A Report to the Commissioner of Food and Drugs from the National Academy of Sciences (1969).” As the report notes, this review has made “an audit of the state of the art of drug usage that has

been uniquely extensive in scope and uniquely intensive in time” and is applicable to more than 80 percent of the currently marketed drugs. The report further notes that the quality of the evidence of efficacy, as well as the quality of the labeling claims, is poor. Labeling and other promotional claims have been evaluated as “effective,” “probably effective,” “possibly effective,” “ineffective,” “ineffective as a fixed combination,” and “effective but,” and a report for each drug in the study has been submitted to the Commissioner.

(2) The Food and Drug Administration is processing the reports, seeking voluntary action on the part of the drug manufacturers and distributors in the elimination or modification of unsupported promotional claims, and initiating administrative actions as necessary to require product and labeling changes.

(3) Delays have been encountered in bringing to the attention of the prescribers of prescription items the conclusions of the expert panels that reviewed the promotional claims.

(b) The Commissioner of Food and Drugs concludes that:

(1) The failure to disclose in the labeling of a drug and in other promotional material the conclusions of the Academy experts that a claim is “ineffective,” “possibly effective,” “probably effective,” or “ineffective as a fixed combination,” while labeling and promotional material bearing any such claim are being used, is a failure to disclose facts that are material in light of the representations made and causes the drug to be misbranded.

(2) The Academy classification of a drug as other than “effective” for a claim for which such drug is recommended establishes that there is a material weight of opinion among qualified experts contrary to the representation made or suggested in the labeling, and failure to reveal this fact causes such labeling to be misleading.

(c) Therefore, after publication in the FEDERAL REGISTER of a Drug Efficacy Study Implementation notice on a prescription drug, unless exempted or otherwise provided for in the notice, all

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package labeling (other than the immediate container or carton label, unless such labeling contains information required by §201.100(c)(1) in lieu of a package insert), promotional labeling, and advertisements shall include, as part of the information for practitioners under which the drug can be safely and effectively used, an appropriate qualification of all claims evaluated as other than “effective” by a panel of the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, if such claims continue to be included in either the labeling or advertisements. However, this qualifying information will be required in advertisements only if promotional material is included therein for claims evaluated as less than “effective” or if such claims are included in the indications section of the portion of the advertisement containing the information required in brief summary by §202.1(e)(1) of this chapter. When, however, the Food and Drug Administration classification of such claim is “effective” (for example, on the basis of revision of the language of the claim or submission or existence of adequate data), such qualification is not necessary. When the Food and Drug Administration classification of the claim, as stated in the implementation notice, differs from that of the Academy but is other than “effective,” the qualifying statement shall refer to this classification in lieu of the Academy’s classification.

(d) For new drugs and antibiotics, supplements to provide for revised labeling in accord with paragraph (c) of this section shall be submitted under the provisions of §314.70 and §514.8 of this chapter within 90 days after publication of the implementation notice in the FEDERAL REGISTER or by May 15, 1972, for those drugs for which notices have been published and such labeling shall be put into use as soon as possible but not later than the end of the time period allowed for submitting supplements to provide for revised labeling.

(e) Qualifying information required in drug labeling by paragraph (c) of this section in order to advise prescribers of a drug of the findings made by a panel of the Academy in evaluating a claim as other than “effective”

shall be at least of the same size and color and degree of prominence as other printing in the labeling and shall be presented in a prominent box using one of the following formats and procedures:

(1) In drug labeling the box statement may entirely replace the indications section and be in the following format:

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication(s) as follows:

Effective: *(list or state in paragraph form)*.

“Probably” effective: *(list or state in paragraph form)*.

“Possibly” effective: *(list or state in paragraph form)*.

Final classification of the less-than-effective indications requires further investigation.

(2) Or the indication(s) for which the drug has been found effective may appear outside the boxed statement and be followed immediately by the following boxed statement:

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the other indication(s) as follows:

“Probably” effective: *(list or state in paragraph form)*.

“Possibly” effective: *(list or state in paragraph form)*.

Final classification of the less-than-effective indications requires further investigation.

(3) In drug labeling (other than that which is required by §201.100(c)(1)) which may contain a promotional message, the promotional message shall be keyed to the boxed statement by the same means as those provided for advertisements in paragraph (f)(2) of this section.

(f) Qualifying information required in prescription drug advertising by paragraph (c) of this section shall contain a prominent boxed statement of the advertised indication(s) and of the limitations of effectiveness using the same format, language, and emphasis as that required in labeling by paragraph (e) of this section.

(1) The boxed statement shall appear in (or next to) the information required in brief summary by §202.1(e)(1) of this chapter and shall have prominence at least equal to that provided for other information presented in the brief summary and shall have type size, captions, color, and other physical characteristics comparable to the information required in the brief summary.

(2) Less-than-effective indication(s) in the promotional message of an advertisement which is a single page or less shall be keyed to the boxed statement by asterisk, by an appropriate statement, or by other suitable means providing adequate emphasis on the boxed statement. On each page where less-than-effective indication(s) appear in a multiple page advertisement, an asterisk shall be placed after the most prominent mention of the indication(s); if the degree of prominence does not vary, an asterisk shall be placed after the first mention of the indication. The asterisk shall refer to a notation at the bottom of the page which shall state "This drug has been evaluated as probably effective (or possibly effective whichever is appropriate) for this indication" and "See Brief Summary" or "See Prescribing Information," the latter legend to be used only if the advertisement carries the required information for professional use as set forth in §201.100(c)(1).

(3) For less-than-effective indications which are included in the advertisement only as a part of the information required in brief summary, the disclosure information shall appear in this portion of the advertisement in the same manner as is specified for labeling in paragraph (e) of this section.

(g) The Commissioner may find circumstances are such that, while the elimination of claims evaluated as other than effective will generally eliminate the need for disclosure about such claims, there will be instances in which the change in the prescribing or promotional profile of the drug is so substantial as to require a disclosure of the reason for the change so that the purchaser or prescriber is not misled by being left unaware through the sponsor's silence that a basic change has taken place. The Food and Drug Administration will identify these situ-

ations in direct correspondence with the drug promoters, after which the failure to make the disclosure will be regarded as misleading and appropriate action will be taken.

[40 FR 13998, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990]

### Subpart G—Specific Labeling Requirements for Specific Drug Products

#### §201.300 Notice to manufacturers, packers, and distributors of glandular preparations.

(a) Under date of December 4, 1941, in a notice to manufacturers of glandular preparations, the Food and Drug Administration expressed the opinion that preparations of inert glandular materials intended for medicinal use should, in view of the requirement of section 201(n) of the Federal Food, Drug, and Cosmetic Act (52 Stat. 1041; 21 U.S.C. 321(n)), be labeled with a statement of the material fact that there is no scientific evidence that the articles contain any therapeutic or physiologically active constituents. Numerous preparations of such inert glandular materials were subsequently marketed with disclaimers of the type suggested. The term *inert glandular materials* means preparations incapable of exerting an action or effect of some significant or measurable benefit in one way or another, i.e., in the diagnosis, cure, mitigation, treatment, or prevention of disease, or in affecting the structure or any function of the body.

(b) Manufacturers have heretofore taken advantage of §201.100 permitting omission of directions for use when the label bears the prescription legend. Section 201.100(c) requires that the labeling of the drug, which may include brochures readily available to licensed practitioners, bear information as to the use of the drug by practitioners licensed by law to administer it. Obviously, information adequate for the use of an inert glandular preparation is not available to practitioners licensed by law.

(c) The Department of Health and Human Services is of the opinion that inert glandular materials may not be exempted from the requirements of



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section 502(f)(1) of the act that they bear adequate directions for use; and, accordingly, that their labeling must include among other things, representations as to the conditions for which such articles are intended to be used or as to the structure or function of the human body that they are intended to affect. Since any such representations offering these articles for use as drugs would be false or misleading, such articles will be considered to be misbranded if they are distributed for use as drugs.

(d) The amended regulations provide also that in the case of drugs intended for parenteral administration there shall be no exemption from the requirement that their labelings bear adequate directions for use. Such inert glandular materials for parenteral use are therefore subject to the same comment as applies to those intended for oral administration.

### **§ 201.301 Notice to manufacturers, packers, and distributors of estrogenic hormone preparations.**

Some drug preparations fabricated wholly or in part from estradiol and labeled as to potency in terms of international units or in terms of international units of estrone activity have been marketed. The international unit of the estrus-producing hormone was established by the International Conference on the Standardization of Sex Hormones at London, England, on August 1, 1932. This unit was defined as "the specific estrus-producing activity contained in 0.1 gamma (= 0.0001 mg.) of the standard" hydroxyketonic hormone found in urine (estrone). The International Conference declared that it did not recommend the determination of the activity of nonhydroxyketonic forms of estrogenic hormones in units of estrone because of the varying ratios between the activity of such nonhydroxyketonic estrogenic hormones and estrone, when measured by different methods on test animals. There is no international unit for measuring the activity of estradiol and no accepted relationship between its activity and that of estrone, either in test animals or in humans. The declaration of potency of estradiol in terms of international units or in

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terms of international units of estrone activity is therefore considered misleading, within the meaning of 21 U.S.C. 352(a). The declaration of the estradiol content of an estrogenic hormone preparation in terms of weight is considered appropriate.

### **§ 201.302 Notice to manufacturers, packers, and distributors of drugs for internal use which contain mineral oil.**

(a) In the past few years research studies have altered medical opinion as to the usefulness and harmfulness of mineral oil in the human body. These studies have indicated that when mineral oil is used orally near mealtime it interferes with absorption from the digestive tract of provitamin A and the fat-soluble vitamins A, D, and K, and consequently interferes with the utilization of calcium and phosphorus, with the result that the user is left liable to deficiency diseases. When so used in pregnancy it predisposes to hemorrhagic disease of the newborn.

(b) There is accumulated evidence that the indiscriminate administration of mineral oil to infants may be followed by aspiration of the mineral oil and subsequent "lipoid pneumonia."

(c) In view of these facts, the Department of Health and Human Services will regard as misbranded under the provisions of the Federal Food, Drug, and Cosmetic Act a drug for oral administration consisting in whole or in part of mineral oil, the labeling of which encourages its use in pregnancy or indicates or implies that such drug is for administration to infants.

(d) It is also this Department's view that the act requires the labelings of such drugs to bear a warning against consumption other than at bedtime and against administration to infants. The following form of warning is suggested: "Caution: To be taken only at bedtime. Do not use at any other time or administer to infants, except upon the advice of a physician."

(e) This statement of interpretation does not in any way exempt mineral oil or preparations containing mineral oil from complying in all other respects with the requirements of the Federal Food, Drug, and Cosmetic Act.

**§ 201.303 Labeling of drug preparations containing significant proportions of wintergreen oil.**

(a) Because methyl salicylate (wintergreen oil) manifests no toxicity in the minute amounts in which it is used as a flavoring, it is mistakenly regarded by the public as harmless even when taken in substantially larger amounts. Actually, it is quite toxic when taken in quantities of a teaspoonful or more. Wintergreen oil and preparations containing it have caused a number of deaths through accidental misuse by both adults and children. Children are particularly attracted by the odor and are likely to swallow these products when left within reach.

(b) To safeguard against fatalities from this cause, the Department of Health and Human Services will regard as misbranded under the provisions of the Federal Food, Drug, and Cosmetic Act any drug containing more than 5 percent methyl salicylate (wintergreen oil), the labeling of which fails to warn that use otherwise than as directed therein may be dangerous and that the article should be kept out of reach of children to prevent accidental poisoning.

(c) This statement of interpretation in no way exempts methyl salicylate (wintergreen oil) or its preparations from complying in all other respects with the requirements of the Federal Food, Drug, and Cosmetic Act.

**§ 201.304 Tannic acid and barium enema preparations.**

(a) It has become a widespread practice for tannic acid to be added to barium enemas to improve X-ray pictures. Tannic acid is capable of causing diminished liver function and severe liver necrosis when absorbed in sufficient amounts. The medical literature reports a number of deaths associated with the addition of tannic acid to barium enemas. There is a lack of scientific evidence to establish the conditions, if any, under which tannic acid is safe and effective for use in enemas. Tannic acid for rectal use to enhance X-ray visualization is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(b) In view of the hazards involved when tannic acid is used in barium enemas, any shipments of tannic acid labeled to come within the exemptions under 502(f) of the Act containing such phrases as: "Caution: For manufacturing, processing, or repackaging," "For prescription compounding," or "Diagnostic reagent—For professional use only" will be regarded by the Commissioner of Food and Drugs as misbranded within the meaning of section 502(f) of the Federal Food, Drug, and Cosmetic Act unless the label and the labeling bear conspicuously a warning to the effect: "Warning—Not for use in enemas."

(c) Any tannic acid intended for use by man and found within the jurisdiction of the Federal Food, Drug, and Cosmetic Act labeled contrary to this section after 60 days from the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

**§ 201.305 Isoproterenol inhalation preparations (pressurized aerosols, nebulizers, powders) for human use; warnings.**

(a) Accumulating reports have been received by the Food and Drug Administration and have appeared in the medical literature of severe paradoxical bronchoconstriction associated with repeated, excessive use of isoproterenol inhalation preparations in the treatment of bronchial asthma and other chronic bronchopulmonary disorders. The cause of this paradoxical reaction is unknown; it has been observed, however, that patients have not responded completely to other forms of therapy until use of the isoproterenol inhalation preparation was discontinued. In addition, sudden unexpected deaths have been associated with the excessive use of isoproterenol inhalation preparations. The mechanism of these deaths and their relationship, if any, to the cases of severe paradoxical bronchospasm are not clear. Cardiac arrest was noted in several of these cases of sudden death.

(b) On the basis of the above information and after discussion with and concurrence of the Respiratory and Anesthetic Drugs Advisory Committee for Food and Drug Administration, the

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Commissioner of Food and Drugs concludes that in order for the labeling of such drugs to bear adequate information for their safe use, as required by § 201.100, such labeling must include the following:

*Warning:* Occasional patients have been reported to develop severe paradoxical airway resistance with repeated, excessive use of isoproterenol inhalation preparations. The cause of this refractory state is unknown. It is advisable that in such instances the use of this preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.

Deaths have been reported following excessive use of isoproterenol inhalation preparations and the exact cause is unknown. Cardiac arrest was noted in several instances.

(c)(1) The Commissioner also concludes that in view of the manner in which these preparations are self-administered for relief of attacks of bronchial asthma and other chronic bronchopulmonary disorders, it is necessary for the protection of users that warning information to patients be included as a part of the label and as part of any instructions to patients included in the package dispensed to the patient as follows:

*Warning:* Do not exceed the dose prescribed by your physician. If difficulty in breathing persists, contact your physician immediately.

(2) The warning on the label may be accomplished (i) by including it on the immediate container label with a statement directed to pharmacists not to remove the label or (ii) by including in the package a printed warning with instructions to pharmacists to place the warning on the container prior to dispensing.

(d) The marketing of isoproterenol inhalation preparations may be continued if all the following conditions are met:

(1) Within 30 days following the date of publication of this section in the FEDERAL REGISTER:

(i) The label and labeling of such preparations shipped within the jurisdiction of the act are in accordance with paragraphs (b) and (c) of this section.

(ii) The holder of an approved new-drug application for such preparation submits a supplement to his new-drug application to provide for appropriate labeling changes as described in paragraphs (b) and (c) of this section.

(2) Within 90 days following the date of publication of this section in the FEDERAL REGISTER, the manufacturer, packer, or distributor of any drug containing isoproterenol intended for inhalation for which a new-drug approval is not in effect submits a new-drug application containing satisfactory information of the kinds required by § 314.50 of this chapter, including appropriate labeling as described in paragraphs (b) and (c) of this section.

(3) The applicant submits additional information required for the approval of the application as may be specified in a written communication from the Food and Drug Administration.

(e) After 270 days following expiration of said 90 days, regulatory proceedings based on section 505(a) of the Federal Food, Drug, and Cosmetic Act may be initiated with regard to any such drug shipped within the jurisdiction of the act for which an approved new-drug application is not in effect.

[40 FR 13998, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990]

### § 201.306 Potassium salt preparations intended for oral ingestion by man.

(a) The Food and Drug Administration will initiate no regulatory action with respect to the continued marketing of coated tablets containing potassium chloride or other potassium salts which supply 100 milligrams or more of potassium per tablet provided all the following conditions are met:

(1) Within 30 days from the date of publication of this statement of policy in the FEDERAL REGISTER:

(i) The labeling of the drug bears the prescription caution statement quoted in section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act;

(ii) The labeling on or within the package from which the drug is to be dispensed bears adequate information for its use by practitioners in accord with the "full disclosure" labeling requirements of § 201.100 of this chapter, including the following warning statement:

*Warning*—There have been several reports, published and unpublished, concerning non-specific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required and deaths have occurred. Based on a large survey of physicians and hospitals, both United States and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Coated potassium tablets should be used only when adequate dietary supplementation is not practicable.

(Although the warning statement includes references to enteric-coated potassium salt preparations, it applies to any capsule or coated tablet of a potassium salt intended for oral ingestion without prior dilution with an adequate volume of liquid to preclude gastrointestinal injury.)

(iii) Any other labeling or additional advertising for the drug conforms to the labeling described in paragraph (a)(1)(ii) of this section, in accordance with §§ 202.1 and 201.100 of this chapter.

(2) Within 90 days from the date of publication of this statement of policy in the FEDERAL REGISTER, the manufacturer, packer, or distributor of the drug shall submit a new-drug application containing satisfactory information of the kind required by § 314.50 of this chapter, with appropriate labeling as described in this paragraph.

(b) The Food and Drug Administration may initiate regulatory proceedings after 30 days from the date of publication of this section, with respect to the marketing of uncoated tablets containing potassium chloride or other potassium salts which supply 100 milligrams or more of potassium per tablet or with respect to liquid preparations containing potassium chloride or other potassium salts which supply 20 milligrams or more of potas-

sium per milliliter, labeled or intended for human use, unless all the following conditions are met:

(1) The labeling of the drug bears the prescription statement quoted in section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act; and

(2) The labeling on or within the package from which the drug is to be dispensed bears adequate information for its use by practitioners in accord with the “full disclosure” labeling requirements of § 201.100 of this chapter, including a recommendation that patients be directed to dissolve any such tablets in an appropriate amount of liquid and to dilute any such liquid preparations adequately to assure against gastrointestinal injury associated with the oral ingestion of concentrated potassium salt preparations.

[40 FR 13998, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990; 67 FR 4906, Feb. 1, 2002]

**§ 201.307 Sodium phosphates; package size limitation, warnings, and directions for over-the-counter sale.**

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that multiple container sizes of sodium phosphates oral solution available in the marketplace have caused consumer confusion and appear to have been involved in several consumer deaths. Sodium phosphates oral solution has been marketed in 45-milliliter (mL), 90-mL, and 240-mL container sizes. The 45-mL and 90-mL container sizes of sodium phosphates oral solution are often recommended and prescribed by physicians for bowel cleansing prior to surgery and diagnostic procedures of the colon. Sodium phosphates oral solution (adult dose 20 mL to 45 mL) is also used as an over-the-counter (OTC) laxative for the relief of occasional constipation. Accidental overdosing and deaths have occurred because the 240-mL container was mistakenly used instead of the 45-mL or 90-mL container. The Food and Drug Administration is limiting the amount of sodium phosphates oral solution to not more than 90 mL (3 ounces (oz)) per OTC container because of the serious health risks associated with the ingestion of larger than intended doses of this product. Further,

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because an overdose of either oral or rectal enema sodium phosphates can cause an electrolyte imbalance, additional warning and direction statements are required for the safe use of any OTC laxative drug product containing sodium phosphates.

(b) Any OTC drug product for laxative or bowel cleansing use containing sodium phosphates as an active ingredient when marketed as described in paragraph (a) of this section is misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless packaged and labeled as follows:

(1) Package size limitation for sodium phosphates oral solution: Container shall not contain more than 90 mL (3 oz).

(2) Warnings. The following sentences shall appear in boldface type as the first statement under the heading "Warnings."

(i) Oral dosage forms. "Taking more than the recommended dose in 24 hours can be harmful."

(ii) Rectal enema dosage forms. "Using more than one enema in 24 hours can be harmful."

(3) Directions—(i) The labeling of all orally or rectally administered OTC drug products containing sodium phosphates shall contain the following directions in boldface type immediately preceding the dosage information: "Do not" ("take" or "use") "more unless directed by a doctor. See Warnings."

(ii) For products containing dibasic sodium phosphate/monobasic sodium phosphate identified in § 334.16(d) marketed as a solution. Adults and children 12 years of age and over: Oral dosage is dibasic sodium phosphate 3.42 to 7.56 grams (g) and monobasic sodium phosphate 9.1 to 20.2 g (20 to 45 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 45 mL (9 teaspoonfuls or 3 tablespoonfuls) in a 24-hour period." Children 10 and 11 years of age: Oral dosage is dibasic sodium phosphate 1.71 to 3.78 g and monobasic sodium phosphate 4.5 to 10.1 g (10 to 20 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 20 mL (4 tea-

spoonfuls) in a 24-hour period." Children 5 to 9 years of age: Oral dosage is dibasic sodium phosphate 0.86 to 1.89 g and monobasic sodium phosphate 2.2 to 5.05 g (5 to 10 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 10 mL (2 teaspoonfuls) in a 24-hour period." Children under 5 years of age: ask a doctor.

(c) After June 22, 1998, for package size limitation and September 18, 1998, for labeling in accord with paragraph (b) of this section, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce, or any such drug product that is repackaged or relabeled after these dates regardless of the date the product was manufactured, initially introduced, or initially delivered for introduction into interstate commerce, that is not in compliance with this section is subject to regulatory action.

[63 FR 27843, May 21, 1998]

**§ 201.308 Ipecac syrup; warnings and directions for use for over-the-counter sale.**

(a) It is estimated that each year about 500,000 accidental poisonings occur in the United States and result in approximately 1,500 deaths, of which over 400 are children. In the emergency treatment of these poisonings, ipecac syrup is considered the emetic of choice. The immediate availability of this drug for use in such situations is critical, since rapid treatment may be the difference between life and death. The restriction of this drug to prescription sale limits its availability in emergencies. On the other hand, it is the consensus of informed medical opinion that ipecac syrup should be used only under medical supervision in the emergency treatment of poisonings. In view of these facts, the question of whether ipecac syrup labeled as an emergency treatment for use in poisonings should be available over the counter has been controversial.

(b) In connection with its study of this problem, the Food and Drug Administration has obtained the views of medical authorities. It is the unanimous recommendation of the American

Academy of Pediatrics, the American Association of Poison Control Centers, the American Medical Association, and the Medical Advisory Board of the Food and Drug Administration that ipecac syrup in 1 fluid ounce containers be permitted to be sold without prescription so that it will be readily available in the household for emergency treatment of poisonings, under medical supervision, and that the drug be appropriately packaged and labeled for this purpose.

(c) In view of the above recommendations, the Commissioner of Food and Drugs has determined that it is in the interest of the public health for ipecac syrup to be available for sale without prescription, provided that it is packaged in a quantity of 1 fluid ounce (30 milliliters), and its label bears, in addition to other required label information, the following, in a prominent and conspicuous manner:

(1) A statement conspicuously boxed and in red letters, to the effect: "For emergency use to cause vomiting in poisoning. Before using, call physician, the Poison Control Center, or hospital emergency room immediately for advice."

(2) A warning to the effect: "Warning—Keep out of reach of children. Do not use in unconscious persons. Ordinarily, this drug should not be used if strychnine, corrosives such as alkalis (lye) and strong acids, or petroleum distillates such as kerosine, gasoline, coal oil, fuel oil, paint thinner, or cleaning fluid have been ingested."

(3) Usual dosage: 1 tablespoon (15 milliliters) in persons over 1 year of age.

**§201.309 Acetophenetidin (phenacetin)-containing preparations; necessary warning statement.**

(a) In 1961, the Food and Drug Administration, pursuant to its statutory responsibility for the safety and effectiveness of drugs shipped in interstate commerce, began an active investigation of reports of possible toxic effects and renal damage due to misuse of the drug acetophenetidin. This study led to the decision that there was probable cause to conclude that misuse and prolonged use of the drug were in fact responsible for kidney lesions and disease. The Commissioner of Food and

Drugs, in December 1963, appointed an ad hoc Advisory Committee of Inquiry on Possible Nephrotoxicity Associated With the Abuse of Acetophenetidin (Phenacetin)-Containing Preparations. This committee, composed of scientists in the fields of pharmacology and medicine, on April 23, 1964, submitted its findings and conclusions in the matter and recommended that all acetophenetidin (phenacetin)-containing preparations bear a warning as provided in section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act.

(b) On the basis of the studies made by the Food and Drug Administration and the report of the Advisory Committee, the Commissioner of Food and Drugs has concluded that it is necessary for the protection of users that the label and labeling of all acetophenetidin (phenacetin)-containing preparations bear a warning statement to the following effect: "Warning—This medication may damage the kidneys when used in large amounts or for a long period of time. Do not take more than the recommended dosage, nor take regularly for longer than 10 days without consulting your physician."

**§201.310 Phenindione; labeling of drug preparations intended for use by man.**

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that phenindione, a synthetic anticoagulant drug, has caused a number of cases of agranulocytosis (with two fatalities). There are also reports implicating the drug in cases of hepatitis and hypersensitivity reactions. In view of the potentially serious effects found to be associated with preparations of this drug intended for use by man, the Commissioner of Food and Drugs will regard such preparations as misbranded within the meaning of section 502(f) (1) and (2) of the Federal Food, Drug, and Cosmetic Act, unless the label and labeling on or within the package from which the drug is to be dispensed, and any other labeling furnishing or purporting to furnish information for use of the drug, bear a conspicuous warning statement to the following effect: "Warning: Agranulocytosis and hepatitis have been associated with the use

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of phenindione. Patients should be instructed to report promptly prodromal symptoms such as marked fatigue, chill, fever, and sore throat. Periodic blood studies and liver function tests should be performed. Use of the drug should be discontinued if leukopenia occurs or if evidence of hypersensitivity, such as dermatitis or fever, appears.”

(b) Regulatory action may be initiated with respect to preparations of phenindione intended for use by man found within the jurisdiction of the act on or after November 25, 1961, unless such preparations are labeled in accordance with paragraph (a) of this section.

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**§ 201.312 Magnesium sulfate heptahydrate; label declaration on drug products.**

Magnesium sulfate heptahydrate should be listed on the label of a drug product as epsom salt, which is its common or usual name.

**§ 201.313 Estradiol labeling.**

The article presently recognized in The National Formulary under the heading “Estradiol” and which is said to be “17-cis-beta estradiol” is the same substance formerly recognized in the United States Pharmacopeia under the designation “Alpha Estradiol.” The substance should no longer be referred to in drug labeling as “Alpha Estradiol.” The Food and Drug Administration would not object to label references to the article as simply “Estradiol”; nor would it object if the label of a preparation containing this substance referred to the presence of “Estradiol (formerly known as Alpha Estradiol).”

**§ 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].

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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. Such a warning statement is required for compliance with section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act and is intended to guard against accidental poisonings. Safety closures that prevent access to the drug by young children are also recommended to guard against accidental poisonings.

(b) Effervescent preparations and preparations containing para-aminosalicylate as the only salicylate ingredient are exempted from this labeling requirement.

(c) Aspirin tablets sold as such and containing no other active ingredients, except tablets which cannot be readily subdivided into a child’s dose because of their coating or size, should always bear dosage directions for each age group down to 3 years of age, with a statement such as “For children under 3 years of age, consult your physician.” It is recommended that:

(1) Aspirin tablets especially made for pediatric use be produced only in 1/4-grain size to reduce the hazard of errors in dosage;

(2) By June 1, 1967, manufacturers and distributors of 1/4-grain size aspirin tablets discontinue the distribution of such tablets in retail containers containing more than 36 tablets, to reduce the hazard of accidental poisoning;

(3) The flavoring of 5-grain aspirin tablets or other “adult aspirin tablets” be discontinued; and

(4) Labeling giving undue emphasis to the pleasant flavor of flavored aspirin tablets be discontinued.

(d) Salicylate preparations other than aspirin tablets sold as such may, at the option of the distributor, be labeled for use by adults only. If their labeling and advertising clearly offer them for administration to adults only.

(e)(1) It is the obligation of the distributor who labels a salicylate preparation for administration to children to make certain that the article is suitable for such use and labeled with adequate directions for use in the age group for which it is offered, but in no

case should such an article bear directions for use in children under 3 years of age. If the directions provide for administration to children as young as 3 years of age, the label should bear the statement, "For children under 3 years of age consult your physician." However, if the directions provide for administration to children only of an age greater than 3 years (for example, the dosage instructions provide for administration of the article to children only down to age 6), the label should bear a statement such as, "For younger children consult your physician."

(2) A statement such as, "For children under 3 years of age consult your physician" or "For younger children consult your physician" is not required on the label of an article clearly offered for administration to adults only.

(f) If the labeling or advertising of a salicylate preparation offers it for use in arthritis or rheumatism, the label and labeling should clearly state that the beneficial effects claimed are limited to: "For the temporary relief of minor aches and pains of arthritis and rheumatism." The qualifying phrase "for the temporary relief of minor aches and pains" should appear with the same degree of prominence and conspicuousness as the phrase "arthritis and rheumatism". The label and labeling should bear in juxtaposition with such directions for use conspicuous warning statements to the effect: "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." The salicylate dosage should not exceed 60 grains in a 24-hour period or 10 grains in a 4-hour period. If the article contains other analgesics, the salicylate dosage should be appropriately reduced.

(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.

(2) If the preparation is a counter-irritant or rubefacient, it should also

bear a caution such as, "Caution: Discontinue use if excessive irritation of the skin develops. Avoid getting into the eyes or on mucous membranes." (See also § 201.303.)

(h)(1) The labeling of orally or rectally administered over-the-counter drug products containing aspirin or nonaspirin salicylates as active ingredients subject to this paragraph is required to prominently bear the following warning: "Reye's syndrome [subheading in bold type]: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness."

(2) This warning statement shall appear on the immediate container labeling. In cases where the immediate container is not the retail package, the retail package also must bear the warning statement. In addition, the warning statement shall appear on any labeling that contains warnings and, in such cases, the warning statement shall be the first warning statement under the heading "Warnings."

(3) Over-the-counter drug products subject to this paragraph and labeled solely for use by children (pediatric products) shall not recommend the product for use in treating flu or chicken pox.

(4) Any product subject to paragraphs (h)(1), (h)(2), and (h)(3) of this section that is not labeled as required by these paragraphs and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(i) Compliance by October 18, 2004, for OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under a new drug application or abbreviated new drug application.

(ii) Compliance by April 19, 2004, for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient



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and have annual sales greater than \$25,000.

(iii) Compliance by April 18, 2005, for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales less than \$25,000.

(iv) Compliance dates for all other OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under an OTC drug monograph (for internal analgesic, antipyretic, and antirheumatic drug products, or for menstrual drug products) will be established when the final monographs for those products are published in a future issue of the FEDERAL REGISTER. In the interim, these products should continue to be labeled with the previous Reye's syndrome warning that appears in paragraph (h)(1) of this section.

[40 FR 13998, Mar. 27, 1985, as amended at 51 FR 8182, Mar. 7, 1986; 53 FR 21637, June 9, 1988; 53 FR 24830, June 30, 1988; 64 FR 13291, Mar. 17, 1999; 65 FR 8, Jan. 3, 2000; 68 FR 18869, Apr. 17, 2003]

**§ 201.315 Over-the-counter drugs for minor sore throats; suggested warning.**

The Food and Drug Administration has studied the problem of the labeling of lozenges or troches containing a local anesthetic, chewing gum containing aspirin, various mouth washes and gargles and other articles sold over the counter for the relief of minor irritations of the mouth or throat. It will not object to the labeling of suitable articles of this type "For the temporary relief of minor sore throats", provided this is immediately followed in the labeling with a warning statement in prominent type essentially as follows: "Warning—Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by physician."

**§ 201.316 Drugs with thyroid hormone activity for human use; required warning.**

(a) Drugs with thyroid hormone activity have been promoted for, and con-

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tinue to be dispensed and prescribed for, use in the treatment of obesity, although their safety and effectiveness for that use have never been established.

(b) Drugs for human use with thyroid hormone activity are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following boxed warning at the beginning of the "Warnings" section:

Drugs with thyroid hormone activity, alone or together with other therapeutic agents, have been used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

[43 FR 22009, May 23, 1978]

**§ 201.317 Digitalis and related cardiotonic drugs for human use in oral dosage forms; required warning.**

(a) Digitalis and related cardiotonic drugs for human use in oral dosage forms have been promoted for, and continue to be dispensed and prescribed for, use in the treatment of obesity, although their safety and effectiveness for that use have never been established.

(b) Digitalis and related cardiotonic drugs for human use in oral dosage forms are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following boxed warning at the beginning of the "Warnings" section:

Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

(c) This section does not apply to digoxin products for oral use.

[43 FR 22009, May 23, 1978, as amended at 85 FR 72907, Nov. 16, 2020]

**§ 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.**

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that esophageal obstruction and asphyxiation have been associated with the ingestion of 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. Esophageal obstruction and asphyxiation due to orally-administered drug products containing water-soluble gums, hydrophilic gums, and hydrophilic mucilloids as active ingredients are significant health risks when these products are taken without adequate fluid or when they are used by individuals with esophageal narrowing or dysfunction, or with difficulty in swallowing. Additional labeling is needed for the safe and effective use of any OTC drug product for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient when marketed in a dry or incompletely hydrated form to include, but not limited to, the following dosage forms: Capsules, granules, powders, tablets, and wafers. Granular dosage forms containing psyllium are not generally recognized as safe and effective as OTC laxatives (see § 310.545(a)(12)(i)(B) of this chapter) and may not be marketed

without an approved new drug application because the warnings and directions in paragraph (b) of this section have been found inadequate for these products.

(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 sub-heading "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."

(c) After February 28, 1994, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce, or any such drug product that is repackaged or relabeled after this date regardless of the date the product was manufactured, initially introduced, or initially delivered for introduction into interstate commerce, that is not in compliance with this section is subject to regulatory action.

[58 FR 45201, Aug. 26, 1993, as amended at 64 FR 13292, Mar. 17, 1999; 72 FR 14674, Mar. 29, 2007]

**§ 201.320 Warning statements for drug products containing or manufactured with chlorofluorocarbons or other ozone-depleting substances.**

(a)(1) All drug products containing or manufactured with chlorofluorocarbons, halons, carbon

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tetrachloride, methyl chloride, or any other class I substance designated by the Environmental Protection Agency (EPA) shall, except as provided in paragraph (b) or (c) of this section, bear the following warning statement:

*Warning:* Contains [or Manufactured with, if applicable] *[insert name of substance]*, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

(2) The warning statement shall be clearly legible and conspicuous on the product, its immediate container, its outer packaging, or other labeling in accordance with the requirements of 40 CFR part 82 and appear with such prominence and conspicuousness as to render it likely to be read and understood by consumers under normal conditions of purchase.

(b)(1) For prescription drug products for human use, the following alternative warning statement may be used:

*NOTE:* The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's) [or name of other class I substance, if applicable]:

This product contains [or is manufactured with, if applicable] *[insert name of substance]*, a substance which harms the environment by destroying ozone in the upper atmosphere.

Your physician has determined that this product is likely to help your personal health. USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN. If you have any questions about alternatives, consult with your physician.

(2) The warning statement shall be clearly legible and conspicuous on the product, its immediate container, its outer packaging, or other labeling in accordance with the requirements of 40 CFR part 82 and appear with such prominence and conspicuousness as to render it likely to be read and understood by consumers under normal conditions of purchase.

(3) If the warning statement in paragraph (b)(1) of this section is used, the following warning statement must be placed on the package labeling intended to be read by the physician (physician package insert) after the "How supplied" section, which de-

scribes special handling and storage conditions on the physician labeling:

*NOTE:* The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's) [or name of other class I substance, if applicable]:

*WARNING:* Contains [or Manufactured with, if applicable] *[insert name of substance]*, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the information for the patient [or patient information leaflet, if applicable] of this product under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

(c)(1) For over-the-counter drug products for human use, the following alternative warning statement may be used:

*NOTE:* The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's) [or other class I substance, if applicable]:

*WARNING:* Contains [or Manufactured with, if applicable] *[insert name of substance]*, a substance which harms public health and environment by destroying ozone in the upper atmosphere.

CONSULT WITH YOUR PHYSICIAN OR HEALTH PROFESSIONAL IF YOU HAVE ANY QUESTION ABOUT THE USE OF THIS PRODUCT.

(2) The warning statement shall be clearly legible and conspicuous on the product, its immediate container, its outer packaging, or other labeling in accordance with the requirements of 40 CFR part 82 and appear with such prominence and conspicuousness as to render it likely to be read and understood by consumers under normal conditions of purchase.

(d) This section does not replace or relieve a person from any requirements imposed under 40 CFR part 82.

[61 FR 20100, May 3, 1996]

**§ 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition.**

(a) The aluminum content of large volume parenteral (LVP) drug products used in total parenteral nutrition

(TPN) therapy must not exceed 25 micrograms per liter ( $\mu\text{g/L}$ ).

(b) The package insert of LVP's used in TPN therapy must state that the drug product contains no more than 25  $\mu\text{g/L}$  of aluminum. This information must be contained in the "Precautions" section of the labeling of all large volume parenterals used in TPN therapy.

(c) Except as provided in paragraph (d) of this section, the maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs) used in the preparation of TPN solutions. The aluminum content must be stated as follows: "Contains no more than \_\_\_  $\mu\text{g/L}$  of aluminum." The immediate container label of all SVP's and PBP's that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than \_\_\_  $\mu\text{g/L}$ ." This maximum level of aluminum must be stated as the highest of:

(1) The highest level for the batches produced during the last 3 years;

(2) The highest level for the latest five batches, or

(3) The maximum historical level, but only until completion of production of the first five batches after July 26, 2004.

(d) If the maximum level of aluminum is 25  $\mu\text{g/L}$  or less, instead of stating the exact amount of aluminum as required in paragraph (c) of this section, the immediate container label may state: "Contains no more than 25  $\mu\text{g/L}$  of aluminum." If the SVP or PBP is a lyophilized powder, the immediate container label may state: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25  $\mu\text{g/L}$ ."

(e) The package insert for all LVP's, all SVP's, and PBP's used in TPN must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling. The warning must state:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5  $\mu\text{g/kg/day}$  accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

(f) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under §314.60 or §314.96 of this chapter.

[65 FR 4110, Jan. 26, 2000, as amended at 67 FR 70691, Nov. 26, 2002; 68 FR 32981, June 3, 2003]

**§ 201.325 Over-the-counter drugs for vaginal contraceptive and spermicide use containing nonoxynol 9 as the active ingredient; required warnings and labeling information.**

(a) Studies indicate that use of vaginal contraceptive drug products containing nonoxynol 9 does not protect against infection from the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), or against the transmission of other sexually transmitted diseases (STDs). Studies also indicate that use of vaginal contraceptive drug products containing nonoxynol 9 can increase vaginal irritation, such as the disruption of the vaginal epithelium, and also can cause epithelial disruption when used in the rectum. These effects may increase the risk of transmission

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of the AIDS virus (HIV) from an infected partner. Therefore, consumers should be warned that these products do not protect against the transmission of the AIDS virus (HIV) or other STDs, that use of these products can increase vaginal and rectal irritation, which may increase the risk of getting the AIDS virus (HIV) from an HIV infected partner, and that the products are not for rectal use. Consumers should also be warned that these products should not be used by persons who have HIV/AIDS or are at high risk for HIV/AIDS.

(b) The labeling of OTC vaginal contraceptive and spermicide drug products containing nonoxynol 9 as the active ingredient, whether subject to the ongoing OTC drug review or an approved drug application, must contain the following warnings under the heading “Warnings,” in accordance with 21 CFR 201.66.

(1) “[bullet] For vaginal use only [bullet] Not for rectal (anal) use” [both warnings in bold type].

(2) “Sexually transmitted diseases (STDs) alert [in bold type]: This product does not [word “not” in bold type] protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner”.

(3) “Do not use” [in bold type] if you or your sex partner has HIV/AIDS. If you do not know if you or your sex partner is infected, choose another form of birth control”.

(4) “When using this product [in bold type] [optional, bullet] you may get vaginal irritation (burning, itching, or a rash)”.

(5) “Stop use and ask a doctor if [in bold type] [optional, bullet] you or your partner get burning, itching, a rash, or other irritation of the vagina or penis”.

(c) The labeling of this product states under the “Other information” section of the Drug Facts labeling in accordance with § 201.66(c)(7), “[bullet] when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS.

(d) The labeling of this product includes the following statements either on the outside container or wrapper of

the retail package, under the “Other information” section of the Drug Facts labeling in accordance with § 201.66(c)(7), or in a package insert:

(1) “[bullet] studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This irritation may increase the risk of getting HIV/AIDS from an infected partner”.

(2) “[bullet] you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors”.

(3) “[bullet] use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors”.

(4) “[bullet] ask a health professional if you have questions about your best birth control and STD prevention methods”.

(e) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after June 19, 2008, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352), is a new drug under section 505 of the act (21 U.S.C. 355), and is subject to regulatory action.

[72 FR 71785, Dec. 19, 2007]

**§ 201.326 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.**

(a) *Labeling.* The labeling for all over-the-counter (OTC) drug products containing any internal analgesic/antipyretic active ingredients (including, but not limited to, acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate) alone or in combination must bear the following labeling in accordance with §§ 201.60, 201.61, and 201.66.

(1) *Acetaminophen*—(i) *Statement of identity.* The statement of identity appears in accord with §§ 201.61 and 299.4 of this chapter. The ingredient name

“acetaminophen” must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(A) At least one-quarter as large as the size of the most prominent printed matter on the principal display panel (PDP), or

(B) At least as large as the size of the “Drug Facts” title, as required in § 201.66(d)(2). The presence of acetaminophen must appear as part of the established name of the drug, as defined in § 299.4 of this chapter. Combination products containing acetaminophen and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name “acetaminophen” and the name(s) of the other active ingredient(s) in the product on the PDP in accord with this paragraph. Only the name “acetaminophen” must appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(ii) *Active Ingredient and Purpose Headings.* The information required under § 201.66(c)(2) and (c)(3) of this chapter must be included under these headings. The information under these headings, but not the headings, may appear highlighted.

(iii) *For products labeled for adults only.* The labeling of the product states the following warnings under the heading “Warnings”:

(A) The liver warning states “Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if you take [bullet] more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: ‘for this product’] [bullet] with other drugs containing acetaminophen [bullet] 3 or more alcoholic drinks every day while using this product”. This “Liver” warning must be the first warning under the “Warnings” heading. For products that contain both acetaminophen and aspirin, this “Liver” warning must appear after the “Reye’s syndrome” and “Allergy alert” warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B) and before the “Stomach bleeding” warning in paragraph (a)(2)(iii)(A) of this section. If there is

an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning does not need to be included on each blister unit.

(B) “Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”

(C) “Ask a doctor before use if you have liver disease”.

(D) “Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin” except on the labeling of combination products that contain acetaminophen and NSAID(s).

(iv) *For products labeled only for children under 12 years of age.*

(A) *Warnings.* The labeling of the product states the following warnings under the heading “Warnings”:

(1) The liver warning states “Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if your child takes [bullet] more than 5 doses in 24 hours, which is the maximum daily amount [optional: ‘for this product’] [bullet] with other drugs containing acetaminophen”. This “Liver” warning must be the first warning under the “Warnings” heading. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(2) “Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”

(3) “Ask a doctor before use if your child has liver disease”.

(4) “Ask a doctor or pharmacist before use if your child is taking the blood thinning drug warfarin” except

on the labeling of combination products that contain acetaminophen and NSAID(s).

(B) *Directions.* The labeling of the product contains the following information under the heading “Directions”: “this product does not contain directions or complete warnings for adult use” [in bold type].

(v) *For products labeled for adults and children under 12 years of age.* The labeling of the product states all of the warnings in paragraphs (a)(1)(iii)(A), (a)(1)(iii)(B), and (a)(1)(iii)(C) of this section with the following modifications:

(A) The liver warning states “Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if [bullet] adult takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: ‘for this product’] [bullet] child takes more than 5 doses in 24 hours [bullet] taken with other drugs containing acetaminophen [bullet] adult has 3 or more alcoholic drinks everyday while using this product.” If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) “Ask a doctor before use if the user has liver disease.”

(C) “Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”

(D) “Ask a doctor or pharmacist before use if the user is taking the blood thinning drug warfarin” except on the labeling of combination products that contain acetaminophen and NSAID(s).

(2) *Nonsteroidal anti-inflammatory analgesic/antipyretic active ingredients—including, but not limited to, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.*

(i) *Statement of identity.* The statement of identity appears in accord with §§201.61 and 299.4 of this chapter. The word “(NSAID)” must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(A) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or

(B) At least as large as the size of the “Drug Facts” title, as required in §201.66(d)(2). The word “(NSAID)” must appear as part of the established name of the drug, as defined in §299.4 of this chapter, or after the general pharmacological (principal intended) action of the NSAID ingredient. Combination products containing an NSAID and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name of the NSAID ingredient and the word “(NSAID)” in accordance with this paragraph, and the name(s) of the other active ingredient(s) in the product on the PDP. Only the word “(NSAID)” needs to appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(ii) *Active Ingredient and Purpose Headings.* The information required under §201.66(c)(2) and (c)(3) of this chapter must be included under these headings. The active ingredient(s) section of the product’s labeling, as defined in §201.66(c)(2), contains the term “(NSAID\*)” after the NSAID active ingredient with an asterisk statement at the end of the active ingredient(s) section that defines the term “NSAID” and states “\*nonsteroidal anti-inflammatory drug.” The information under these headings may appear highlighted. However, the headings “Active Ingredient” and “Purpose” may not appear highlighted.

(iii) *For products labeled for adults only.* The labeling of the product states the following warnings under the heading “Warnings”:

(A) The stomach bleeding warning states “Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is

higher if you [bullet] are age 60 or older [bullet] have had stomach ulcers or bleeding problems [bullet] take a blood thinning (anticoagulant) or steroid drug [bullet] take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] have 3 or more alcoholic drinks every day while using this product [bullet] take more or for a longer time than directed". This "Stomach bleeding" warning must appear after the "Reye's syndrome" and "Allergy alert" warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). For products that contain both acetaminophen and aspirin, the acetaminophen "Liver" warning in paragraph (a)(1)(iii) of this section must appear before the "Stomach bleeding" warning in this paragraph. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) "Ask a doctor before use if [bullet] stomach bleeding warning applies to you [bullet] you have a history of stomach problems, such as heartburn [bullet] you have high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] you are taking a diuretic".

(C) "Stop use and ask a doctor if [bullet] you experience any of the following signs of stomach bleeding:" [add the following as second level of statements: "[bullet] feel faint [bullet] vomit blood [bullet] have bloody or black stools [bullet] have stomach pain that does not get better"].

(iv) *For products labeled only for children under 12 years of age.*

(A) *Warnings.* The labeling of the product states the following warnings under the heading "Warnings":

(1) The stomach bleeding warning states "Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if your child [bullet] has had stomach ulcers or bleeding problems

[bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] takes more or for a longer time than directed". The "Stomach bleeding" warning must appear after the "Reye's syndrome" and "Allergy alert" warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(2) "Ask a doctor before use if [bullet] stomach bleeding warning applies to your child [bullet] child has a history of stomach problems, such as heartburn [bullet] child has not been drinking fluids [bullet] child has lost a lot of fluid due to vomiting or diarrhea [bullet] child has high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] child is taking a diuretic".

(3) "Stop use and ask a doctor if [bullet] child experiences any of the following signs of stomach bleeding:" [add the following as second level of statements: "[bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better"].

(B) *Directions.* The labeling of the product contains the following information under the heading "Directions": "this product does not contain directions or complete warnings for adult use" [in bold type].

(v) *For products labeled for adults and children under 12 years of age.* The labeling of the product states all of the warnings in paragraphs (a)(2)(iii)(A) through (a)(2)(iii)(C) of this section with the following modifications:

(A) The Stomach bleeding warning states "Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if the user [bullet] has had stomach ulcers or bleeding problems



[bullet] takes a blood thinning (anti-coagulant) or steroid drug [bullet] takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] takes more or for a longer time than directed [bullet] is age 60 or older [bullet] has 3 or more alcoholic drinks everyday while using this product”. The “Stomach bleeding” warning must appear after the “Reye’s syndrome” and “Allergy alert” warnings in §201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) The labeling states “Ask a doctor before use if [bullet] stomach bleeding warning applies to user [bullet] user has history of stomach problems, such as heartburn [bullet] user has high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] user takes a diuretic [bullet] user has not been drinking fluids [bullet] user has lost a lot of fluid due to vomiting or diarrhea”.

(C) The labeling states “Stop use and ask a doctor if [bullet] user experiences any of the following signs of stomach bleeding:” [add the following as second level of statements: [bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better”].

(b) *New warnings information statement.* The labeling of any drug product subject to this section that is initially introduced or initially delivered for introduction into interstate commerce before or on April 29, 2010, must bear on its PDP, as defined in §201.60, the statement “See new warnings information”. This statement must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or

(2) At least as large as the size of the “Drug Facts” title, as required in §201.66(d)(2). The new warnings information statement must remain on the PDP of the drug product for at least 1 year from the date the product is initially introduced into interstate commerce.

(c) *Requirements to supplement approved application.* Holders of approved applications for OTC drug products that contain internal analgesic/antipyretic active ingredients that are subject to the requirements of paragraph (a) of this section must submit supplements under §314.70(c) of this chapter to include the required information in the product’s labeling. Such labeling may be put into use without advance approval of FDA provided it includes at least the exact information included in paragraph (a) of this section.

[74 FR 19407, Apr. 29, 2009, as amended at 74 FR 31180, June 30, 2009; 74 FR 61514, Nov. 25, 2009]

**§ 201.327 Over-the-counter sunscreen drug products; required labeling based on effectiveness testing.**

The following provisions apply to sunscreen products containing amino-benzoic acid, avobenzone, cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, oxybenzone, padimate O, sulisobenzene, titanium dioxide, trolamine salicylate, or zinc oxide, alone or in combination. The provisions do not apply to sunscreen products marketed under approved new drug applications or abbreviated new drug applications.

(a) *Principal display panel.* In addition to the statement of identity in paragraph (b) of this section, the following labeling shall be prominently placed on the principal display panel:

(1) *Effectiveness claim—(i) For products that pass the broad spectrum test in paragraph (j) of this section.* (A) The labeling states “Broad Spectrum SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section]”.

(B) *Prominence.* The Broad Spectrum SPF statement shall appear as continuous text with no intervening text or graphic. The entire text shall appear in the same font style, size, and color with the same background color.

(ii) *For sunscreen products that do not pass the broad spectrum test in paragraph (j) of this section.* The labeling states “SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section]”. The entire text shall appear in the same font style, size, and color with the same background color.

(2) *Water resistance statements—(i) For products that provide 40 minutes of water resistance according to the test in paragraph (i)(7)(i) of this section.* The labeling states “Water Resistant (40 minutes)”.

(ii) *For products that provide 80 minutes of water resistance according to the test in paragraph (i)(7)(ii) of this section.* The labeling states “Water Resistant (80 minutes)”.

(b) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the drug as a “sunscreen.”

(c) *Indications.* The labeling of the product states, under the heading “Uses,” the phrases listed in this paragraph (c), as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in this paragraph (c), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) relating to misbranding and the prohibition in section 301(d) of the FD&C Act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act.

(1) For all sunscreen products, the following indication statement must be included under the heading “Uses”: “[Bullet] helps prevent sunburn”. See § 201.66(b)(4) of this chapter for definition of bullet.

(2) For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in paragraphs (i) and (j) of this section, the labeling may include the following state-

ment in addition to the indication in § 201.327(c)(1): “[Bullet] if used as directed with other sun protection measures (see Directions [in bold italic font]), decreases the risk of skin cancer and early skin aging caused by the sun”.

(3) Any labeling or promotional materials that suggest or imply that the use, alone, of any sunscreen reduces the risk of or prevents skin cancer or early skin aging will cause the product to be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).

(d) *Warnings.* The labeling of the product contains the following warnings under the heading “Warnings”.

(1) *For all sunscreen products.* (i) The labeling states “Do not use [bullet] on damaged or broken skin”.

(ii) The labeling states “When using this product [bullet] keep out of eyes. Rinse with water to remove.”

(iii) The labeling states “Stop use and ask a doctor if [bullet] rash occurs”.

(2) *For sunscreen products that are broad spectrum with SPF values of at least 2 but less than 15 according to the SPF test in paragraph (i) of this section or that do not pass the broad spectrum test in paragraph (j) of this section.* The first statement under the heading “Warnings” states “Skin Cancer/Skin Aging Alert [in bold font]; Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging.”

(e) *Directions.* The labeling of the product contains the following statements, as appropriate, under the heading “Directions.” More detailed directions applicable to a particular product formulation may also be included.

(1) *For all sunscreen products.* (i) As an option, the labeling may state “For sunscreen use:”.

(ii) The labeling states “[bullet] apply [select one of the following: ‘Liberal’ or ‘generously’] [and, as an option: ‘And evenly’] 15 minutes before sun exposure”.

(iii) As an option, the labeling may state “[bullet] apply to all skin exposed to the sun”.

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(iv) The labeling states “[bullet] children under 6 months of age: Ask a doctor”.

(2) For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in paragraphs (i) and (j) of this section. The labeling states “[bullet] Sun Protection Measures. [in bold font] Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF value of 15 or higher and other sun protection measures including: [Bullet] limit time in the sun, especially from 10 a.m.–2 p.m. [bullet] wear long-sleeved shirts, pants, hats, and sunglasses”.

(3) For products that satisfy the water resistance test in paragraph (i)(7) of this section. The labeling states “[bullet] reapply: [Bullet] after [select one of the following determined by water resistance test: ‘40 minutes of’ or ‘80 minutes of’] swimming or sweating [bullet] immediately after towel drying [bullet] at least every 2 hours”.

(4) For products that do not satisfy the water resistance test in paragraph (i)(7) of this section. The labeling states “[bullet] reapply at least every 2 hours [bullet] use a water resistant sunscreen if swimming or sweating”.

(f) Other information. The labeling of the product contains the following statement under the heading “Other information:” “[bullet] protect the product in this container from excessive heat and direct sun”.

(g) False and misleading claims. There are claims that would be false and/or misleading on sunscreen products. These claims include but are not limited to the following: “Sunblock,” “sweatproof,” and “waterproof.” These or similar claims will cause the product to be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).

(h) Labeling of products containing a combination of sunscreen and skin protectant active ingredients. Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. Labeling provisions in

§ 347.50(e) of this chapter shall not apply to these products.

(i) SPF test procedure—(1) UV source (solar simulator). (i) Emission spectrum. A single port or multiport solar simulator should be filtered so that it provides a continuous emission spectrum from 290 to 400 nanometers (nm) with a limit of 1,500 Watts per square meter (W/m<sup>2</sup>) on total irradiance for all wavelengths between 250 and 1,400 nm.

(A) The solar simulator should have the following percentage of erythema-effective radiation in each specified range of wavelengths:

SOLAR SIMULATOR EMISSION SPECTRUM

Wavelength range (nm)	Percent erythema contribution <sup>1</sup>
<290 .....	<0.1
290–300 .....	1.0–8.0
290–310 .....	49.0–65.0
290–320 .....	85.0–90.0
290–330 .....	91.5–95.5
290–340 .....	94.0–97.0
290–400 .....	99.9–100.0

<sup>1</sup>Calculation of erythema action spectrum described in § 201.327(i)(1)(ii) of this section.

(B) In addition, UVA II (320–340 nm) irradiance should equal or exceed 20 percent of the total UV (290–400 nm) irradiance. UVA I (340–400 nm) irradiance should equal or exceed 60 percent of the total UV irradiance.

(ii) Erythema action spectrum. (A) Calculate the erythema action spectrum weighting factor (V<sub>i</sub>) at each wavelength λ:

- (1) V<sub>i</sub> (λ) = 1.0 (250 < λ ≤ 298 nm)
- (2) V<sub>i</sub> (λ) = 10<sup>0.094\*</sup> (298-λ) (298 < λ ≤ 328 nm)
- (3) V<sub>i</sub> (λ) = 10<sup>0.015\*</sup> (140-λ) (328 < λ ≤ 400 nm)

(B) Calculate the erythema-effective UV dose (E) delivered by a solar simulator as follows:

$$E = \sum_{250}^{400} V_i(\lambda) * I(\lambda) * t$$

Where V<sub>i</sub>(λ) = erythema action spectrum weighting factor at each wavelength λ  
 I(λ) = irradiance (Watts per square meter) at each wavelength λ  
 t = exposure time (seconds)

Erythema-effective dose (E) is expressed as effective Joules per square meter (J/m<sup>2</sup>-eff).

(C) The emission spectrum must be determined using a handheld radiometer with a response weighted to match the spectrum in ISO 17166 CIE S 007/E entitled “Erythema reference action spectrum and standard erythema dose,” dated 1999 (First edition, 1999–12–15; corrected and reprinted 2000–11–15), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain a copy from the ISO Copyright Office, Case Postale 56, CH-1211, Geneva 20, Switzerland, telephone +41-22-749-01-11 or fax +41-22-74-09-47. <http://www.iso.org>. You may inspect a copy at the Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993, call 301-796-2090, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: <http://www.archives.gov/federal-register/>

[code\\_of\\_federal\\_regulations/ibr\\_locations.html](http://www.archives.gov/federal-register/code_of_federal_regulations/ibr_locations.html). The solar simulator output should be measured before and after each phototest or, at a minimum, at the beginning and end of each test day. This radiometer should be calibrated using side-by-side comparison with the spectroradiometer (using the weighting factors determined according to paragraph (i)(1)(ii)(A) of this section) at the time of the annual spectroradiometric measurement of the solar simulator as described in paragraph (i)(1)(iv) of this section.

(iii) *Operation.* A solar simulator should have no significant time-related fluctuations (within 20 percent) in radiation emissions after an appropriate warm-up time and demonstrate good beam uniformity (within 20 percent) in the exposure plane. The delivered dose to the UV exposure site must be within 10 percent of the expected dose.

(iv) *Periodic measurement.* To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, the emission spectrum of the solar simulator should be measured at least annually with an appropriate and accurately calibrated spectroradiometer system (results should be traceable to the National Institute for Standards and Technology). In addition, the solar simulator must be recalibrated if there

is any change in the lamp bulb or the optical filtering components (*i.e.*, filters, mirrors, lenses, collimating devices, or focusing devices). Daily solar simulator radiation intensity should be monitored with a broadband radiometer with a response weighted to match the erythema action spectrum in ISO 17166 CIE S 007/E entitled “Erythema reference action spectrum and standard erythema dose,” which is incorporated by reference in paragraph (i)(1)(ii)(C) of this section. If a lamp must be replaced due to failure or aging during a phototest, broadband device readings consistent with those obtained for the original calibrated lamp will suffice until measurements can be performed with the spectroradiometer at the earliest possible opportunity.

(2) *SPF standard—(i) Preparation.* The SPF standard should be a formulation containing 7-percent padimate O and 3-percent oxybenzone.

COMPOSITION OF THE PADIMATE O/OXYBENZONE SPF STANDARD

Ingredients	Percent by weight
<b>Part A:</b>	
Lanolin .....	4.50
Cocoa butter .....	2.00
Glyceryl monostearate .....	3.00
Stearic acid .....	2.00
Padimate O .....	7.00
Oxybenzone .....	3.00
<b>Part B:</b>	
Purified water USP .....	71.60
Sorbitol solution .....	5.00
Triethanolamine, 99 percent .....	1.00
Methylparaben .....	0.30
Propylparaben .....	0.10
<b>Part C:</b>	
Benzyl alcohol .....	0.50
<b>Part D:</b>	
Purified water USP .....	QS <sup>1</sup>

<sup>1</sup> Quantity sufficient to make 100 grams.

*Step 1.* Add the ingredients of Part A into a suitable stainless steel kettle equipped with a propeller agitator. Mix at 77 to 82 °C until uniform.

*Step 2.* Add the water of Part B into a suitable stainless steel kettle equipped with a propeller agitator and begin mixing at 77 to 82 °C. Add the remaining ingredients of Part B and mix until uniform.

*Step 3.* Add the batch of Step 1 to the batch of Step 2 and mix at 77 to 82 °C until smooth and uniform. Slowly cool the batch to 49 to 54 °C.

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*Step 4.* Add the benzyl alcohol of Part C to the batch of Step 3 at 49 to 54 °C. Mix until uniform. Continue to cool batch to 35 to 41 °C.

*Step 5.* Add sufficient water of Part D to the batch of Step 4 at 35 to 41 °C to obtain 100 grams of SPF standard. Mix until uniform. Cool batch to 27 to 32 °C.

(ii) *HPLC assay.* Use the following high performance liquid chromatography (HPLC) procedure to verify the concentrations of padimate O and oxybenzone in the SPF standard:

(A) *Instrumentation.* (1) Equilibrate a suitable liquid chromatograph to the following or equivalent conditions:

(i) Column ..	C-18, 250 millimeters (mm) length, 4.6 mm inner diameter (5 microns)
(ii) Mobile Phase.	85:15:0.5 methanol: water: acetic acid
(iii) Flow Rate.	1.5 milliliters (mL) per minute
(iv) Temperature.	Ambient
(v) Detector	UV spectrophotometer at 308 nanometers
(vi) Attenuation.	As needed

(2) Use HPLC grade reagents for mobile phase.

(B) *Preparation of the HPLC reference standard.* (1) Weigh 0.50 gram (g) of oxybenzone USP reference standard into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(2) Weigh 0.50 g of padimate O USP reference standard into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(3) Pipet 3.0 mL of the oxybenzone solution and 7.0 mL of the padimate O solution into a 100-mL volumetric flask. Dilute to volume with isopropanol and mix well.

(C) *HPLC system suitability.* (1) Make three replicate 10-microliter injections of the HPLC reference standard (described in paragraph (i)(2)(ii)(B) of this section). The relative standard deviation in peak areas should not be more than 2.0 percent for either oxybenzone or padimate O.

(2) Calculate the resolution (R) between the oxybenzone and padimate O peaks from one chromatogram as follows:

$$R = \frac{2 * (t_o - t_p)}{W_o + W_p}$$

Where  $t_o$  = retention time for oxybenzone  
 $t_p$  = retention time for padimate O  
 $W_o$  = oxybenzone peak width at baseline  
 $W_p$  = padimate O peak width at baseline

If the resolution (R) is less than 3.0, adjust the mobile phase or replace the column.

(D) *SPF standard assay*—(1) The SPF standard is diluted to the same concentration as the HPLC reference standard according to the following steps:

(i) *Step 1.* Weigh 1.0 g of the SPF standard (described in paragraph (i)(2)(i) of this section) into a 50-mL volumetric flask.

(ii) *Step 2.* Add approximately 30 mL of isopropanol and heat with swirling until contents are evenly dispersed.

(iii) *Step 3.* Cool to room temperature (15 to 30 °C) and dilute to volume with isopropanol. Mix well.

(iv) *Step 4.* Pipet 5.0 mL of the preparation into a 50-mL volumetric flask and dilute to volume with isopropanol. Mix well.

(2)(i) Inject 10-microliter of diluted SPF standard from paragraph (i)(2)(D)(1) of this section and calculate the amount of oxybenzone and padimate O as follows:

$$\text{Percent Oxybenzone} = \frac{\text{Peak area of oxybenzone in sunscreen standard}}{\text{Peak area of oxybenzone in HPLC reference standard}} * 100$$

$$\text{Percent Padimate O} = \frac{\text{Peak area of padimate O in sunscreen standard}}{\text{Peak area of padimate O in HPLC reference standard}} * 100$$

(ii) The percent of oxybenzone and padimate O in the SPF standard should be between 95 and 105.

(3) *Test subjects*—(i) *Number of subjects.* A test panel should include enough subjects to produce a minimum of 10 valid test results. A maximum of three subjects may be rejected from this panel based on paragraph (i)(5)(v) of this section.

(ii) *Medical history.* (A) Obtain a medical history from each subject with emphasis on the effects of sunlight on the subject's skin. Determine that each subject is in good general health with skin type I, II, or III as follows:

(1) Always burns easily; never tans (sensitive).

(2) Always burns easily; tans minimally (sensitive).

(3) Burns moderately; tans gradually (light brown) (normal).

(4) Burns minimally; always tans well (moderate brown) (normal).

(5) Rarely burns; tans profusely (dark brown) (insensitive).

(6) Never burns; deeply pigmented (insensitive).

(B) Skin type is based on first 30 to 45 minutes of sun exposure after a winter season of no sun exposure. Determine that each subject is not taking topical or systemic medication that is known to alter responses to UV radiation. Determine that each subject has no history of sensitivities to topical products and/or abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(iii) *Physical examination.* Conduct a physical examination to determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. A suitable source of low power UVA, such as a Woods lamp, is helpful in this process. If any of these conditions are present, the subject is not qualified to participate in the study. The presence of nevi, blemishes, or moles will be acceptable if, in the physician's judgment, they will neither compromise the study nor jeopardize a subject's safety. Subjects with dysplastic nevi should not be enrolled. Excess hair on the back is acceptable if the hair is clipped. Shaving is unacceptable because it may remove a significant portion of the stratum

corneum and temporarily alter the skin's response to UV radiation.

(iv) *Informed consent.* Obtain legally effective written informed consent from all test subjects.

(4) *Sunscreen application.* (i) *Test site.* Test sites are locations on each subject's back, between the beltline and the shoulder blades (scapulae) and lateral to the midline, where skin responses to UV radiation are determined. Responses on unprotected skin (no test material applied) and protected skin (sunscreen test product(s) or SPF standard applied) are determined at separate unprotected and protected test sites, respectively. Test sites should be randomly located in a blinded manner. Each test site should be a minimum of 30 square centimeters and outlined with indelible ink.

(ii) *Test subsite.* Test subsites are the locations to which UV radiation is administered within a test site. At least five test subsites should receive UV doses within each test site. Test subsites should be at least 0.5 square centimeters (cm<sup>2</sup>) in area and should be separated from each other by at least 0.8 cm. Each test subsite should be outlined with indelible ink.

(iii) *Applying test materials.* Apply the sunscreen test product and the SPF standard at 2 milligrams per square centimeter (mg/cm<sup>2</sup>) to their respective test sites. Use a finger cot compatible with the sunscreen to spread the product as evenly as possible.

(iv) *Waiting period.* Wait at least 15 minutes after applying a sunscreen product before exposing the test sites to UV radiation as described in paragraph (i)(5) of this section. For water resistant sunscreen products, proceed with the water resistance testing procedure described in paragraph (i)(7) of this section after waiting at least 15 minutes.

(5) *UV exposure*—(i) *Definition of minimal erythema dose (MED).* The minimal erythema dose (MED) is the smallest UV dose that produces perceptible redness of the skin (erythema) with clearly defined borders at 16 to 24 hours after UV exposure. The MED for unprotected skin (MED<sub>u</sub>) is determined on a test site that does not have sunscreen applied. The MED for protected skin (MED<sub>p</sub>) is determined on a test site

that has sunscreen applied. An  $MED_p$  is determined for the SPF standard ( $ssMED_p$ ). An  $MED_p$  is determined for the sunscreen test product ( $tpMED_p$ ).

(ii) *UV exposure for initial  $MED_u$ .* For each test subject, administer a series of UV radiation doses expressed as  $J/m^2$ -eff (as determined according to paragraph (a)(2) of this section) to the test subsites within an unprotected test site using an accurately calibrated solar simulator. Select doses that are a geometric series represented by 1.25<sup>n</sup> (i.e., each dose is 25 percent greater than the previous dose).

(iii) *UV exposure for final  $MED_u$ ,  $ssMED_p$ , and  $tpMED_p$ .* For each subject, determine the final  $MED_u$ ,  $ssMED_p$ , and  $tpMED_p$  by administering a series of five UV doses to the appropriate test sites. The middle dose (X) in each of these dose series (i.e., the third dose) should equal the initial  $MED_u$  times the expected SPF. Note that the expected SPF equals 1 and 16.3 for the final  $MED_u$  and  $ssMED_p$ , respectively. The remaining UV doses in the series depend upon the expected SPF value of the sunscreen test product(s).

For products with an expected SPF less than 8, administer UV doses that increase by 25 percent with each successive dose (i.e., 0.64X, 0.80X, 1.00X, 1.25X, and 1.56X). For products with an expected SPF from 8 to 15, administer UV doses that increase by 20 percent with each successive dose (i.e., 0.69X, 0.83X, 1.00X, 1.20X, and 1.44X). For products with an expected SPF higher than 15, administer UV doses that increase by 15 percent with each successive dose (i.e., 0.76X, 0.87X, 1.00X, 1.15X, and 1.32X).

(iv) *Evaluation of test subsites.* In order that the person who evaluates the test subsites is not biased, he/she should not be the same person who applied the sunscreen drug product to the test site or administered the UV doses. After UV doses are administered, all immediate responses should be recorded. These may include an immediate darkening or tanning, typically grayish or purplish in color, which fades in 30 to 60 minutes; an immediate reddening at the subsite, due to heating of the skin, which fades rapidly; and an immediate generalized heat response, spreading beyond the subsite,

which fades in 30 to 60 minutes. After the immediate responses are noted, each subject should shield the exposed area from further UV radiation until the MED is determined. Determine the MED 16 to 24 hours after UV exposure. Because erythema is evaluated 16 to 24 hours after UV exposure, the final  $MED_u$ ,  $ssMED_p$ , and  $tpMED_p$  are typically determined the day following determination of the initial  $MED_u$ . Evaluate the erythema responses of each test subsite using either tungsten or warm white fluorescent lighting that provides at least 450 lux of illumination at the test site. For the evaluation, the test subject should be in the same position as when the test site was irradiated.

(v) *Invalid test data.* Reject test data for a test subject if erythema is not present on either the unprotected or protected test sites; or erythema is present at all subsites; or the responses are inconsistent with the series of UV doses administered; or the subject was noncompliant (e.g., the subject withdraws from the test due to illness or work conflicts or does not shield the exposed testing sites from further UV radiation until the MED is determined).

(6) *Determination of SPF.* (i) Calculate an SPF value for each test subject ( $SPF_i$ ) as follows:

$$SPF_i = \frac{MED_p}{MED_u}$$

(ii) Calculate the mean

$$SPF (\overline{SPF})$$

and the standard deviation (s) from the  $SPF_i$  values. Calculate the standard error (SE), which equals  $s/\sqrt{n}$  (where n equals the number of subjects who provided valid test results). Obtain the t value from Student's t distribution table corresponding to the upper 5-percent point with n–1 degrees of freedom. Determine the labeled SPF value, which equals the largest whole number less than

$$\overline{SPF} - (t * SE).$$

In order for the SPF determination of a test product to be considered valid, the SPF value of the SPF standard

should fall within the standard deviation range of the expected SPF (*i.e.*,  $16.3 \pm 3.43$ ).

(7) *Determination of water resistance.* The following procedure should be performed in an indoor fresh water pool, whirlpool, and/or hot tub maintained at 23 to 32 °C. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity should be recorded.

(i) *Water resistance (40 minutes).* The labeled SPF should be determined after 40 minutes of water immersion using the following procedure:

(A) Step 1: Apply the sunscreen as described in paragraph (d) of this section.

(B) Step 2: Perform moderate activity in water for 20 minutes.

(C) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(D) Step 4: Perform moderate activity in water for 20 minutes.

(E) Step 5: Allow test sites to dry completely without toweling.

(F) Step 6: Apply the SPF standard as described in paragraph (d) of this section.

*Step 1.* Expose test sites to UV doses as described in paragraph (e) of this section.

(ii) *Water resistance (80 minutes).* The labeled SPF should be determined after 80 minutes of water immersion using the following procedure:

(A) Step 1: Apply the sunscreen as described in paragraph (d) of this section.

(B) Step 2: Perform moderate activity in water for 20 minutes.

(C) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(D) Step 4: Perform moderate activity in water for 20 minutes.

(E) Step 5: Rest out of water for 15 minutes. Do not towel test site(s).

(F) Step 6: Perform moderate activity in water for 20 minutes.

(G) Step 7: Rest out of water for 15 minutes. Do not towel test site(s).

(H) Step 8: Perform moderate activity in water for 20 minutes.

(I) Step 9: Allow test sites to dry completely without toweling.

(J) Step 10: Apply the SPF standard as described in paragraph (d) of this section.

(K) Step 11: Expose test sites to UV doses as described in paragraph (e) of this section.

(j) *Broad spectrum test procedure—(1) UV Spectrometry.* (i) *Plate.* Use optical-grade polymethylmethacrylate (PMMA) plates suitable for UV transmittance measurements. The plate should be roughened on one side to a three dimensional surface topography measure (Sa) between 2 and 7 micrometers and must have a rectangular application area of at least 16 square centimeters (with no side shorter than 4 cm).

(ii) *Sample holder.* The sample holder should hold the PMMA plate in a horizontal position to avoid flowing of the sunscreen drug product from one edge of the PMMA plate to the other. It should be mounted as close as possible to the input optics of the spectrometer to maximize capture of forward scattered radiation. The sample holder should be a thin, flat plate with a suitable aperture through which UV radiation can pass. The PMMA plate should be placed on the upper surface of the sample holder with the roughened side facing up.

(iii) *Light source.* The light source should produce a continuous spectral distribution of UV radiation from 290 to 400 nanometers.

(iv) *Input optics.* Unless the spectrometer is equipped with an integrating sphere, an ultraviolet radiation diffuser should be placed between the sample and the input optics of the spectrometer. The diffuser will be constructed from any UV radiation transparent material (*e.g.*, Teflon® or quartz). The diffuser ensures that the radiation received by the spectrometer is not collimated. The spectrometer input slits should be set to provide a bandwidth that is less than or equal to 1 nanometer.

(v) *Dynamic range of the spectrometer.* The dynamic range of the spectrometer should be sufficient to measure transmittance accurately through a highly absorbing sunscreen product at all terrestrial solar UV wavelengths (290 to 400 nm).

(2) *Sunscreen product application to PMMA plate.* The accuracy of the test depends upon the application of a precisely controlled amount of sunscreen



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product with a uniform distribution over the PMMA plate. The product is applied at 0.75 mg per square centimeter to the roughened side of the PMMA plate. The sunscreen product should be applied in a series of small dots over the entire PMMA plate and then spread evenly using a gloved finger. Spreading should be done with a very light spreading action for approximately 30 seconds followed by spreading with greater pressure for approximately 30 seconds. The plate should then be allowed to equilibrate for 15 minutes in the dark before the pre-irradiation described in paragraph (c) of this section.

(3) *Sunscreen product pre-irradiation.* To account for lack of photostability, apply the sunscreen product to the PMMA plate as described in paragraph (b) of this section and then irradiate with a solar simulator described in section 352.70(b) of this chapter. The irradiation dose should be 4 MEDs which is equivalent to an erythemal effective dose of 800 J/m<sup>2</sup> (i.e., 800 J/m<sup>2</sup>-eff).

(4) *Calculation of mean transmittance values.* After pre-irradiation described in paragraph (c) of this section, mean transmittance values should be determined for each wavelength λ over the full UV spectrum (290 to 400 nanometers). The transmittance values should be measured at 1 nanometer intervals. Measurements of spectral irradiance transmitted for each wavelength λ through control PMMA plates coated with 15 microliters of glycerin (no sunscreen product) should be obtained from at least 5 different locations on the PMMA plate [C1(λ), C2(λ), C3(λ), C4(λ), and C5(λ)]. In addition, a minimum of 5 measurements of spectral irradiance transmitted for each wavelength λ through the PMMA plate covered with the sunscreen product will be similarly obtained after pre-irradiation of the sunscreen product [P1(λ), P2(λ), P3(λ), P4(λ), and P5(λ)].

The mean transmittance for each wavelength,

$$\overline{T(\lambda)},$$

is the ratio of the mean of the C(λ) values to the mean of the P(λ) values, as follows:

$$\overline{T(\lambda)} = \frac{\sum_1^n P(\lambda) / n}{\sum_1^n C(\lambda) / n}$$

Where n ≥ 5

(5) *Calculation of mean absorbance values.* (i) Mean transmittance values,

$$\overline{T(\lambda)},$$

are converted into mean absorbance values,

$$\overline{A(\lambda)},$$

at each wavelength by taking the negative logarithm of the mean transmittance value as follows:

$$\overline{A(\lambda)} = -\log \overline{T(\lambda)}$$

(ii) The calculation yields 111 monochromatic absorbance values in 1 nanometer increments from 290 to 400 nanometers.

(6) *Number of plates.* For each sunscreen product, mean absorbance values should be determined from at least three individual PMMA plates. Because paragraph (d) of this section requires at least 5 measurements per plate, there should be a total of at least 15 measurements.

(7) *Calculation of the critical wavelength.* The critical wavelength is identified as the wavelength at which the integral of the spectral absorbance curve reaches 90 percent of the integral over the UV spectrum from 290 to 400 nm. The following equation defines the critical wavelength:

$$\int_{290}^{\lambda_c} A(\lambda)d\lambda = 0.9 \int_{290}^{400} A(\lambda)d\lambda$$

Where λ<sub>c</sub> = critical wavelength  
A(λ) = mean absorbance at each wavelength  
dλ = wavelength interval between measurements

A mean critical wavelength of 370 nm or greater is classified as broad spectrum protection.

[76 FR 35660, June 17, 2011, as amended at 76 FR 38975, July 5, 2011]

**§ 201.328 Labeling of medical gas containers.**

(a) *Portable cryogenic medical gas containers.* For the purposes of this section a “portable cryogenic medical gas container” is one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, health care entity, nursing home, other facility, or home health care setting, or is a base unit used to fill small cryogenic gas containers for use by individual patients. The term does not include cryogenic containers that are not designed to be connected to a medical gas supply system, *e.g.*, tank trucks, trailers, rail cars, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at § 868.5655 of this chapter).

(1) Each portable cryogenic medical gas container must be conspicuously marked with a 360° wraparound label identifying its contents. Such label must meet the requirements of § 211.94(e)(2) of this chapter and the following additional requirements.

(i) If the container holds a single gas, the name of the gas held in the container must be printed on the label in one of the following ways:

(A) Using lettering that appears in the color designated for the gas in paragraph (c) of this section and that is printed against a white background, or

(B) Using lettering that appears in white against a background that is painted in the color for the gas designated in paragraph (c) of this section.

(ii) The lettering for the name of the gas on the label must be at least 2 inches high.

(iii) The name of the gas must be printed continuously around the label and be capable of being read around the entire container.

(iv) The label must be on the sidewall of the container, as close to the top of the container as possible but below the top weld seam.

(v) A portable cryogenic medical gas container may only be colored in the color or colors designated in paragraph (c) of this section if the gas or gases held within the container correspond to that color or those colors.

(2) A label on the container (either the 360° wraparound label required in

paragraph (a)(1) of this section or a separate label) must include, in conspicuous lettering, the phrase “For Medical Use”, “Medical Gas,” or some similar phrase that indicates the gas is for medical use.

(b) *High-pressure medical gas cylinders.* Each high-pressure medical gas cylinder must be colored on the shoulder portion of the cylinder in the color or colors designated in paragraph (c) of this section. The color or colors must be visible when viewed from the top of cylinder.

(c) *Medical gas colors.* The colors required to identify medical gases under paragraph (a) and (b) of this section are:

Medical gas	Color
Medical Air .....	Yellow.
Carbon Dioxide .....	Gray.
Helium .....	Brown.
Nitrogen .....	Black.
Nitrous Oxide .....	Blue.
Oxygen .....	Green.
Mixture or Blend .....	Colors corresponding to each component gas.

[81 FR 81696, Nov. 18, 2016]

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.

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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.

**III. EXAMPLES OF §201.66 STANDARD LABELING  
AND MODIFIED LABELING FORMATS**

A. SECTION 201.66 STANDARD LABELING FORMAT

Title: 14 pt. Helvetica Bold Italic, left justified

Body text: 6 pt. Helvetica Regular with 6.5 pts. leading, left justified

Subheadings: 6 pt. Helvetica Bold, left justified

Bullet: 5 pt. Solid square

Headings: 8 pt. Helvetica Bold Italic, left justified

Title for continued panel: 8 pt. Helvetica Bold Italic

**Drug Facts**

<b>Active ingredient (in each tablet)</b>	<b>Purpose</b>
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

**Directions**  
 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.

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

Right justified

2.5 point barline

2.5 point box barline

0.5 point hairline

Table format for 3 or more dosages

Graphic leading to next panel

**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

8 pt. Helvetica Regular

B. SECTION 201.66 MODIFIED LABELING FORMAT

Title: 9 pt. Helvetica Bold Italic, left justified

Body text: 6 pt. Helvetica Regular with 6.5 pts. leading, left justified

Bullet: 5 pt. Solid square

Subheadings: 6 pt. Helvetica Bold, left justified

Headings: 8 pt. Helvetica Bold Italic, left justified

**Drug Facts**

<b>Active ingredients (in each tablet)</b>	<b>Purpose</b>
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

Right justified

2.5 point barline

0.5 point hairline

Bulleted information may start on same line as headings (except Warnings) and subheadings and need not be vertically aligned

Dark type on light background

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

PART 202—PRESCRIPTION DRUG ADVERTISING

§ 202.1 Prescription-drug advertisements.

AUTHORITY: 21 U.S.C. 321, 331, 352, 355, 360b, 371.

(a)(1) The ingredient information required by section 502(m) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening