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201.315 Over-the-counter drugs for minor sore throats: suggested warning.
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201.319 Water-soluble gums, hydrophilic gums, and hydrophilic muciloids (including, but not limited to agar, alginic acid, calcium polycarbophil, carboxymethylcellulose sodium, carrageenan, chondrus, glucomanann (β-1,4 linked) polymannose acetate), guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil tragacanth, and xanthan gum) as active ingredients; required ingredients; required warnings and directions.
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APPENDIX A TO PART 201—EXAMPLES OF GRAPHIC ENHANCEMENTS USED BY FDA


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


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.

(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)”;

(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 “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 practice 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;

(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 §207.3(b) 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
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§ 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:

(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]

§ 201.10 Drugs; statement of ingredients.

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

(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]

§ 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.

§ 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”.

§ 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.

§ 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.

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§ 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 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.


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 methyl ester 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-α-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
§ 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.

§ 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 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 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
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§ 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:

(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. 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

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§ 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.

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.

§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 be rounded off 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 express with prominence and conspicuousness the number of the largest whole unit, as specified in paragraph (b) of this section, that are contained
§ 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), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200 North, Rockville, MD 20852–1448. The waiver must be granted or denied 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]

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 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, eighths, 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.

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.

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.

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.

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 "Net contents 6 fl oz".

(k) Examples:

(1) A declaration of 1 1⁄2 pounds weight shall be expressed as "Net wt. 24 oz (1 lb 8 oz)," or "Net wt. 24 oz (1 1⁄2 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 1⁄4 quart liquid measure shall be expressed as "Net contents 8 fl oz (1⁄4 qt)," or "Net contents 8 fl oz (1 qt 2 pt 8 oz)" or "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 21 oz)."

(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 "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 1 1⁄2 pounds weight shall be expressed as "Net wt. 24 oz (1 lb 8 oz)," or "Net wt. 24 oz (1 1⁄2 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 1⁄4 quart liquid measure shall be expressed as "Net contents 8 fl oz (1⁄4 qt)," or "Net contents 8 fl oz (1 qt 2 pt 8 oz)" or "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 21 oz)."

(5) A declaration of 2 1⁄2 gallons liquid measure shall be expressed as "Net contents 2 gal 2 qt," "Net contents 2.5 gallons," or "Net contents 2 1⁄2 gal" but not as "2 gal 4 pt".

(l) 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 (2 1⁄2 yd)," "30 inches (2.5 ft)," "3⁄4 inch by 36 in (1 yd)," etc.

(m) 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)."
§ 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:

“[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.’”


§ 201.64 Sodium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral
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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]1 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 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.

(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

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

§ 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)(ix) of this section.

(ix) The pregnancy/breast-feeding 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(c), (g), (h), (i), (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.
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(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)(2) of this section shall be right justified. If more than one active ingredient has the same purpose, the purpose need not be repeated for each active ingredient, provided the information is presented in a manner that readily associates each active ingredient with its purpose (i.e., through the use of brackets, dot leaders, or other graphical features). The information described in paragraphs (c)(4) and (c)(6) through (c)(9) of this section may start on the same line as the required headings. None of the information described in paragraph (c)(5) of this section shall appear on the same line as the “Warning” or “Warnings” heading.

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

(8) The information described in paragraphs (c)(1) through (c)(9) of this section shall be set off in a box or similar enclosure by the use of a barline. A distinctive horizontal barline extending to each end of the “Drug Facts” box or similar enclosure shall provide separation between each of the headings listed in paragraphs (c)(2) through (c)(9) of this section. When a heading listed in paragraphs (c)(2) through (c)(9) of this section appears on a subsequent panel immediately after the “Drug Facts (continued)” title, a horizontal hairline shall follow the title and immediately precede the heading. A horizontal hairline extending within two spaces on either side of the “Drug Facts” box or similar enclosure shall immediately follow the title and shall immediately precede each of the subheadings set forth in paragraph (c)(5) of this section, except the subheadings in paragraphs (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section.

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

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

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

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

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

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

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

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

OTC Drug Product Labeling Outline

<table>
<thead>
<tr>
<th>Drug Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient (in each dosage unit)</td>
</tr>
<tr>
<td>Uses</td>
</tr>
<tr>
<td>Warnings</td>
</tr>
<tr>
<td>Do not use</td>
</tr>
<tr>
<td>Ask a doctor before use if you have</td>
</tr>
<tr>
<td>Ask a doctor or pharmacist before use if you are</td>
</tr>
<tr>
<td>When using this product</td>
</tr>
<tr>
<td>Stop use and ask a doctor if</td>
</tr>
<tr>
<td>Pregnancy or breastfeeding, 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.</td>
</tr>
</tbody>
</table>

Drug Facts (continued)

Directions

Other information

Inactive ingredients

Questions? 1-800-533-1234

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

§ 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]1 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.

§ 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 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 per dosage unit 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).

1 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]1 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.

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

1See §201.66(b)(4) of this chapter for definition of bullet symbol.
Food and Drug Administration, HHS

§ 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 metabolites, 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 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
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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) Pregnancy category A. If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus, the labeling shall state: “Pregnancy Category A. 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) Pregnancy category 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: “Pregnancy Category B. 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: “Pregnancy Category B. 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, it is necessary to balance the risk of harm to the fetus (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) Pregnancy category 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: “Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (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: “Pregnancy Category C. 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) Pregnancy category 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: “Pregnancy Category D. 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.) (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.”

(e) Pregnancy category X. 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: “Pregnancy Category X. 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: “It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a nursing woman.”

(iii) If a drug is absorbed systematically 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 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 exercised 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. Appropriate pediatric dosage shall be given under the “Dosage and Administration” section of the labeling. The “Pediatric use” subsection of the labeling shall be given under the “Dosage and Administration” section of the labeling. The “Pediatric use” subsection of 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 exercised when (name of drug) is administered to a nursing woman.”

(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 state: “It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a nursing woman.”

(iv) If a 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.”
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 (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 patients 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, 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)(ii) 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 psychological 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.

(1) Overdosage. Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdose 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 overdose of the drug.

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

(3) Oral LD$_{50}$ 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 overdose 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 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.

(l) 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 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.


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;

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

(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.

EFFECTIVE DATE NOTE: At 79 FR 72103, Dec. 4, 2014, §201.80 was amended by: a. Removing the paragraph heading “Pregnancy category A.” and the words “Pregnancy Category A.” from paragraph (f)(6)(i)(a); b. Removing the paragraph heading “Pregnancy category B.” and the words “Pregnancy Category B.” both times they appear from paragraph (f)(6)(i)(b); c. Removing the paragraph heading “Pregnancy category C.” and the words “Pregnancy Category C.” both times they appear from paragraph (f)(6)(i)(c); d. Removing the paragraph heading “Pregnancy category D.” and the words “Pregnancy Category D.” from paragraph (f)(6)(i)(d); and e. Removing the paragraph heading “Pregnancy category X.” and the words “Pregnancy Category X.” from paragraph (f)(6)(i)(e), effective June 30, 2015.