AUTHENTICATED
U.S. GOVERNMENT
INFORMATION
GPO

Title 21—Food and Drugs

(This book contains parts 200 to 299)

Part

CHAPTER I—Food and Drug Administration, Department of Health and Human Services (Continued) 200

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

EDITORIAL NOTE: Nomenclature changes to chapter I appear at 59 FR 14366, Mar. 28, 1994, and 66 FR 56035, Nov. 6, 2001.

SUBCHAPTER C—DRUGS: GENERAL

Part		*Page*
200	General	5
201	Labeling	8
202	Prescription drug advertising	107
203	Prescription drug marketing	116
205	Guidelines for State licensing of wholesale prescription drug distributors	128
206	Imprinting of solid oral dosage form drug products for human use	133
207	Registration of producers of drugs and listing of drugs in commercial distribution	135
208	Medication Guides for prescription drug products	145
209	Requirement for authorized dispensers and pharmacies to distribute a side effects statement	149
210	Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general	150
211	Current good manufacturing practice for finished pharmaceuticals	152
212	Current good manufacturing practice for positron emission tomography drugs	173
216	Pharmacy compounding	182
225	Current good manufacturing practice for medicated feeds	183
226	Current good manufacturing practice for Type A medicated articles	191
250	Special requirements for specific human drugs	195
290	Controlled drugs	203
299	Drugs; official names and established names	204

SUBCHAPTER C—DRUGS: GENERAL

PART 200—GENERAL

Subpart A—General Provisions

Sec.
200.5 Mailing of important information about drugs.
200.7 Supplying pharmacists with indications and dosage information.
200.10 Contract facilities (including consulting laboratories) utilized as extramural facilities by pharmaceutical manufacturers.
200.11 Use of octadecylamine in steam lines of drug establishments.
200.15 Definition of term ''insulin''.

Subpart B [Reserved]

Subpart C—Requirements for Specific Classes of Drugs

200.50 Ophthalmic preparations and dispensers.
200.51 Aqueous-based drug products for oral inhalation.

Subpart D [Reserved]

Subpart E—Prescription Drug Consumer Price Listing

200.200 Prescription drugs; reminder advertisements and reminder labeling to provide price information to consumers.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360e, 371, 374, 375.

SOURCE: 40 FR 13996, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 200.5 Mailing of important information about drugs.

Manufacturers and distributors of drugs and the Food and Drug Administration occasionally are required to mail important information about drugs to physicians and others responsible for patient care. In the public interest, such mail should be distinctive in appearance so that it will be promptly recognized and read. The Food and Drug Administration will make such mailings in accordance with the specifications set forth in this section. Manufacturers and distributors of drugs are asked to make such mailings as prescribed by this section and not to use the distinctive envelopes for ordinary mail.

(a) Use first class mail and No. 10 white envelopes.

(b) The name and address of the agency or the drug manufacturer or distributor is to appear in the upper left corner of the envelope.

(c) The following statements are to appear in the far left third of the envelope front, in the type and size indicated, centered in a rectangular space approximately 3 inches wide and 2¼ inches high with an approximately ⅜ inch-wide border in the color indicated:

(1) When the information concerns a significant hazard to health, the statement:

IMPORTANT

DRUG

WARNING

The statement shall be in three lines, all capitals, and centered. ''Important'' shall be in 36 point Gothic Bold type. ''Drug'' and ''Warning'' shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be red.

(2) When the information concerns important changes in drug package labeling, the statement:

IMPORTANT

PRESCRIBING

INFORMATION

The statement shall be in three lines, all capitals, and centered. ''Important'' shall be in 36 point Gothic Bold type. ''Prescribing'' and ''Information'' shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be blue.

(3) When the information concerns a correction of prescription drug advertising or labeling, the statement:

IMPORTANT

CORRECTION

OF DRUG

INFORMATION

The statement shall be in four lines, all capitals, and centered. ''Important'' shall be in 36 point Gothic Bold type. ''Correction,'' ''Of Drug,'' and ''Information'' shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be brown.

§ 200.7 Supplying pharmacists with indications and dosage information.

There are presently no regulations under the Federal Food, Drug, and Cosmetic Act that prevent a manufacturer of prescription drugs from sending the pharmacist data he needs on indications and dosage in exercising his important professional function of checking against possible mistakes in a prescription. The Food and Drug Administration believes manufacturers should be encouraged to supply such printed matter to the pharmacist for his professional information. Obviously, such printed matter should not be displayed to prospective purchasers to promote over-the-counter sale of prescription drugs.

§ 200.10 Contract facilities (including consulting laboratories) utilized as extramural facilities by pharmaceutical manufacturers.

(a) Section 704(a) of the Federal Food, Drug, and Cosmetic Act specifically authorizes inspection of consulting laboratories as well as any factory, warehouse, or establishment in which prescription drugs are manufactured, processed, packed, or held.

(b) The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer's own facility.

(c) The Food and Drug Administration reserves the right to disclose to the pharmaceutical manufacturer, or to the applicant of a new drug application (NDA) or to the sponsor of an Investigational New Drug (IND) Application, any information obtained during the inspection of an extramural facility having a specific bearing on the compliance of the manufacturer's, applicant's, or sponsor's product with the Federal Food, Drug, and Cosmetic Act. The Food and Drug Administration's position is that by the acceptance of such contract work, the extramural facility authorizes such disclosures.

(d) The Food and Drug Administration does not consider results of validation studies of analytical and assay methods and control procedures to be trade secrets that may be withheld from the drug manufacturer by the contracted extramural facility.

[40 FR 13996, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990]

§ 200.11 Use of octadecylamine in steam lines of drug establishments.

The Food and Drug Administration will not object to the use of octadecylamine in steam lines where the steam may be used for autoclaving surgical instruments and gauze if the octadecylamine in the steam is not more than 2.4 parts per million.

§ 200.15 Definition of term "insulin."

For purposes of sections 801 and 802 of the act and this title, the term *insulin* means the active principle of the pancreas that affects the metabolism of carbohydrates in the animal body and which is of value in the treatment of diabetes mellitus. The term includes synthetic and biotechnologically derived products that are the same as, or similar to, naturally occurring insulins in structure, use, and intended effect and are of value in the treatment of diabetes mellitus.

[63 FR 26698, May 13, 1998]

Subpart B [Reserved]

Subpart C—Requirements for Specific Classes of Drugs

§ 200.50 Ophthalmic preparations and dispensers.

(a)(1) Informed medical opinion is in agreement that all preparations offered

or intended for ophthalmic use, including preparations for cleansing the eyes, should be sterile. It is further evident that such preparations purport to be of such purity and quality as to be suitable for safe use in the eye.

(2) The Food and Drug Administration concludes that all such preparations, if they are not sterile, fall below their professed standard of purity or quality and may be unsafe. In a statement of policy issued on September 1, 1964, the Food and Drug Administration ruled that liquid preparations offered or intended for ophthalmic use that are not sterile may be regarded as adulterated within the meaning of section 501(c) of the Federal Food, Drug, and Cosmetic Act (the act), and, further, may be deemed misbranded within the meaning of section 502(j) of the act. This ruling is extended to affect all preparations for ophthalmic use. By this regulation, this ruling is applicable to ophthalmic preparations that are regulated as drugs. By the regulation in § 800.10 of this chapter, this ruling is applicable to ophthalmic preparations that are regulated as medical devices.

(3) The containers of ophthalmic preparations shall be sterile at the time of filling and closing, and the container or individual carton shall be so sealed that the contents cannot be used without destroying the seal. The packaging and labeling of ophthalmic preparations that are over-the-counter drugs shall also comply with § 211.132 of this chapter on tamper-resistant packaging requirements.

(b) Liquid ophthalmic preparations packed in multiple-dose containers should:

(1) Contain one or more suitable and harmless substances that will inhibit the growth of microorganisms; or

(2) Be so packaged as to volume and type of container and so labeled as to duration of use and with such necessary warnings as to afford adequate protection and minimize the hazard of injury resulting from contamination during use.

(c) Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. These articles, which are regulated as drugs if packaged with the drugs with which they are to be used, should be packaged so as to maintain sterility until the package is opened and be labeled, on or within the retail package, so as to afford adequate directions and necessary warnings to minimize the hazard of injury resulting from contamination during use.

[40 FR 13996, Mar. 27, 1975, as amended at 47 FR 50455, Nov. 5, 1982]

§ 200.51 Aqueous-based drug products for oral inhalation.

(a) All aqueous-based drug products for oral inhalation must be manufactured to be sterile.

(b) Manufacturers must also comply with the requirements in § 211.113(b) of this chapter.

[65 FR 34089, May 26, 2000]

Subpart D [Reserved]

Subpart E—Prescription Drug Consumer Price Listing

§ 200.200 Prescription drugs; reminder advertisements and reminder labeling to provide price information to consumers.

(a) Prescription drug reminder advertisements and reminder labeling intended to provide price information to consumers are exempt from the requirements of §§ 201 .100 and 202.1 of this chapter if all of the following conditions are met:

(1) The only purpose of the reminder advertisement or reminder labeling is to provide consumers with information concerning the price charged for a prescription for a particular drug product, and the reminder advertisement or reminder labeling contains no representation or suggestion concerning the drug product's safety, effectiveness, or indications for use.

(2) The reminder advertisement or reminder labeling contains the proprietary name of the drug product, if any; the established (generic) name of the drug product, if any; the drug product's strength if the product contains a single active ingredient or if the product contains more than one active ingredient and a relevant strength can be

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

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

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

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

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

[40 FR 58799, Dec. 18, 1975]

PART 201—LABELING

Subpart A—General Labeling Provisions

Sec.
201.1 Drugs; name and place of business of manufacturer, packer, or distributor.
201.2 Drugs and devices; National Drug Code numbers.
201.5 Drugs; adequate directions for use.
201.6 Drugs; misleading statements.
201.10 Drugs; statement of ingredients.
201.15 Drugs; prominence of required label statements.
201.16 Drugs; Spanish-language version of certain required statements.
201.17 Drugs; location of expiration date.
201.18 Drugs; significance of control numbers.
201.19 Drugs; use of term ''infant''.
201.20 Declaration of presence of FD&C Yellow No. 5 and/or FD&C Yellow No. 6 in certain drugs for human use.
201.21 Declaration of presence of phenylalanine as a component of aspartame in over-the-counter and prescription drugs for human use.
201.22 Prescription drugs containing sulfites; required warning statements.
201.23 Required pediatric studies.
201.24 Labeling for systemic antibacterial drug products.
201.25 Bar code label requirements.
201.26 Exceptions or alternatives to labeling requirements for human drug products held by the Strategic National Stockpile.

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

201.50 Statement of identity.
201.51 Declaration of net quantity of contents.
201.55 Statement of dosage.
201.56 Requirements on content and format of labeling for human prescription drug and biological products.
201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in §201.56(b)(1).
201.58 Waiver of labeling requirements.

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

201.60 Principal display panel.
201.61 Statement of identity.
201.62 Declaration of net quantity of contents.
201.63 Pregnancy/breast-feeding warning.
201.64 Sodium labeling.
201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.
201.70 Calcium labeling.
201.71 Magnesium labeling.
201.72 Potassium labeling.
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).

Subpart D—Exemptions From Adequate Directions for Use

201.100 Prescription drugs for human use.
201.105 Veterinary drugs.
201.115 New drugs or new animal drugs.

201.116 Drugs having commonly known directions.
201.117 Inactive ingredients.
201.119 In vitro diagnostic products.
201.120 Prescription chemicals and other prescription components.
201.122 Drugs for processing, repacking, or manufacturing.
201.125 Drugs for use in teaching, law enforcement, research, and analysis.
201.127 Drugs; expiration of exemptions.
201.128 Meaning of ''intended uses''.
201.129 Drugs; exemption for radioactive drugs for research use.

Subpart E—Other Exemptions

201.150 Drugs; processing, labeling, or repacking.
201.161 Carbon dioxide and certain other gases.

Subpart F—Labeling Claims for Drugs in Drug Efficacy Study

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

Subpart G—Specific Labeling Requirements for Specific Drug Products

201.300 Notice to manufacturers, packers, and distributors of glandular preparations.
201.301 Notice to manufacturers, packers, and distributors of estrogenic hormone preparations.
201.302 Notice to manufacturers, packers, and distributors of drugs for internal use which contain mineral oil.
201.303 Labeling of drug preparations containing significant proportions of wintergreen oil.
201.304 Tannic acid and barium enema preparations.
201.305 Isoproterenol inhalation preparations (pressurized aerosols, nebulizers, powders) for human use; warnings.
201.306 Potassium salt preparations intended for oral ingestion by man.
201.307 Sodium phosphates; package size limitation, warnings, and directions for over-the-counter sale.
201.308 Ipecac syrup; warnings and directions for use for over-the-counter sale.
201.309 Acetophenetidin (phenacetin)-containing preparations; necessary warning statement.
201.310 Phenindione; labeling of drug preparations intended for use by man.
201.311 [Reserved]
201.312 Magnesium sulfate heptahydrate; label declaration on drug products.
201.313 Estradiol labeling.
201.314 Labeling of drug preparations containing salicylates.
201.315 Over-the-counter drugs for minor sore throats; suggested warning.
201.316 Drugs with thyroid hormone activity for human use; required warning.
201.317 Digitalis and related cardiotonic drugs for human use in oral dosage forms; required warning.
201.319 Water-soluble gums, hydrophilic gums, and hydrophilic mucilloids (including, but not limited to agar, alginic acid, calcium polycarbophil, carboxymethylcellulose sodium, carrageenan, chondrus, glucomannan ((B-1,4 linked) polymannose acetate), guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil tragacanth, and xanthan gum) as active ingredients; required warnings and directions.
201.320 Warning statements for drug products containing or manufactured with chlorofluorocarbons or other ozone-depleting substances.
201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition.
201.325 Over-the-counter drugs for vaginal contraceptive and spermicide use containing nonoxynol 9 as the active ingredient; required warnings and labeling information.
201.326 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.
201.327 Over-the-counter sunscreen drug products; required labeling based on effectiveness testing.
APPENDIX A TO PART 201—EXAMPLES OF GRAPHIC ENHANCEMENTS USED BY FDA

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

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

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

Subpart A—General Labeling Provisions

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

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

or drug product dispensed in accordance with section 503(b)(1) of the act.

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

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

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

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

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

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

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

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

(f) The name of the person represented as manufacturer under paragraph (b) or (c) of this section must be the same as either (1) the name of the establishment (as defined in § 207.3(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

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

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

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

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

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

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

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

(i) The statement of the place of business shall include the street address, city, State, and ZIP Code. For a foreign manufacturer, the statement of the place of business shall include the street address, city, country, and any applicable mailing code. The street address may be omitted if it is shown in a current city directory or telephone directory. The requirement for inclusion of the ZIP Code shall apply to consumer commodity labels developed or revised after July 1, 1969. In the case of nonconsumer packages, the ZIP Code shall appear either on the label or the labeling (including the invoice).

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

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

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

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

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

§ 201.2 Drugs and devices; National Drug Code numbers.

The National Drug Code (NDC) number is requested but not required to appear on all drug labels and in all drug labeling, including the label of any prescription drug container furnished to a consumer. If the NDC number is shown on a drug label, it shall be displayed as required in § 207.35(b)(3) of this chapter.

[40 FR 52002, Nov. 7, 1975]

§ 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]

§ 201.6 Drugs; misleading statements.

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

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

[41 FR 6908, Feb. 13, 1976]

§ 201.10 Drugs; statement of ingredients.

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

[41 FR 6908, Feb. 13, 1976]

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

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

[67 FR 4906, Feb. 1, 2002]

§ 201.17 Drugs; location of expiration date.

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

[43 FR 45076, Sept. 29, 1978]

§ 201.18 Drugs; significance of control numbers.

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

§ 201.19 Drugs; use of term "infant".

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

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

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

(a) The label for over-the-counter and prescription drug products intended for human use administered orally, nasally, rectally, or vaginally, or for use in the area of the eye, containing FD&C Yellow No. 5 as a color additive using the names FD&C Yellow No. 5 and tartrazine. The labeling for over-the-counter and prescription drug products shall bear a statement such as ''Contains FD&C Yellow No. 5 (tartrazine) as a color additive'' or ''Contains color additives including FD&C Yellow No. 5 (tartrazine)''. The labels of certain drug products subject to this labeling requirement that are also cosmetics, such as antibacterial mouthwashes and fluoride toothpastes, need not comply with this requirement provided they comply with the requirements of § 701.3 of this chapter.

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

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

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

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

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

(a) Aspartame is the methylester of a dipeptide composed of two amino acids, phenylalanine and aspartic acid. When these two amino acids are so combined to form aspartame (1-methyl *N*-L-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

the new composition and the labeling changes.

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

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

§ 201.22 Prescription drugs containing sulfites; required warning statements.

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

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

(c) The labeling required by §§ 201.57 and 201.100(d) for sulfite-containing epinephrine for injection for use in allergic emergency situations shall bear the warning statement ''Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains (*insert the name of the sulfite, e.g., sodium metabisulfite*), a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.'' This statement shall appear in the ''Warnings'' section of the labeling.

[51 FR 43904, Dec. 5, 1986]

§ 201.23 Required pediatric studies.

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

(b) The Food and Drug Administration (FDA) may by order, in the form of a letter, after notifying the manufacturer of its intent to require an assessment of pediatric safety and effectiveness of a pediatric formulation, and after offering an opportunity for a written response and a meeting, which

may include an advisory committee meeting, require a manufacturer to submit an application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within a 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

should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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

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

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

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

[68 FR 6081, Feb. 6, 2003]

§ 201.25 Bar code label requirements.

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

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

(1) Prescription drug products, however:

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

(A) Prescription drug samples;

(B) Allergenic extracts;

(C) Intrauterine contraceptive devices regulated as drugs;

(D) Medical gases;

(E) Radiopharmaceuticals; and

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

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

(2) Biological products; and

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

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

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

(ii) Remain intact under normal conditions of use.

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

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

(i) compliance with the bar code requirement would adversely affect the

safety, effectiveness, purity or potency of the drug or not be technologically feasible, and the concerns underlying the request could not reasonably be addressed by measures such as package redesign or use of overwraps; or

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

(2) Requests for an exemption should be sent to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993–0002 (requests involving a drug product) or to the Office of Compliance and Biologics Quality (HFM–600), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852 (requests involving a biological product).

[69 FR 9170, Feb. 26, 2004, as amended at 76 FR 12847, Mar. 9, 2011]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(2) You must report any grant of a request for an exception or alternative under this section as part of your annual report under §§ 314.70(d) or 601.12(f)(3) of this chapter.

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

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

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

(3) § 201.17;

(4) § 201.18;

(5) § 201.19;

(6) § 201.20;

(7) § 201.21;

(8) § 201.22;

(9) § 201.24; and

(10) § 312.6.

[72 FR 73599, Dec. 28, 2007]

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

§ 201.50 Statement of identity.

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

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

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

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

§ 201.51 Declaration of net quantity of contents.

(a) The label of a prescription or insulin-containing drug in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination of numerical count and weight or measure. The statement of quantity of drugs in tablet, capsule, ampule, or other unit dosage form shall be expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semi-solid, or viscous, or in terms of fluid measure if the drug is liquid. When the drug quantity statement is in terms of the numerical count of the drug units, it shall be augmented to give the weight or measure of the drug units or the quantity of each active ingredient in each drug unit or, when quantity does not accurately reflect drug potency, a statement of the drug potency.

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

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

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

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

(f) A statement of the quantity of a prescription or insulin-containing drug in terms of weight or measure applicable to such drug, under the provisions of paragraph (a) of this section, shall express with prominence and conspicuousness the number of the largest whole unit, as specified in paragraph (b) of this section, that are contained

in the package. Any remainder shall be expressed in terms of common or decimal fractions of such unit or in terms of the next smaller whole unit and common or decimal fractions thereof.

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

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

§ 201.55 Statement of dosage.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Highlights of Prescribing Information
- Product Names, Other Required Information
- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations

Full Prescribing Information: Contents

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

(2) Additional nonstandard subheadings that are used to enhance labeling organization, presentation, or ease of use (e.g., for individual warnings or precautions, or for each drug

interaction) must be assigned a decimal number that corresponds to their placement in labeling. The decimal numbers must be consistent with the standardized identifying numbers listed in paragraph (d)(1) of this section (e.g., subheadings added to the ''Warnings and Precautions'' section must be numbered 5.1, 5.2, and so on).

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

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

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

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

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

Description
Clinical Pharmacology
Indications and Usage
Contraindications
Warnings
Precautions
Adverse Reactions
Drug Abuse and Dependence
Overdosage
Dosage and Administration
How Supplied

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

Animal Pharmacology and/or Animal Toxicology
Clinical Studies
References

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

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

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

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

[71 FR 3986, Jan. 24, 2006]

EFFECTIVE DATE NOTE: At 79 FR 72101, Dec. 4, 2014, paragraph (d)(1) of § 201.56 was amended by removing from the list of headings and subheadings the subheadings ''8.2 Labor and delivery'' and ''8.3 Nursing mothers'' and adding in their places the subheadings ''8.2 Lactation'' and ''8.3 Females and Males of Reproductive Potential'', respectively, effective June 30, 2015.

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

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

prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(A) The dosage range,

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

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(7) *6 Adverse reactions.* This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

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

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

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

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

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

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

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

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

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

(i) *8.1 Pregnancy.* This subsection 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 must contain the following information:

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

(*1*) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must 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 must also contain a description of the human studies. If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must 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 must also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*2*) *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 must 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 must 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. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling must 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.

(*3*) 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 must state: ''Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'' The labeling must 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 must 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 must contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*4*) *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 must state: ''Pregnancy Category D. See 'Warnings and Precautions' section.'' Under the ''Warnings and Precautions'' section, the labeling must state: ''(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.''

(*5*) *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 must state: ''Pregnancy Category X. See 'Contraindications' section.'' Under ''Contraindications,'' the labeling must 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 a fetus.''

(B) *Nonteratogenic effects.* Under this subheading the labeling must 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 must 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.

(ii) *8.2 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 and Usage section, this subsection must 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, it must state that the information is unknown.

(iii) *8.3 Nursing mothers.* (A) If a drug is absorbed systemically, this subsection must 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 must be described.

(B) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection must 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 must 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 must state: ''Caution should be exercised when (*name of drug*) is administered to a nursing woman.''

(C) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection must 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 must state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling must 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) *8.4 Pediatric use.* (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H) of this section, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the ''Indications and Usage'' section, and appropriate pediatric dosage information must be given

under the ''Dosage and Administration'' section. The ''Pediatric use'' subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection should be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or ''Clinical Studies'' section. As appropriate, this information must also be contained in the ''Contraindications'' and/or ''Warnings and Precautions'' section(s).

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the ''Pediatric use'' subsection and discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' and ''Clinical Studies'' sections. Appropriate pediatric dosage must be given under the ''Dosage and Administration'' section. The ''Pediatric use'' subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the ''Contraindications'' and/or ''Warnings and Precautions'' section(s).

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

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

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

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

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

hazard must be stated in the ''Contraindications'' or ''Warnings and Precautions'' section and this subsection must refer to it.

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

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

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

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

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

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

(*2*) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed,

and other reported clinical experience has not identified such differences, the ''Geriatric use'' subsection must contain the following statement:

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

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

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

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

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

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

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

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

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

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

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

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

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

(iii) *9.3 Dependence.* This subsection must describe characteristic effects resulting from both psychological and physical dependence that occur with

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

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

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

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

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

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

(v) Whether the drug is dialyzable; and

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

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

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

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

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

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

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

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

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

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

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

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

(B) *12.2 Pharmacodynamics*. This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or

toxicity. Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., ''Warnings and Precautions'' or ''Dosage and Administration'') must not be repeated in this subsection, but the location of such recommendations must be referenced.

(C) *12.3 Pharmacokinetics*. This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), pertinent half-lives ($t_{1/2}$), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (V_d) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., ''Warnings and Precautions,'' ''Dosage and Administration'' or ''Use in Specific Populations'') must not be repeated in this subsection, but the location of such recommendations must be referenced.

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

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

(B) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled studies, as defined in § 314.126(b) of this chapter, to be necessary for the safe and effective use may be included in this section only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

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

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

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

animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

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

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

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

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

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

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

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

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

(iv) Special handling and storage conditions.

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

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

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

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

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

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

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

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

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

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

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

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

[71 FR 3988, Jan. 24, 2006]

EFFECTIVE DATE NOTE: At 79 FR 72101, Dec. 4, 2014, § 201.57 was amended by revising paragraphs (c)(9)(i), (ii), and (iii), effective June 30, 2015. For the convenience of the user, the revised text is set forth as follows:

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

* * * * *

(c) * * *

(9) * * *

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

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

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

(*1*) *Risk statement based on human data*. When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with

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

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

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

(C) *Clinical considerations*. Under the subheading ''Clinical Considerations,'' the labeling must provide relevant information, to the extent it is available, under the headings ''Disease-associated maternal and/or embryo/fetal risk,'' ''Dose adjustments during pregnancy and the postpartum period,'' ''Maternal adverse reactions,'' ''Fetal/Neonatal adverse reactions,'' and ''Labor or delivery'':

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

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

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

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

(*5*) *Labor or delivery*. If the drug is expected to affect labor or delivery, the labeling must provide information about the effect of the drug on the pregnant woman and the fetus or neonate; the effect of the drug on the duration of labor and delivery; any increased risk of adverse reactions, including their potential severity and reversibility; and must provide information about available intervention(s) that can mitigate these effects and/or adverse reactions. The information described under this heading is not required for drugs approved for use only during labor and delivery.

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

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

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

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

and the basis for those calculations must be included.

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

(A) *Risk summary*. When relevant human and/or animal lactation data are available, the Risk Summary must include a cross-reference to the ''Data'' subheading in the ''Lactation'' subsection of the labeling. When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans. When use of a drug is contraindicated during breastfeeding, this information must be stated first in the Risk Summary.

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

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

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

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

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

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

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

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

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

(C) *Data*. Under the subheading ''Data,'' the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

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

* * * * *

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

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

(e) The declaration shall appear as a distinct item on the principal display panel, shall be separated, by at least a space equal to the height of the lettering used in the declaration, from other printed label information appearing above or below the declaration and, by at least a space equal to twice the width of the letter ''N'' of the style of type used in the quantity of contents statement, from other printed label information appearing to the left or right of the declaration. It shall not include any term qualifying a unit of weight, measure, or count, such as ''giant pint''

and ''full quart'', that tends to exaggerate the amount of the drug in the container. It shall be placed on the principal display panel within the bottom 30 percent of the area of the label panel in lines generally parallel to the base on which the package rests as it is designed to be displayed: *Provided*, That:

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

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

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

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

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

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

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

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

(h) The declaration shall be in letters and numerals in a type size established in relationship to the area of the principal display panel of the package and shall be uniform for all packages of substantially the same size by complying with the following type specifications:

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

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

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

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

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

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

(1) The declaration shall be expressed both in ounces, with identification by weight or by liquid measure and, if applicable (1 pound or 1 pint or more) followed in parentheses by a declaration in pounds for weight units, with any remainder in terms of ounces or common or decimal fractions of the pound (see

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

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

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

(k) Examples:

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

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

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

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

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

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

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

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

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

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

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

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

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

§ 201.63 Pregnancy/breast-feeding warning.

(a) The labeling for all over-the-counter (OTC) drug products that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading ''Warning'' (or ''Warnings'' if it appears with additional warning statements) as follows: ''If pregnant or breast-feeding, ask a health professional before use.'' [first four words of this statement in bold type] In addition to the written warning, a symbol that conveys the intent of the warning may be used in labeling.

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

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

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

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

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

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

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

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

§ 201.64 Sodium labeling.

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

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

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

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading ''Warning'' (or ''Warnings'' if it appears with additional warning statements) if the amount of sodium present in the labeled maximum daily dose of the product is more than 140 milligrams: ''Ask a doctor before use if you have [in bold type] [bullet][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.

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

(k) The labeling of OTC drug products intended for rectal administration containing dibasic sodium phosphate and/or monobasic sodium phosphate shall contain the sodium content per delivered dose if the sodium content is 5 milligrams or more. The sodium content shall be expressed in milligrams or grams. If less than 1 gram, milligrams should be used. The sodium content shall be rounded-off to the nearest whole number if expressed in milligrams (or nearest tenth of a gram if expressed in grams). The sodium content

[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.

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

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

(a) *Scope*. This section sets forth the content and format requirements for the labeling of all OTC drug products. Where an OTC drug product is the subject of an applicable monograph or regulation that contains content and format requirements that conflict with this section, the content and format requirements in this section must be followed unless otherwise specifically provided in the applicable monograph or regulation.

(b) *Definitions*. The following definitions apply to this section:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act (secs. 201 *et seq*. (21 U.S.C. 321 *et seq*.)).

(2) *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

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

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

(5) *Established name* of a drug or ingredient thereof means the applicable official name designated under section 508 of the act (21 U.S.C. 358), or, if there is no designated official name and the drug or ingredient is recognized in an official compendium, the official title of the drug or ingredient in such compendium, or, if there is no designated official name and the drug or ingredient is not recognized in an official compendium, the common or usual name of the drug or ingredient.

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

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

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

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

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

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

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

(c) *Content requirements*. The outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper, shall contain the title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(8)

of this section, and may contain the information under the heading in paragraph (c)(9) of this section, in the order listed.

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

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

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

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

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

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

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

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

(B) *Allergic reaction and asthma alert warnings.* Allergic reaction warnings set forth in any applicable OTC drug monograph or approved drug application for any product that requires a separate allergy warning. This warning shall follow the subheading ''Allergy alert:'' The asthma alert warning set forth in §§ 341.76(c)(5) and 341.76(c)(6) of this chapter. This warning shall follow the subheading ''Asthma alert:''

(C) Flammability warning, with appropriate flammability signal word(s) (e.g., §§ 341.74(c)(5)(iii), 344.52(c), 358.150(c), and 358.550(c) of this chapter). This warning shall follow a subheading containing the appropriate flammability signal word(s) described in an applicable OTC drug monograph or approved drug application.

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

(E) Liver warning set forth in § 201.326(a)(1)(iii) and/or stomach bleeding warning set forth in § 201.326(a)(2)(iii). The liver warning shall follow the subheading ''Liver warning:'' and the stomach bleeding warning shall follow the subheading ''Stomach bleeding warning:''

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

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

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

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

whether a doctor or health professional is consulted.

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

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

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

(vii) ''Stop use and ask a doctor if'' [in bold type], followed by any signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product. For all OTC drug products under an approved drug application whose packaging does not include a toll-free number through which consumers can report complaints to the manufacturer or distributor of the drug product, the following text shall immediately follow the subheading: ''[Bullet] side effects occur. You may report side effects to FDA at 1–800–FDA–1088.'' The telephone number must appear in a minimum 6–point bold letter height or type size.

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

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

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

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

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

(i) Required information about certain ingredients in OTC drug products (e.g., sodium in § 201.64(b), calcium in § 201.70(b), magnesium in § 201.71(b), and potassium in § 201.72(b)) shall appear as follows: ''each (insert appropriate dosage unit) contains:'' [in bold type (insert name(s) of ingredient(s) (in alphabetical order) and the quantity of each ingredient). This information shall be the first statement under this heading.

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

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

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

chapter and § 720.8 of this chapter may also apply, as appropriate. If there is a difference in the labeling provisions in this § 201.66 and §§ 701.3 and 720.8 of this chapter, the labeling provisions in this § 201.66 shall be used.

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

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

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

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

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

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

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

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

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

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

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

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

monograph, as provided in § 330.1(c)(2) of this chapter.

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

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

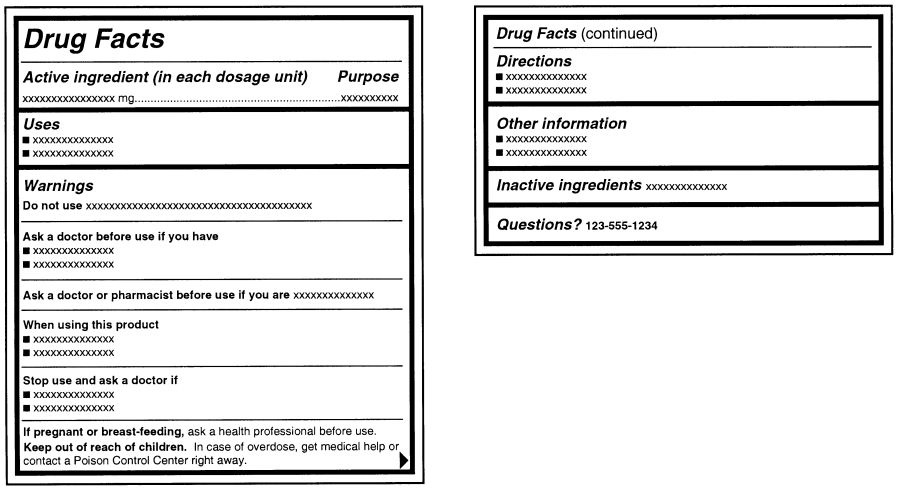
(iii) Paragraph (d)(3) of this section shall apply except that less than 0.5-point leading may be used, provided the ascenders and descenders do not touch.

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

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

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

OTC Drug Product Labeling Outline



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

Drug Facts

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

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

Warnings

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

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

When using this product
■ you may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

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

Directions

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

Drug Facts (continued)

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

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

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

Drug Facts

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

Uses

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

Warnings

Ask a doctor before use if you have kidney disease

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

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

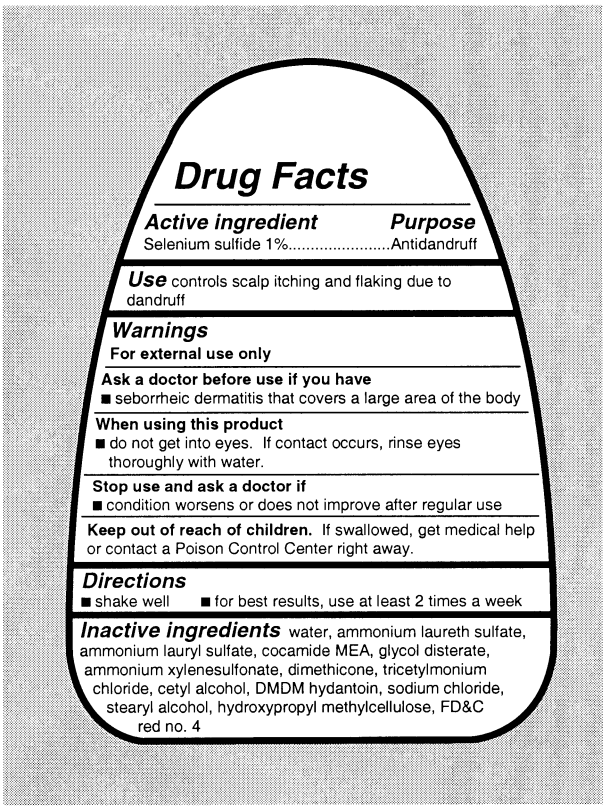
Keep out of reach of children.

Directions

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

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

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



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

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

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

(f) *Interchangeable terms and connecting terms.* The terms listed in § 330.1(i) of this chapter may be used

interchangeably in the labeling of OTC drug products, provided such use does not alter the meaning of the labeling that has been established and identified in an applicable OTC drug monograph or by regulation. The terms listed in § 330.1(j) of this chapter may be deleted from the labeling of OTC drug products when the labeling is revised to comply with this section, provided such deletion does not alter the meaning of the labeling that has been established and identified in an applicable OTC drug monograph or by regulation. The terms listed in § 330.1(i) and (j) of this chapter shall not be used to change in any way the specific title, headings, and subheadings required under paragraphs (c)(1) through (c)(9) of this section.

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

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

§ 201.70 Calcium labeling.

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

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

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading ''Warning'' (or ''Warnings'' if it appears with additional warning statements) if the amount of calcium present in the labeled maximum daily dose of the product is more than 3.2 grams: ''Ask a doctor before use if you have [in bold type] [bullet][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.

[69 FR 13733, Mar. 24, 2004]

§ 201.71 Magnesium labeling.

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

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

[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.

[69 FR 13734, Mar. 24, 2004]

§ 201.72 Potassium labeling.

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

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

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading ''Warning'' (or ''Warnings'' if it appears with additional warning statements) if the amount of potassium present in the labeled maximum daily dose of the product is more than 975 milligrams: ''Ask a doctor before use if you have [in bold type] [bullet][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

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

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

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

[69 FR 13734, Mar. 24, 2004]

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

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

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

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

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

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

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

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

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

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

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

(b) *Clinical Pharmacology*. (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and 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, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

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

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

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

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

in patients with vasomotor rhinitis; and/or

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

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

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

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

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

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

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

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

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

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

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

adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the ''Indications and Usage'' section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes 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 in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), 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. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth,

development, and functional maturation of the child.

(*c*) *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 (*name*(*s*) *of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'' The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: ''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.*) 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 pertinant animal data.*) (*Name of drug*) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.''

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

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

subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) *Nursing mothers.* (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

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

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

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

the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the ''Contraindications,'' ''Warnings,'' and elsewhere in the ''Precautions'' sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the ''Pediatric use'' subsection of the labeling shall contain either the following statement, or a reasonable alternative: ''The safety and effectiveness of (*drug name*) have been established in the age groups __ to __ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).'' Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or the ''Clinical Studies'' section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the ''Clinical Pharmacology'' section. Pediatric dosing instructions shall be included in the ''Dosage and Administration'' section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the ''Pediatric use'' subsection and, as appropriate, in the ''Contraindications,'' ''Warnings,'' ''Precautions,'' and ''Dosage and Administration'' sections.

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

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

in the ''Contraindications'' or ''Warnings'' section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

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

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

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

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

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

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

''Geriatric use'' subsection shall contain the following statement:

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

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

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

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

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

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

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

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

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

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

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

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency.

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

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

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

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

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

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

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

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

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

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

(3) Oral LD_{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 overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, gastric lavage, and

forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless 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 uses or dosing regimens not stated in the ''Indications and Usage'' or ''Dosage and Administration'' section.

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

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

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

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.

Subpart D—Exemptions From Adequate Directions for Use

§ 201.100 Prescription drugs for human use.

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

(a) The drug is:

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

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

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

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

(b) The label of the drug bears:

(1) The statement ''Rx only'' and

(2) The recommended or usual dosage and

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

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

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

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

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

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

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

(7) A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity. Where there are standards and test procedures for determining that the container meets the requirements for specified types of containers as defined in an official compendium, such terms may be used. For example, ''Dispense in tight, light-resistant container as defined in the National Formulary''. Where standards and test procedures for determining the types of containers to be used in dispensing the drug product are not included in an official compendium, the specific container or types of containers known to be adequate to maintain the identity, strength, quality, and purity of the drug products shall be described. For example, ''Dispense in containers which (statement of specifications which clearly enable the dispensing pharmacist to select an adequate container)'': *Provided, however,* That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraph (b) (2), (3), (5), and (7) of this section may be contained in other labeling on or within the package from which it is to be dispensed; the information referred to in paragraph (b)(1) of this section may be placed on such outer container only; and the information required by paragraph (b)(6) of this section may be on the crimp of the dispensing tube. The information required by this paragraph (b)(7) is not required for prescription drug products packaged in unit-dose, unit-of-use, on other packaging format in which the manufacturer's original package is designed and intended to be dispensed to patients without repackaging.

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

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

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and § 201.105(b)(2) contains:

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

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

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

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

(f) Reminder labeling which calls attention to the name of the drug product but does not include indications or dosage recommendations for use of the drug product is exempted from the provisions of paragraph (d) of this section. This reminder labeling shall contain only the proprietary name of the drug product, if any; the established name of the drug product, if any; the established name of each active ingredient in the drug product; and, optionally, information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, the name and address of the manufacturer, packer, or distributor or other written, printed, or graphic matter containing no representation or suggestion relating to the drug product. If the Commissioner finds that there is evidence of significant incidence of fatalities or serious injury associated with the use of a particular prescription drug, he may withdraw this exemption by so notifying the manufacturer, packer, or distributor of the drug by letter. Reminder labeling, other than price lists and catalogs solely intended to convey price information including, but not limited to, those subject to the requirements of § 200.200 of this chapter, is not permitted for a prescription drug product whose labeling contains a boxed warning relating to a serious hazard associated with the use of the drug product. Reminder labeling which is intended to provide consumers with information concerning the price charged for a prescription for a particular drug product shall meet all of the conditions contained in § 200.200 of this chapter. Reminder labeling, other than that subject to the requirements of § 200.200 of this chapter, is not permitted for a drug for which an announcement has been published pursuant to a review of the labeling claims for the drug by the National Academy of Sciences/National Research Council (NAS/NRC), Drug Efficacy Study Group, and for which no claim has been evaluated as higher than ''possibly effective.'' If the Commissioner finds the circumstances are such that reminder labeling may be misleading to prescribers of drugs subject to NAS/NRC evaluation, such reminder labeling will not be allowed and the manufacturer, packer, or distributor will be notified either in the publication of the conclusions on the effectiveness of the drug or by letter.

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

§ 201.105 Veterinary drugs.

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

(a) The drug is:

(1)(i) In the possession of a person (or his agents or employees) regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of drugs that are to be used only by or on the prescription or other order of a licensed veterinarian; or

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

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

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

(b) The label of the drug bears:

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

(2) The recommended or usual dosage; and

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

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

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

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

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

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

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

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

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

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

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

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and § 201.100(b)(2)) contains:

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

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

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

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

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

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

§ 201.115 New drugs or new animal drugs.

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

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

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

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

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

§ 201.116 Drugs having commonly known directions.

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

[41 FR 6910, Feb. 13, 1976]

§ 201.117 Inactive ingredients.

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

§ 201.119 In vitro diagnostic products.

(a) ''In vitro diagnostic products'' are those reagents, instruments and systems intended for use in the diagnosis of disease or in the determination of the state of health in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation and examination of specimens taken from the human body. These products are drugs or devices as defined in section 201(g) and 201(h), respectively, of the Federal Food, Drug, and Cosmetic Act (the act) or are a combination of drugs and devices, and may also be a biological product subject to section 351 of the Public Health Service Act.

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

[41 FR 6910, Feb. 13, 1976]

§ 201.120 Prescription chemicals and other prescription components.

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

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

(b) The label of the drug bears:

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

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

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

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

(c) This exemption shall not apply to any substance intended for use in compounding which results in a new drug, unless an approved new-drug application covers such use of the drug in compounding prescriptions.

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

§ 201.122 Drugs for processing, repacking, or manufacturing.

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

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

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

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

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

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

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

[41 FR 6911, Feb. 13, 1976]

§ 201.127 Drugs; expiration of exemptions.

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

(b) The exemptions conferred by §§ 201.117, 201.119, 201.120, 201.122, and 201.125 shall continue until the drugs are used for the purposes for which they are exempted, or until they are relabeled to comply with section 502(f)(1) of the act. If, however, the drug is converted, compounded, or manufactured into a dosage form limited to prescription dispensing, no exemption shall thereafter apply to the article unless the dosage form is labeled as required by section 503(b) and §§ 201.100 or 201.105.

[41 FR 6911, Feb. 13, 1976]

§ 201.128 Meaning of "intended uses".

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

[41 FR 6911, Feb. 13, 1976]

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

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

[41 FR 6911, Feb. 13, 1976]

Subpart E—Other Exemptions

§ 201.150 Drugs; processing, labeling, or repacking.

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

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

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

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

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

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

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

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

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

§ 201.161 Carbon dioxide and certain other gases.

(a) Carbon dioxide, cyclopropane, ethylene, helium, and nitrous oxide gases intended for drug use are exempted from the requirements of § 201.100(b)(2), (3), and (c)(1) provided the labeling bears, in addition to any other information required by the Federal Food, Drug, and Cosmetic Act, the following:

(1) The warning statement ''Warning—Administration of (name of gas) may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of (name of gas) and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken''; and

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

(b) This labeling exemption does not apply to mixtures of any one or more of these gases with oxygen or with each other.

(c) Regulatory action may be initiated with respect to any article shipped within the jurisdiction of the Act contrary to the provisions of this section after 60 days following publication of this section in the FEDERAL REGISTER.

Subpart F—Labeling Claims for Drugs in Drug Efficacy Study

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

(a)(1) The National Academy of Sciences—National Research Council, Drug Efficacy Study Group, has completed an exhaustive review of labeling

claims made for drugs marketed under new-drug and antibiotic drug procedures between 1938 and 1962. The results are compiled in ''Drug Efficacy Study, A Report to the Commissioner of Food and Drugs from the National Academy of Sciences (1969).'' As the report notes, this review has made ''an audit of the state of the art of drug usage that has been uniquely extensive in scope and uniquely intensive in time'' and is applicable to more than 80 percent of the currently marketed drugs. The report further notes that the quality of the evidence of efficacy, as well as the quality of the labeling claims, is poor. Labeling and other promotional claims have been evaluated as ''effective,'' ''probably effective,'' ''possibly effective,'' ''ineffective,'' ''ineffective as a fixed combination,'' and ''effective but,'' and a report for each drug in the study has been submitted to the Commissioner.

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

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

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

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

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

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

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

period allowed for submitting supplements to provide for revised labeling.

(e) Qualifying information required in drug labeling by paragraph (c) of this section in order to advise prescribers of a drug of the findings made by a panel of the Academy in evaluating a claim as other than ''effective'' shall be at least of the same size and color and degree of prominence as other printing in the labeling and shall be presented in a prominent box using one of the following formats and procedures:

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

INDICATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(g) The Commissioner may find circumstances are such that, while the elimination of claims evaluated as other than effective will generally eliminate the need for disclosure about such claims, there will be instances in which the change in the prescribing or promotional profile of the drug is so

substantial as to require a disclosure of the reason for the change so that the purchaser or prescriber is not misled by being left unaware through the sponsor's silence that a basic change has taken place. The Food and Drug Administration will identify these situations in direct correspondence with the drug promoters, after which the failure to make the disclosure will be regarded as misleading and appropriate action will be taken.

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

Subpart G—Specific Labeling Requirements for Specific Drug Products

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

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

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

(c) The Department of Health and Human Services is of the opinion that inert glandular materials may not be exempted from the requirements of section 502(f)(1) of the act that they bear adequate directions for use; and, accordingly, that their labeling must include among other things, representations as to the conditions for which such articles are intended to be used or as to the structure or function of the human body that they are intended to affect. Since any such representations offering these articles for use as drugs would be false or misleading, such articles will be considered to be misbranded if they are distributed for use as drugs.

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

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

Some drug preparations fabricated wholly or in part from estradiol and labeled as to potency in terms of international units or in terms of international units of estrone activity have been marketed. The international unit of the estrus-producing hormone was established by the International Conference on the Standardization of Sex Hormones at London, England, on August 1, 1932. This unit was defined as ''the specific estrus-producing activity contained in 0.1 gamma (=0.0001 mg.) of the standard'' hydroxyketonic hormone found in urine (estrone). The International Conference declared that it did not recommend the determination of the activity of nonhydroxyketonic forms of estrogenic hormones in units of estrone because of the varying ratios between the activity of such nonhydroxyketonic estrogenic hormones and estrone, when measured by different methods on test animals.

There is no international unit for measuring the activity of estradiol and no accepted relationship between its activity and that of estrone, either in test animals or in humans. The declaration of potency of estradiol in terms of international units or in terms of international units of estrone activity is therefore considered misleading, within the meaning of 21 U.S.C. 352(a). The declaration of the estradiol content of an estrogenic hormone preparation in terms of weight is considered appropriate.

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

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

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

(c) In view of these facts, the Department of Health and Human Services will regard as misbranded under the provisions of the Federal Food, Drug, and Cosmetic Act a drug for oral administration consisting in whole or in part of mineral oil, the labeling of which encourages its use in pregnancy or indicates or implies that such drug is for administration to infants.

(d) It is also this Department's view that the act requires the labelings of such drugs to bear a warning against consumption other than at bedtime and against administration to infants. The following form of warning is suggested: ''Caution: To be taken only at bedtime. Do not use at any other time or administer to infants, except upon the advice of a physician.''

(e) This statement of interpretation does not in any way exempt mineral oil or preparations containing mineral oil from complying in all other respects with the requirements of the Federal Food, Drug, and Cosmetic Act.

§ 201.303 Labeling of drug preparations containing significant proportions of wintergreen oil.

(a) Because methyl salicylate (wintergreen oil) manifests no toxicity in the minute amounts in which it is used as a flavoring, it is mistakenly regarded by the public as harmless even when taken in substantially larger amounts. Actually, it is quite toxic when taken in quantities of a teaspoonful or more. Wintergreen oil and preparations containing it have caused a number of deaths through accidental misuse by both adults and children. Children are particularly attracted by the odor and are likely to swallow these products when left within reach.

(b) To safeguard against fatalities from this cause, the Department of Health and Human Services will regard as misbranded under the provisions of the Federal Food, Drug, and Cosmetic Act any drug containing more than 5 percent methyl salicylate (wintergreen oil), the labeling of which fails to warn that use otherwise than as directed therein may be dangerous and that the article should be kept out of reach of children to prevent accidental poisoning.

(c) This statement of interpretation in no way exempts methyl salicylate (wintergreen oil) or its preparations from complying in all other respects with the requirements of the Federal Food, Drug, and Cosmetic Act.

§ 201.304 Tannic acid and barium enema preparations.

(a) It has become a widespread practice for tannic acid to be added to barium enemas to improve X-ray pictures. Tannic acid is capable of causing diminished liver function and severe liver necrosis when absorbed in sufficient amounts. The medical literature reports a number of deaths associated with the addition of tannic acid to barium enemas. There is a lack of scientific evidence to establish the conditions, if any, under which tannic acid

is safe and effective for use in enemas. Tannic acid for rectal use to enhance X-ray visualization is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(b) In view of the hazards involved when tannic acid is used in barium enemas, any shipments of tannic acid labeled to come within the exemptions under 502(f) of the Act containing such phrases as: ''Caution: For manufacturing, processing, or repackaging,'' ''For prescription compounding,'' or ''Diagnostic reagent—For professional use only'' will be regarded by the Commissioner of Food and Drugs as misbranded within the meaning of section 502(f) of the Federal Food, Drug, and Cosmetic Act unless the label and the labeling bear conspicuously a warning to the effect: ''*Warning*— Not for use in enemas.''

(c) Any tannic acid intended for use by man and found within the jurisdiction of the Federal Food, Drug, and Cosmetic Act labeled contrary to this section after 60 days from the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

§ 201.305 Isoproterenol inhalation preparations (pressurized aerosols, nebulizers, powders) for human use; warnings.

(a) Accumulating reports have been received by the Food and Drug Administration and have appeared in the medical literature of severe paradoxical bronchoconstriction associated with repeated, excessive use of isoproterenol inhalation preparations in the treatment of bronchial asthma and other chronic bronchopulmonary disorders. The cause of this paradoxical reaction is unknown; it has been observed, however, that patients have not responded completely to other forms of therapy until use of the isoproterenol inhalation preparation was discontinued. In addition, sudden unexpected deaths have been associated with the excessive use of isoproterenol inhalation preparations. The mechanism of these deaths and their relationship, if any, to the cases of severe paradoxical bronchospasm are not clear. Cardiac arrest was noted in several of these cases of sudden death.

(b) On the basis of the above information and after discussion with and concurrence of the Respiratory and Anesthetic Drugs Advisory Committee for Food and Drug Administration, the Commissioner of Food and Drugs concludes that in order for the labeling of such drugs to bear adequate information for their safe use, as required by § 201.100, such labeling must include the following:

Warning: Occasional patients have been reported to develop severe paradoxical airway resistance with repeated, excessive use of isoproterenol inhalation preparations. The cause of this refractory state is unknown. It is advisable that in such instances the use of this preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.

Deaths have been reported following excessive use of isoproterenol inhalation preparations and the exact cause is unknown. Cardiac arrest was noted in several instances.

(c)(1) The Commissioner also concludes that in view of the manner in which these preparations are self-administered for relief of attacks of bronchial asthma and other chronic bronchopulmonary disorders, it is necessary for the protection of users that warning information to patients be included as a part of the label and as part of any instructions to patients included in the package dispensed to the patient as follows:

Warning: Do not exceed the dose prescribed by your physician. If difficulty in breathing persists, contact your physician immediately.

(2) The warning on the label may be accomplished (i) by including it on the immediate container label with a statement directed to pharmacists not to remove the label or (ii) by including in the package a printed warning with instructions to pharmacists to place the warning on the container prior to dispensing.

(d) The marketing of isoproterenol inhalation preparations may be continued if all the following conditions are met:

(1) Within 30 days following the date of publication of this section in the FEDERAL REGISTER:

(i) The label and labeling of such preparations shipped within the jurisdiction of the act are in accordance with paragraphs (b) and (c) of this section.

(ii) The holder of an approved new-drug application for such preparation submits a supplement to his new-drug application to provide for appropriate labeling changes as described in paragraphs (b) and (c) of this section.

(2) Within 90 days following the date of publication of this section in the FEDERAL REGISTER, the manufacturer, packer, or distributor of any drug containing isoproterenol intended for inhalation for which a new-drug approval is not in effect submits a new-drug application containing satisfactory information of the kinds required by § 314.50 of this chapter, including appropriate labeling as described in paragraphs (b) and (c) of this section.

(3) The applicant submits additional information required for the approval of the application as may be specified in a written communication from the Food and Drug Administration.

(e) After 270 days following expiration of said 90 days, regulatory proceedings based on section 505(a) of the Federal Food, Drug, and Cosmetic Act may be initiated with regard to any such drug shipped within the jurisdiction of the act for which an approved new-drug application is not in effect.

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

§ 201.306 Potassium salt preparations intended for oral ingestion by man.

(a) The Food and Drug Administration will initiate no regulatory action with respect to the continued marketing of coated tablets containing potassium chloride or other potassium salts which supply 100 milligrams or more of potassium per tablet provided all the following conditions are met:

(1) Within 30 days from the date of publication of this statement of policy in the FEDERAL REGISTER:

(i) The labeling of the drug bears the prescription caution statement quoted in section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act;

(ii) The labeling on or within the package from which the drug is to be dispensed bears adequate information for its use by practitioners in accord with the ''full disclosure'' labeling requirements of § 201.100 of this chapter, including the following warning statement:

Warning—There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required and deaths have occurred. Based on a large survey of physicians and hospitals, both United States and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Coated potassium tablets should be used only when adequate dietary supplementation is not practicable.

(Although the warning statement includes references to enteric-coated potassium salt preparations, it applies to any capsule or coated tablet of a potassium salt intended for oral ingestion without prior dilution with an adequate volume of liquid to preclude gastrointestinal injury.)

(iii) Any other labeling or additional advertising for the drug conforms to the labeling described in paragraph (a)(1)(ii) of this section, in accordance with §§ 202.1 and 201.100 of this chapter.

(2) Within 90 days from the date of publication of this statement of policy in the FEDERAL REGISTER, the manufacturer, packer, or distributor of the drug shall submit a new-drug application containing satisfactory information of the kind required by § 314.50 of this chapter, with appropriate labeling as described in this paragraph.

(b) The Food and Drug Administration may initiate regulatory proceedings after 30 days from the date of

publication of this section, with respect to the marketing of uncoated tablets containing potassium chloride or other potassium salts which supply 100 milligrams or more of potassium per tablet or with respect to liquid preparations containing potassium chloride or other potassium salts which supply 20 milligrams or more of potassium per milliliter, labeled or intended for human use, unless all the following conditions are met:

(1) The labeling of the drug bears the prescription statement quoted in section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act; and

(2) The labeling on or within the package from which the drug is to be dispensed bears adequate information for its use by practitioners in accord with the ''full disclosure'' labeling requirements of § 201.100 of this chapter, including a recommendation that patients be directed to dissolve any such tablets in an appropriate amount of liquid and to dilute any such liquid preparations adequately to assure against gastrointestinal injury associated with the oral ingestion of concentrated potassium salt preparations.

[40 FR 13998, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990; 67 FR 4906, Feb. 1, 2002]

§ 201.307 Sodium phosphates; package size limitation, warnings, and directions for over-the-counter sale.

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that multiple container sizes of sodium phosphates oral solution available in the marketplace have caused consumer confusion and appear to have been involved in several consumer deaths. Sodium phosphates oral solution has been marketed in 45-milliliter (mL), 90-mL, and 240-mL container sizes. The 45-mL and 90-mL container sizes of sodium phosphates oral solution are often recommended and prescribed by physicians for bowel cleansing prior to surgery and diagnostic procedures of the colon. Sodium phosphates oral solution (adult dose 20 mL to 45 mL) is also used as an over-the-counter (OTC) laxative for the relief of occasional constipation. Accidental overdosing and deaths have occurred because the 240-mL container was mistakenly used instead of the 45-mL or 90-mL container. The Food and Drug Administration is limiting the amount of sodium phosphates oral solution to not more than 90 mL (3 ounces (oz)) per OTC container because of the serious health risks associated with the ingestion of larger than intended doses of this product. Further, because an overdose of either oral or rectal enema sodium phosphates can cause an electrolyte imbalance, additional warning and direction statements are required for the safe use of any OTC laxative drug product containing sodium phosphates.

(b) Any OTC drug product for laxative or bowel cleansing use containing sodium phosphates as an active ingredient when marketed as described in paragraph (a) of this section is misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless packaged and labeled as follows:

(1) Package size limitation for sodium phosphates oral solution: Container shall not contain more than 90 mL (3 oz).

(2) Warnings. The following sentences shall appear in boldface type as the first statement under the heading ''Warnings.''

(i) Oral dosage forms. ''Taking more than the recommended dose in 24 hours can be harmful.''

(ii) Rectal enema dosage forms. ''Using more than one enema in 24 hours can be harmful.''

(3) Directions—(i) The labeling of all orally or rectally administered OTC drug products containing sodium phosphates shall contain the following directions in boldface type immediately preceding the dosage information: ''Do not'' (''take'' or ''use'') ''more unless directed by a doctor. See Warnings.''

(ii) For products containing dibasic sodium phosphate/monobasic sodium phosphate identified in § 334.16(d) marketed as a solution. Adults and children 12 years of age and over: Oral dosage is dibasic sodium phosphate 3.42 to 7.56 grams (g) and monobasic sodium phosphate 9.1 to 20.2 g (20 to 45 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. ''Do not take more than

45 mL (9 teaspoonfuls or 3 tablespoonfuls) in a 24-hour period.'' Children 10 and 11 years of age: Oral dosage is dibasic sodium phosphate 1.71 to 3.78 g and monobasic sodium phosphate 4.5 to 10.1 g (10 to 20 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. ''Do not take more than 20 mL (4 teaspoonfuls) in a 24-hour period.'' Children 5 to 9 years of age: Oral dosage is dibasic sodium phosphate 0.86 to 1.89 g and monobasic sodium phosphate 2.2 to 5.05 g (5 to 10 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. ''Do not take more than 10 mL (2 teaspoonfuls) in a 24-hour period.'' Children under 5 years of age: ask a doctor.

(c) After June 22, 1998, for package size limitation and September 18, 1998, for labeling in accord with paragraph (b) of this section, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce, or any such drug product that is repackaged or relabeled after these dates regardless of the date the product was manufactured, initially introduced, or initially delivered for introduction into interstate commerce, that is not in compliance with this section is subject to regulatory action.

[63 FR 27843, May 21, 1998]

§ 201.308 Ipecac syrup; warnings and directions for use for over-the-counter sale.

(a) It is estimated that each year about 500,000 accidental poisonings occur in the United States and result in approximately 1,500 deaths, of which over 400 are children. In the emergency treatment of these poisonings, ipecac syrup is considered the emetic of choice. The immediate availability of this drug for use in such situations is critical, since rapid treatment may be the difference between life and death. The restriction of this drug to prescription sale limits its availability in emergencies. On the other hand, it is the consensus of informed medical opinion that ipecac syrup should be used only under medical supervision in the emergency treatment of poisonings. In view of these facts, the question of whether ipecac syrup labeled as an emergency treatment for use in poisonings should be available over the counter has been controversial.

(b) In connection with its study of this problem, the Food and Drug Administration has obtained the views of medical authorities. It is the unanimous recommendation of the American Academy of Pediatrics, the American Association of Poison Control Centers, the American Medical Association, and the Medical Advisory Board of the Food and Drug Administration that ipecac syrup in 1 fluid ounce containers be permitted to be sold without prescription so that it will be readily available in the household for emergency treatment of poisonings, under medical supervision, and that the drug be appropriately packaged and labeled for this purpose.

(c) In view of the above recommendations, the Commissioner of Food and Drugs has determined that it is in the interest of the public health for ipecac syrup to be available for sale without prescription, provided that it is packaged in a quantity of 1 fluid ounce (30 milliliters), and its label bears, in addition to other required label information, the following, in a prominent and conspicuous manner:

(1) A statement conspicuously boxed and in red letters, to the effect: ''For emergency use to cause vomiting in poisoning. Before using, call physician, the Poison Control Center, or hospital emergency room immediately for advice.''

(2) A warning to the effect: ''Warning—Keep out of reach of children. Do not use in unconscious persons. Ordinarily, this drug should not be used if strychnine, corrosives such as alkalies (lye) and strong acids, or petroleum distillates such as kerosine, gasoline, coal oil, fuel oil, paint thinner, or cleaning fluid have been ingested.''

(3) Usual dosage: 1 tablespoon (15 milliliters) in persons over 1 year of age.

§ 201.309 Acetophenetidin (phenacetin)-containing preparations; necessary warning statement.

(a) In 1961, the Food and Drug Administration, pursuant to its statutory responsibility for the safety and effectiveness of drugs shipped in interstate

commerce, began an active investigation of reports of possible toxic effects and renal damage due to misuse of the drug acetophenetidin. This study led to the decision that there was probable cause to conclude that misuse and prolonged use of the drug were in fact responsible for kidney lesions and disease. The Commissioner of Food and Drugs, in December 1963, appointed an ad hoc Advisory Committee of Inquiry on Possible Nephrotoxicity Associated With the Abuse of Acetophenetidin (Phenacetin)-Containing Preparations. This committee, composed of scientists in the fields of pharmacology and medicine, on April 23, 1964, submitted its findings and conclusions in the matter and recommended that all acetophenetidin (phenacetin)-containing preparations bear a warning as provided in section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act.

(b) On the basis of the studies made by the Food and Drug Administration and the report of the Advisory Committee, the Commissioner of Food and Drugs has concluded that it is necessary for the protection of users that the label and labeling of all acetophenetidin (phenacetin)-containing preparations bear a warning statement to the following effect: ''Warning—This medication may damage the kidneys when used in large amounts or for a long period of time. Do not take more than the recommended dosage, nor take regularly for longer than 10 days without consulting your physician.''

§ 201.310 Phenindione; labeling of drug preparations intended for use by man.

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that phenindione, a synthetic anticoagulant drug, has caused a number of cases of agranulocytosis (with two fatalities). There are also reports implicating the drug in cases of hepatitis and hypersensitivity reactions. In view of the potentially serious effects found to be associated with preparations of this drug intended for use by man, the Commissioner of Food and Drugs will regard such preparations as misbranded within the meaning of section 502(f) (1) and (2) of the Federal Food, Drug, and Cosmetic Act, unless the label and labeling on or within the package from which the drug is to be dispensed, and any other labeling furnishing or purporting to furnish information for use of the drug, bear a conspicuous warning statement to the following effect: ''Warning: Agranulocytosis and hepatitis have been associated with the use of phenindione. Patients should be instructed to report promptly prodromal symptoms such as marked fatigue, chill, fever, and sore throat. Periodic blood studies and liver function tests should be performed. Use of the drug should be discontinued if leukopenia occurs or if evidence of hypersensitivity, such as dermatitis or fever, appears.''

(b) Regulatory action may be initiated with respect to preparations of phenindione intended for use by man found within the jurisdiction of the act on or after November 25, 1961, unless such preparations are labeled in accordance with paragraph (a) of this section.

§ 201.311 [Reserved]

§ 201.312 Magnesium sulfate heptahydrate; label declaration on drug products.

Magnesium sulfate heptahydrate should be listed on the label of a drug product as epsom salt, which is its common or usual name.

§ 201.313 Estradiol labeling.

The article presently recognized in The National Formulary under the heading ''Estradiol'' and which is said to be ''17-cis-beta estradiol'' is the same substance formerly recognized in the United States Pharmacopeia under the designation ''Alpha Estradiol.'' The substance should no longer be referred to in drug labeling as ''Alpha Estradiol.'' The Food and Drug Administration would not object to label references to the article as simply ''Estradiol''; nor would it object if the label of a preparation containing this substance referred to the presence of ''Estradiol (formerly known as Alpha Estradiol).''

§ 201.314 Labeling of drug preparations containing salicylates.

(a) The label of any oral drug preparation intended for sale without prescription and which contains any salicylate ingredient (including aspirin, salicylamide, other salicylates, and combinations) must conspicuously bear, on a clearly contrasting background, the warning statement: ''Keep out of reach of children [highlighted in bold type]. In case of overdose, get medical help or contact a Poison Control Center right away,'' or ''Keep out of reach of children [highlighted in bold type],'' except that if the article is an aspirin preparation, it shall bear the first of these warning statements. Such a warning statement is required for compliance with section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act and is intended to guard against accidental poisonings. Safety closures that prevent access to the drug by young children are also recommended to guard against accidental poisonings.

(b) Effervescent preparations and preparations containing para-aminosalicylate as the only salicylate ingredient are exempted from this labeling requirement.

(c) Aspirin tablets sold as such and containing no other active ingredients, except tablets which cannot be readily subdivided into a child's dose because of their coating or size, should always bear dosage directions for each age group down to 3 years of age, with a statement such as ''For children under 3 years of age, consult your physician.'' It is recommended that:

(1) Aspirin tablets especially made for pediatric use be produced only in 1¼-grain size to reduce the hazard of errors in dosage;

(2) By June 1, 1967, manufacturers and distributors of 1¼-grain size aspirin tablets discontinue the distribution of such tablets in retail containers containing more than 36 tablets, to reduce the hazard of accidental poisoning;

(3) The flavoring of 5-grain aspirin tablets or other ''adult aspirin tablets'' be discontinued; and

(4) Labeling giving undue emphasis to the pleasant flavor of flavored aspirin tablets be discontinued.

(d) Salicylate preparations other than aspirin tablets sold as such may, at the option of the distributor, be labeled for use by adults only. If their labeling and advertising clearly offer them for administration to adults only.

(e)(1) It is the obligation of the distributor who labels a salicylate preparation for administration to children to make certain that the article is suitable for such use and labeled with adequate directions for use in the age group for which it is offered, but in no case should such an article bear directions for use in children under 3 years of age. If the directions provide for administration to children as young as 3 years of age, the label should bear the statement, ''For children under 3 years of age consult your physician.'' However, if the directions provide for administration to children only of an age greater than 3 years (for example, the dosage instructions provide for administration of the article to children only down to age 6), the label should bear a statement such as, ''For younger children consult your physician.''

(2) A statement such as, ''For children under 3 years of age consult your physician'' or ''For younger children consult your physician'' is not required on the label of an article clearly offered for administration to adults only.

(f) If the labeling or advertising of a salicylate preparation offers it for use in arthritis or rheumatism, the label and labeling should clearly state that the beneficial effects claimed are limited to: ''For the temporary relief of minor aches and pains of arthritis and rheumatism.'' The qualifying phrase ''for the temporary relief of minor aches and pains'' should appear with the same degree of prominence and conspicuousness as the phrase ''arthritis and rheumatism''. The label and labeling should bear in juxtaposition with such directions for use conspicuous warning statements to the effect: ''Caution: If pain persists for more than 10 days, or redness is present, or in conditions affecting children under 12 years of age, consult a physician immediately.'' The salicylate dosage should not exceed 60 grains in a 24-hour period or 10 grains in a 4-hour period. If the article contains other analgesics, the salicylate dosage should be appropriately reduced.

(g)(1) The label of any drug containing more than 5 percent methyl salicylate (wintergreen oil) should bear a conspicuous warning such as: ''Do not use otherwise than as directed.'' These drug products must also include the ''Keep out of reach of children'' warning and the accidental ingestion warning as required in § 330.1(g) of this chapter.

(2) If the preparation is a counterirritant or rubefacient, it should also bear a caution such as, ''Caution: Discontinue use if excessive irritation of the skin develops. Avoid getting into the eyes or on mucous membranes.'' (See also § 201.303.)

(h)(1) The labeling of orally or rectally administered over-the-counter drug products containing aspirin or nonaspirin salicylates as active ingredients subject to this paragraph is required to prominently bear the following warning: ''Reye's syndrome [subheading in bold type]: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness.''

(2) This warning statement shall appear on the immediate container labeling. In cases where the immediate container is not the retail package, the retail package also must bear the warning statement. In addition, the warning statement shall appear on any labeling that contains warnings and, in such cases, the warning statement shall be the first warning statement under the heading ''Warnings.''

(3) Over-the-counter drug products subject to this paragraph and labeled solely for use by children (pediatric products) shall not recommend the product for use in treating flu or chicken pox.

(4) Any product subject to paragraphs (h)(1), (h)(2), and (h)(3) of this section that is not labeled as required by these paragraphs and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(i) Compliance by October 18, 2004, for OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under a new drug application or abbreviated new drug application.

(ii) Compliance by April 19, 2004, for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales greater than $25,000.

(iii) Compliance by April 18, 2005, for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales less than $25,000.

(iv) Compliance dates for all other OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under an OTC drug monograph (for internal analgesic, antipyretic, and antirheumatic drug products, or for menstrual drug products) will be established when the final monographs for those products are published in a future issue of the FEDERAL REGISTER. In the interim, these products should continue to be labeled with the previous Reye's syndrome warning that appears in paragraph (h)(1) of this section.

[40 FR 13998, Mar. 27, 1985, as amended at 51 FR 8182, Mar. 7, 1986; 53 FR 21637, June 9, 1988; 53 FR 24830, June 30, 1988; 64 FR 13291, Mar. 17, 1999; 65 FR 8, Jan. 3, 2000; 68 FR 18869, Apr. 17, 2003]

§ 201.315 Over-the-counter drugs for minor sore throats; suggested warning.

The Food and Drug Administration has studied the problem of the labeling of lozenges or troches containing a local anesthetic, chewing gum containing aspirin, various mouth washes and gargles and other articles sold over the counter for the relief of minor irritations of the mouth or throat. It will not object to the labeling of suitable articles of this type ''For the temporary relief of minor sore throats'', provided this is immediately followed in the labeling with a warning statement in prominent type essentially as

follows: ''Warning—Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by physician.''

§ 201.316 Drugs with thyroid hormone activity for human use; required warning.

(a) Drugs with thyroid hormone activity have been promoted for, and continue to be dispensed and prescribed for, use in the treatment of obesity, although their safety and effectiveness for that use have never been established.

(b) Drugs for human use with thyroid hormone activity are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following boxed warning at the beginning of the ''Warnings'' section:

> Drugs with thyroid hormone activity, alone or together with other therapeutic agents, have been used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

[43 FR 22009, May 23, 1978]

§ 201.317 Digitalis and related cardiotonic drugs for human use in oral dosage forms; required warning.

(a) Digitalis and related cardiotonic drugs for human use in oral dosage forms have been promoted for, and continue to be dispensed and prescribed for, use in the treatment of obesity, although their safety and effectiveness for that use have never been established.

(b) Digitalis and related cardiotonic drugs for human use in oral dosage forms are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following boxed warning at the beginning of the ''Warnings'' section:

> Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

(c) This section does not apply to digoxin products for oral use, which shall be labeled according to the requirements of § 310.500 of this chapter.

[43 FR 22009, May 23, 1978]

§ 201.319 Water-soluble gums, hydrophilic gums, and hydrophilic mucilloids (including, but not limited to agar, alginic acid, calcium polycarbophil, carboxymethylcellulose sodium, carrageenan, chondrus, glucomannan ((B-1,4 linked) polymannose acetate), guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil tragacanth, and xanthan gum) as active ingredients; required warnings and directions.

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that esophageal obstruction and asphyxiation have been associated with the ingestion of water-soluble gums, hydrophilic gums, and hydrophilic mucilloids including, but not limited to, agar, alginic acid, calcium polycarbophil, carboxymethylcellulose sodium, carrageenan, chondrus, glucomannan ((B–1,4 linked) polymannose acetate), guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil, tragacanth, and xanthan gum. Esophageal obstruction and asphyxiation due to orally-administered drug products containing water-soluble gums, hydrophilic gums, and hydrophilic mucilloids as active ingredients are significant health risks when these products are taken without adequate fluid or when they are used

by individuals with esophageal narrowing or dysfunction, or with difficulty in swallowing. Additional labeling is needed for the safe and effective use of any OTC drug product for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient when marketed in a dry or incompletely hydrated form to include, but not limited to, the following dosage forms: Capsules, granules, powders, tablets, and wafers. Granular dosage forms containing psyllium are not generally recognized as safe and effective as OTC laxatives (see § 310.545(a)(12)(i)(B) of this chapter) and may not be marketed without an approved new drug application because the warnings and directions in paragraph (b) of this section have been found inadequate for these products.

(b) Any drug products for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient in an oral dosage form when marketed in a dry or incompletely hydrated form as described in paragraph (a) of this section are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following warnings (under the subheading ''Choking'') and directions:

''‘Choking’ [highlighted in bold type]: Taking this product without adequate fluid may cause it to swell and block your throat or esophagus and may cause choking. Do not take this product if you have difficulty in swallowing. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention;'' and

''‘Directions’ [highlighted in bold type]:'' (Select one of the following, as appropriate: ''Take'' or ''Mix'') ''this product (child or adult dose) with at least 8 ounces (a full glass) of water or other fluid. Taking this product without enough liquid may cause choking. See choking warning.''

(c) After February 28, 1994, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce, or any such drug product that is repackaged or relabeled after this date regardless of the date the product was manufactured, initially introduced, or initially delivered for introduction into interstate commerce, that is not in compliance with this section is subject to regulatory action.

[58 FR 45201, Aug. 26, 1993, as amended at 64 FR 13292, Mar. 17, 1999; 72 FR 14674, Mar. 29, 2007]

§ 201.320 Warning statements for drug products containing or manufactured with chlorofluorocarbons or other ozone-depleting substances.

(a)(1) All drug products containing or manufactured with chlorofluorocarbons, halons, carbon tetrachloride, methyl chloride, or any other class I substance designated by the Environmental Protection Agency (EPA) shall, except as provided in paragraph (b) or (c) of this section, bear the following warning statement:

Warning: Contains [or Manufactured with, if applicable] [*insert name of substance*], a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

(2) The warning statement shall be clearly legible and conspicuous on the product, its immediate container, its outer packaging, or other labeling in accordance with the requirements of 40 CFR part 82 and appear with such prominence and conspicuousness as to render it likely to be read and understood by consumers under normal conditions of purchase.

(b)(1) For prescription drug products for human use, the following alternative warning statement may be used:

NOTE: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's) [or name of other class I substance, if applicable]:

This product contains [or is manufactured with, if applicable] [*insert name of substance*], a substance which harms the environment by destroying ozone in the upper atmosphere.

Your physician has determined that this product is likely to help your personal health. USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN. If you have any questions about alternatives, consult with your physician.

(2) The warning statement shall be clearly legible and conspicuous on the product, its immediate container, its outer packaging, or other labeling in accordance with the requirements of 40 CFR part 82 and appear with such prominence and conspicuousness as to render it likely to be read and understood by consumers under normal conditions of purchase.

(3) If the warning statement in paragraph (b)(1) of this section is used, the following warning statement must be placed on the package labeling intended to be read by the physician (physician package insert) after the ''How supplied'' section, which describes special handling and storage conditions on the physician labeling:

NOTE: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's) [or name of other class I substance, if applicable]:

WARNING: Contains [or Manufactured with, if applicable] [*insert name of substance*], a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the information for the patient [or patient information leaflet, if applicable] of this product under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

(c)(1) For over-the-counter drug products for human use, the following alternative warning statement may be used:

NOTE: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's) [or other class I substance, if applicable]:

WARNING: Contains [or Manufactured with, if applicable] [*insert name of substance*], a substance which harms public health and environment by destroying ozone in the upper atmosphere.

CONSULT WITH YOUR PHYSICIAN OR HEALTH PROFESSIONAL IF YOU HAVE ANY QUESTION ABOUT THE USE OF THIS PRODUCT.

(2) The warning statement shall be clearly legible and conspicuous on the product, its immediate container, its outer packaging, or other labeling in accordance with the requirements of 40 CFR part 82 and appear with such prominence and conspicuousness as to render it likely to be read and understood by consumers under normal conditions of purchase.

(d) This section does not replace or relieve a person from any requirements imposed under 40 CFR part 82.

[61 FR 20100, May 3, 1996]

§ 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition.

(a) The aluminum content of large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter (μg/L).

(b) The package insert of LVP's used in TPN therapy must state that the drug product contains no more than 25 μg/L of aluminum. This information must be contained in the ''Precautions'' section of the labeling of all large volume parenterals used in TPN therapy.

(c) Except as provided in paragraph (d) of this section, the maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs) used in the preparation of TPN solutions. The aluminum content must be stated as follows: ''Contains no more than ___ μg/L of aluminum.'' The immediate container label of all SVP's and PBP's that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: ''When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than ___ μg/L.'' This maximum level of aluminum must be stated as the highest of:

(1) The highest level for the batches produced during the last 3 years;

(2) The highest level for the latest five batches, or

(3) The maximum historical level, but only until completion of production of the first five batches after July 26, 2004.

(d) If the maximum level of aluminum is 25 μg/L or less, instead of stating the exact amount of aluminum

as required in paragraph (c) of this section, the immediate container label may state: ''Contains no more than 25 μg/L of aluminum.'' If the SVP or PBP is a lyophilized powder, the immediate container label may state: ''When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 μg/L''.

(e) The package insert for all LVP's, all SVP's, and PBP's used in TPN must contain a warning statement. This warning must be contained in the ''Warnings'' section of the labeling. The warning must state:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 μg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

(f) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under § 314.60 or § 314.96 of this chapter.

[65 FR 4110, Jan. 26, 2000, as amended at 67 FR 70691, Nov. 26, 2002; 68 FR 32981, June 3, 2003]

§ 201.325 Over-the-counter drugs for vaginal contraceptive and spermicide use containing nonoxynol 9 as the active ingredient; required warnings and labeling information.

(a) Studies indicate that use of vaginal contraceptive drug products containing nonoxynol 9 does not protect against infection from the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), or against the transmission of other sexually transmitted diseases (STDs). Studies also indicate that use of vaginal contraceptive drug products containing nonoxynol 9 can increase vaginal irritation, such as the disruption of the vaginal epithelium, and also can cause epithelial disruption when used in the rectum. These effects may increase the risk of transmission of the AIDS virus (HIV) from an infected partner. Therefore, consumers should be warned that these products do not protect against the transmission of the AIDS virus (HIV) or other STDs, that use of these products can increase vaginal and rectal irritation, which may increase the risk of getting the AIDS virus (HIV) from an HIV infected partner, and that the products are not for rectal use. Consumers should also be warned that these products should not be used by persons who have HIV/AIDS or are at high risk for HIV/AIDS.

(b) The labeling of OTC vaginal contraceptive and spermicide drug products containing nonoxynol 9 as the active ingredient, whether subject to the ongoing OTC drug review or an approved drug application, must contain the following warnings under the heading ''Warnings,'' in accordance with 21 CFR 201.66.

(1) ''[bullet] For vaginal use only [bullet] Not for rectal (anal) use'' [both warnings in bold type].

(2) ''Sexually transmitted diseases (STDs) alert [in bold type]: This product does not [word ''not'' in bold type] protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner''.

(3) ''Do not use'' [in bold type] if you or your sex partner has HIV/AIDS. If you do not know if you or your sex

partner is infected, choose another form of birth control''.

(4) ''When using this product [in bold type] [optional, bullet] you may get vaginal irritation (burning, itching, or a rash)''.

(5) ''Stop use and ask a doctor if [in bold type] [optional, bullet] you or your partner get burning, itching, a rash, or other irritation of the vagina or penis''.

(c) The labeling of this product states under the ''Other information'' section of the Drug Facts labeling in accordance with § 201.66(c)(7), ''[bullet] when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS.

(d) The labeling of this product includes the following statements either on the outside container or wrapper of the retail package, under the ''Other information'' section of the Drug Facts labeling in accordance with § 201.66(c)(7), or in a package insert:

(1) ''[bullet] studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This irritation may increase the risk of getting HIV/AIDS from an infected partner''.

(2) ''[bullet] you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors''.

(3) ''[bullet] use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors''.

(4) ''[bullet] ask a health professional if you have questions about your best birth control and STD prevention methods''.

(e) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after June 19, 2008, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352), is a new drug under section 505 of the act (21 U.S.C. 355), and is subject to regulatory action.

[72 FR 71785, Dec. 19, 2007]

§ 201.326 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.

(a) *Labeling*. The labeling for all over-the-counter (OTC) drug products containing any internal analgesic/antipyretic active ingredients (including, but not limited to, acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate) alone or in combination must bear the following labeling in accordance with §§ 201.60, 201.61, and 201.66.

(1) *Acetaminophen*—(i) *Statement of identity*. The statement of identity appears in accord with §§ 201.61 and 299.4 of this chapter. The ingredient name ''acetaminophen'' must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(A) At least one-quarter as large as the size of the most prominent printed matter on the principal display panel (PDP), or

(B) At least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2). The presence of acetaminophen must appear as part of the established name of the drug, as defined in § 299.4 of this chapter. Combination products containing acetaminophen and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name ''acetaminophen'' and the name(s) of the other active ingredient(s) in the product on the PDP in accord with this paragraph. Only the name ''acetaminophen'' must appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(ii) *Active Ingredient and Purpose Headings*. The information required under § 201.66(c)(2) and (c)(3) of this chapter must be included under these headings. The information under these headings, but not the headings, may appear highlighted.

(iii) *For products labeled for adults only*. The labeling of the product states the following warnings under the heading ''Warnings'':

(A) The liver warning states ''Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if you take [bullet] more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: 'for this product'] [bullet] with other drugs containing acetaminophen [bullet] 3 or more alcoholic drinks every day while using this product''. This ''Liver'' warning must be the first warning under the ''Warnings'' heading. For products that contain both acetaminophen and aspirin, this ''Liver'' warning must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B) and before the ''Stomach bleeding'' warning in paragraph (a)(2)(iii)(A) of this section. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning does not need to be included on each blister unit.

(B) ''Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.''

(C) ''Ask a doctor before use if you have liver disease''.

(D) ''Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin'' except on the labeling of combination products that contain acetaminophen and NSAID(s).

(iv) *For products labeled only for children under 12 years of age*.

(A) *Warnings*. The labeling of the product states the following warnings under the heading ''Warnings'':

(*1*) The liver warning states ''Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if your child takes [bullet] more than 5 doses in 24 hours, which is the maximum daily amount [optional: 'for this product'] [bullet] with other drugs containing acetaminophen''. This ''Liver'' warning must be the first warning under the ''Warnings'' heading. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(*2*) ''Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.''

(*3*) ''Ask a doctor before use if your child has liver disease''.

(*4*) ''Ask a doctor or pharmacist before use if your child is taking the blood thinning drug warfarin'' except on the labeling of combination products that contain acetaminophen and NSAID(s).

(B) *Directions*. The labeling of the product contains the following information under the heading ''Directions'': ''this product does not contain directions or complete warnings for adult use'' [in bold type].

(v) *For products labeled for adults and children under 12 years of age*. The labeling of the product states all of the warnings in paragraphs (a)(1)(iii)(A), (a)(1)(iii)(B), and (a)(1)(iii)(C) of this section with the following modifications:

(A) The liver warning states ''Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if [bullet] adult takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: 'for this product'] [bullet] child takes more than 5 doses in 24 hours [bullet] taken with other drugs containing acetaminophen [bullet] adult has 3 or more alcoholic drinks everyday while using this product.'' If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister

card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) ''Ask a doctor before use if the user has liver disease.''

(C) ''Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.''

(D) ''Ask a doctor or pharmacist before use if the user is taking the blood thinning drug warfarin'' except on the labeling of combination products that contain acetaminophen and NSAID(s).

(2) *Nonsteroidal anti-inflammatory analgesic/antipyretic active ingredients—including, but not limited to, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.*

(i) *Statement of identity.* The statement of identity appears in accord with §§ 201.61 and 299.4 of this chapter. The word ''(NSAID)'' must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(A) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or

(B) At least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2). The word ''(NSAID)'' must appear as part of the established name of the drug, as defined in § 299.4 of this chapter, or after the general pharmacological (principal intended) action of the NSAID ingredient. Combination products containing an NSAID and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name of the NSAID ingredient and the word ''(NSAID)'' in accordance with this paragraph, and the name(s) of the other active ingredient(s) in the product on the PDP. Only the word ''(NSAID)'' needs to appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(ii) *Active Ingredient and Purpose Headings.* The information required under § 201.66(c)(2) and (c)(3) of this chapter must be included under these headings. The active ingredient(s) section of the product's labeling, as defined in § 201.66(c)(2), contains the term ''(NSAID*)'' after the NSAID active ingredient with an asterisk statement at the end of the active ingredient(s) section that defines the term ''NSAID'' and states ''*nonsteroidal anti-inflammatory drug.'' The information under these headings may appear highlighted. However, the headings ''Active Ingredient'' and ''Purpose'' may not appear highlighted.

(iii) *For products labeled for adults only.* The labeling of the product states the following warnings under the heading ''Warnings'':

(A) The stomach bleeding warning states ''Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you [bullet] are age 60 or older [bullet] have had stomach ulcers or bleeding problems [bullet] take a blood thinning (anticoagulant) or steroid drug [bullet] take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] have 3 or more alcoholic drinks every day while using this product [bullet] take more or for a longer time than directed''. This ''Stomach bleeding'' warning must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). For products that contain both acetaminophen and aspirin, the acetaminophen ''Liver'' warning in paragraph (a)(1)(iii) of this section must appear before the ''Stomach bleeding'' warning in this paragraph. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) ''Ask a doctor before use if [bullet] stomach bleeding warning applies to you [bullet] you have a history of stomach problems, such as heartburn

[bullet] you have high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] you are taking a diuretic''.

(C) ''Stop use and ask a doctor if [bullet] you experience any of the following signs of stomach bleeding:'' [add the following as second level of statements: ''[bullet] feel faint [bullet] vomit blood [bullet] have bloody or black stools [bullet] have stomach pain that does not get better''].

(iv) *For products labeled only for children under 12 years of age.*

(A) *Warnings.* The labeling of the product states the following warnings under the heading ''Warnings'':

(*1*) The stomach bleeding warning states ''Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if your child [bullet] has had stomach ulcers or bleeding problems [bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] takes more or for a longer time than directed''. The ''Stomach bleeding'' warning must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(*2*) ''Ask a doctor before use if [bullet] stomach bleeding warning applies to your child [bullet] child has a history of stomach problems, such as heartburn [bullet] child has not been drinking fluids [bullet] child has lost a lot of fluid due to vomiting or diarrhea [bullet] child has high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] child is taking a diuretic''.

(*3*) ''Stop use and ask a doctor if [bullet] child experiences any of the following signs of stomach bleeding:'' [add the following as second level of statements: [bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better''].

(B) *Directions.* The labeling of the product contains the following information under the heading ''Directions'': ''this product does not contain directions or complete warnings for adult use'' [in bold type].

(v) *For products labeled for adults and children under 12 years of age.* The labeling of the product states all of the warnings in paragraphs (a)(2)(iii)(A) through (a)(2)(iii)(C) of this section with the following modifications:

(A) The Stomach bleeding warning states ''Stomach bleeding warning [heading in bold type]: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if the user [bullet] has had stomach ulcers or bleeding problems [bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) [bullet] takes more or for a longer time than directed [bullet] is age 60 or older [bullet] has 3 or more alcoholic drinks everyday while using this product''. The ''Stomach bleeding'' warning must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers. If the immediate container is a blister card, the warning must appear on the blister card and remain intact and readable when drug product is removed from the blister card. The warning is not required to be included on each blister unit.

(B) The labeling states ''Ask a doctor before use if [bullet] stomach bleeding warning applies to user [bullet] user has history of stomach problems, such as heartburn [bullet] user has high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] user takes a diuretic [bullet] user has not been drinking fluids [bullet] user has lost a lot of fluid due to vomiting or diarrhea''.

(C) The labeling states ''Stop use and ask a doctor if [bullet] user experiences any of the following signs of stomach bleeding:'' [add the following as second level of statements: [bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better'']].

(b) *New warnings information statement*. The labeling of any drug product subject to this section that is initially introduced or initially delivered for introduction into interstate commerce before or on April 29, 2010, must bear on its PDP, as defined in § 201.60, the statement ''See new warnings information''. This statement must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or

(2) At least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2). The new warnings information statement must remain on the PDP of the drug product for at least 1 year from the date the product is initially introduced into interstate commerce.

(c) *Requirements to supplement approved application*. Holders of approved applications for OTC drug products that contain internal analgesic/antipyretic active ingredients that are subject to the requirements of paragraph (a) of this section must submit supplements under § 314.70(c) of this chapter to include the required information in the product's labeling. Such labeling may be put into use without advance approval of FDA provided it includes at least the exact information included in paragraph (a) of this section.

[74 FR 19407, Apr. 29, 2009, as amended at 74 FR 31180, June 30, 2009; 74 FR 61514, Nov. 25, 2009]

§ 201.327 Over-the-counter sunscreen drug products; required labeling based on effectiveness testing.

The following provisions apply to sunscreen products containing aminobenzoic acid, avobenzone, cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, oxybenzone, padimate O, sulisobenzone, titanium dioxide, trolamine salicylate, or zinc oxide, alone or in combination. The provisions do not apply to sunscreen products marketed under approved new drug applications or abbreviated new drug applications.

(a) *Principal display panel*. In addition to the statement of identity in paragraph (b) of this section, the following labeling shall be prominently placed on the principal display panel:

(1) *Effectiveness claim*—(i) *For products that pass the broad spectrum test in paragraph (j) of this section*. (A) The labeling states ''Broad Spectrum SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section]''.

(B) *Prominence*. The Broad Spectrum SPF statement shall appear as continuous text with no intervening text or graphic. The entire text shall appear in the same font style, size, and color with the same background color.

(ii) *For sunscreen products that do not pass the broad spectrum test in paragraph (j) of this section*. The labeling states ''SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section]''. The entire text shall appear in the same font style, size, and color with the same background color.

(2) *Water resistance statements*—(i) *For products that provide 40 minutes of water resistance according to the test in paragraph (i)(7)(i) of this section*. The labeling states ''Water Resistant (40 minutes)''.

(ii) *For products that provide 80 minutes of water resistance according to the test in paragraph (i)(7)(ii) of this section*. The labeling states ''Water Resistant (80 minutes)''.

(b) *Statement of identity*. The labeling of the product contains the established name of the drug, if any, and identifies the drug as a ''sunscreen.''

(c) *Indications*. The labeling of the product states, under the heading ''Uses,'' the phrases listed in this paragraph (c), as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in this paragraph

(c), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) relating to misbranding and the prohibition in section 301(d) of the FD&C Act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act.

(1) For all sunscreen products, the following indication statement must be included under the heading ''Uses'': ''[Bullet] helps prevent sunburn''. See § 201.66(b)(4) of this chapter for definition of bullet.

(2) For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in paragraphs (i) and (j) of this section, the labeling may include the following statement in addition to the indication in § 201.327(c)(1): ''[Bullet] if used as directed with other sun protection measures (see Directions [in bold italic font]), decreases the risk of skin cancer and early skin aging caused by the sun''.

(3) Any labeling or promotional materials that suggest or imply that the use, alone, of any sunscreen reduces the risk of or prevents skin cancer or early skin aging will cause the product to be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).

(d) *Warnings.* The labeling of the product contains the following warnings under the heading ''Warnings''.

(1) *For all sunscreen products.* (i) The labeling states ''Do not use [bullet] on damaged or broken skin''.

(ii) The labeling states ''When using this product [bullet] keep out of eyes. Rinse with water to remove.''

(iii) The labeling states ''Stop use and ask a doctor if [bullet] rash occurs''.

(2) *For sunscreen products that are broad spectrum with SPF values of at least 2 but less than 15 according to the SPF test in paragraph (i) of this section or that do not pass the broad spectrum test in paragraph (j) of this section.* The first statement under the heading ''Warnings'' states ''Skin Cancer/Skin Aging Alert [in bold font]; Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging.''

(e) *Directions.* The labeling of the product contains the following statements, as appropriate, under the heading ''Directions.'' More detailed directions applicable to a particular product formulation may also be included.

(1) *For all sunscreen products.* (i) As an option, the labeling may state ''For sunscreen use:''.

(ii) The labeling states ''[bullet] apply [select one of the following: 'Liberally' or 'generously'] [and, as an option: 'And evenly'] 15 minutes before sun exposure''.

(iii) As an option, the labeling may state ''[bullet] apply to all skin exposed to the sun''.

(iv) The labeling states ''[bullet] children under 6 months of age: Ask a doctor''.

(2) *For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in paragraphs (i) and (j) of this section.* The labeling states ''[bullet] Sun Protection Measures. [in bold font] Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF value of 15 or higher and other sun protection measures including: [Bullet] limit time in the sun, especially from 10 a.m.–2 p.m. [bullet] wear long-sleeved shirts, pants, hats, and sunglasses''.

(3) *For products that satisfy the water resistance test in paragraph (i)(7) of this section.* The labeling states ''[bullet] reapply: [Bullet] after [select one of the following determined by water resistance test: '40 minutes of' or '80 minutes of'] swimming or sweating [bullet] immediately after towel drying [bullet] at least every 2 hours''.

(4) *For products that do not satisfy the water resistance test in paragraph (i)(7) of this section.* The labeling states ''[bullet] reapply at least every 2 hours [bullet] use a water resistant sunscreen if swimming or sweating''.

(f) *Other information.* The labeling of the product contains the following statement under the heading ''Other information:'' ''[bullet] protect the product in this container from excessive heat and direct sun''.

(g) *False and misleading claims.* There are claims that would be false and/or misleading on sunscreen products. These claims include but are not limited to the following: ''Sunblock,'' ''sweatproof,'' and ''waterproof.'' These or similar claims will cause the product to be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).

(h) *Labeling of products containing a combination of sunscreen and skin protectant active ingredients.* Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. Labeling provisions in § 347.50(e) of this chapter shall not apply to these products.

(i) *SPF test procedure*—(1) *UV source (solar simulator).* (i) *Emission spectrum.* A single port or multiport solar simulator should be filtered so that it provides a continuous emission spectrum from 290 to 400 nanometers (nm) with a limit of 1,500 Watts per square meter (W/m^2) on total irradiance for all wavelengths between 250 and 1,400 nm.

(A) The solar simulator should have the following percentage of erythema-effective radiation in each specified range of wavelengths:

SOLAR SIMULATOR EMISSION SPECTRUM

Wavelength range (nm)	Percent erythemal contribution [1]
<290	<0.1
290–300	1.0–8.0
290–310	49.0–65.0
290–320	85.0–90.0
290–330	91.5–95.5
290–340	94.0–97.0
290–400	99.9–100.0

[1] Calculation of erythema action spectrum described in § 201.327(i)(1)(ii) of this section.

(B) In addition, UVA II (320–340 nm) irradiance should equal or exceed 20 percent of the total UV (290–400 nm) irradiance. UVA I (340–400 nm) irradiance should equal or exceed 60 percent of the total UV irradiance.

(ii) *Erythema action spectrum.* (A) Calculate the erythema action spectrum weighting factor (V_i) at each wavelength λ:

(*1*) $V_i(\lambda) = 1.0$ ($250 < \lambda \leq 298$ nm)

(*2*) $V_i(\lambda) = 10^{0.094 * (298-\lambda)}$ ($298 < \lambda \leq 328$ nm)

(*3*) $V_i(\lambda) = 10^{0.015 * (140-\lambda)}$ ($328 < \lambda \leq 400$ nm)

(B) Calculate the erythema-effective UV dose (E) delivered by a solar simulator as follows:

$$E = \sum_{250}^{400} V_i(\lambda) * I(\lambda) * t$$

Where $V_i(\lambda)$ = erythema action spectrum weighting factor at each wavelength λ
$I(\lambda)$ = irradiance (Watts per square meter) at each wavelength λ
t = exposure time (seconds)

Erythema-effective dose (E) is expressed as effective Joules per square meter (J/m^2-eff).

(C) The emission spectrum must be determined using a handheld radiometer with a response weighted to match the spectrum in ISO 17166 CIE S 007/E entitled ''Erythemal reference action spectrum and standard erythema dose,'' dated 1999 (First edition, 1999–12–15; corrected and reprinted 2000–11–15), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain a copy from the ISO Copyright Office, Case Postale 56, CH–1211, Geneva 20, Switzerland, telephone +41–22–749–01–11 or fax +41–22–74 -09–47. *http://www.iso.org.* You may inspect a copy at the Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993, call 301–796–2090, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www/archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.* The solar simulator output should be measured before and after each phototest or, at a minimum, at the beginning and end of each test day. This radiometer should be calibrated using side-by-side comparison with the spectroradiometer (using the weighting factors determined according to paragraph (i)(1)(ii)(A) of this section) at the time of the annual spectroradiometric measurement of the solar simulator as described in paragraph (i)(1)(iv) of this section.

(iii) *Operation.* A solar simulator should have no significant time-related fluctuations (within 20 percent) in radiation emissions after an appropriate

warm-up time and demonstrate good beam uniformity (within 20 percent) in the exposure plane. The delivered dose to the UV exposure site must be within 10 percent of the expected dose.

(iv) *Periodic measurement.* To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, the emission spectrum of the solar simulator should be measured at least annually with an appropriate and accurately calibrated spectroradiometer system (results should be traceable to the National Institute for Standards and Technology). In addition, the solar simulator must be recalibrated if there is any change in the lamp bulb or the optical filtering components (*i.e.*, filters, mirrors, lenses, collimating devices, or focusing devices). Daily solar simulator radiation intensity should be monitored with a broadband radiometer with a response weighted to match the erythema action spectrum in ISO 17166 CIE S 007/E entitled ''Erythemal reference action spectrum and standard erythema dose,'' which is incorporated by reference in paragraph (i)(1)(ii)(C) of this section. If a lamp must be replaced due to failure or aging during a phototest, broadband device readings consistent with those obtained for the original calibrated lamp will suffice until measurements can be performed with the spectroradiometer at the earliest possible opportunity.

(2) *SPF standard*—(i) *Preparation.* The SPF standard should be a formulation containing 7-percent padimate O and 3-percent oxybenzone.

COMPOSITION OF THE PADIMATE O/OXYBENZONE SPF STANDARD

Ingredients	Percent by weight
Part A:	
Lanolin	4.50
Cocoa butter	2.00
Glyceryl monostearate	3.00
Stearic acid	2.00
Padimate O	7.00
Oxybenzone	3.00
Part B:	
Purified water USP	71.60
Sorbitol solution	5.00
Triethanolamine, 99 percent	1.00
Methylparaben	0.30
Propylparaben	0.10
Part C:	
Benzyl alcohol	0.50
Part D:	
Purified water USP	QS [1]

[1] Quantity sufficient to make 100 grams.

Step 1. Add the ingredients of Part A into a suitable stainless steel kettle equipped with a propeller agitator. Mix at 77 to 82 °C until uniform.

Step 2. Add the water of Part B into a suitable stainless steel kettle equipped with a propeller agitator and begin mixing at 77 to 82 °C. Add the remaining ingredients of Part B and mix until uniform.

Step 3. Add the batch of Step 1 to the batch of Step 2 and mix at 77 to 82 °C until smooth and uniform. Slowly cool the batch to 49 to 54 °C.

Step 4. Add the benzyl alcohol of Part C to the batch of Step 3 at 49 to 54 °C. Mix until uniform. Continue to cool batch to 35 to 41 °C.

Step 5. Add sufficient water of Part D to the batch of Step 4 at 35 to 41 °C to obtain 100 grams of SPF standard. Mix until uniform. Cool batch to 27 to 32 °C.

(ii) *HPLC assay.* Use the following high performance liquid chromatography (HPLC) procedure to verify the concentrations of padimate O and oxybenzone in the SPF standard:

(A) *Instrumentation.* (*1*) Equilibrate a suitable liquid chromatograph to the following or equivalent conditions:

(*i*) Column	C–18, 250 millimeters (mm) length, 4.6 mm inner diameter (5 microns)
(*ii*) Mobile Phase.	85:15:0.5 methanol: water: acetic acid
(*iii*) Flow Rate.	1.5 milliliters (mL) per minute
(*iv*) Temperature.	Ambient
(*v*) Detector	UV spectrophotometer at 308 nanometers
(*vi*) Attenuation.	As needed

(*2*) Use HPLC grade reagents for mobile phase.

(B) *Preparation of the HPLC reference standard.* (*1*) Weigh 0.50 gram (g) of oxybenzone USP reference standard

into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(*2*) Weigh 0.50 g of padimate O USP reference standard into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(*3*) Pipet 3.0 mL of the oxybenzone solution and 7.0 mL of the padimate O solution into a 100-mL volumetric flask. Dilute to volume with isopropanol and mix well.

(C) *HPLC system suitability*. (*1*) Make three replicate 10-microliter injections of the HPLC reference standard (described in paragraph (i)(2)(ii)(B) of this section). The relative standard deviation in peak areas should not be more than 2.0 percent for either oxybenzone or padimate O.

(*2*) Calculate the resolution (R) between the oxybenzone and padimate O peaks from one chromatogram as follows:

$$R = \frac{2 * (to - tp)}{Wo + Wp}$$

Where t_o = retention time for oxybenzone
t_p = retention time for padimate O
W_o = oxybenzone peak width at baseline
W_p = padimate O peak width at baseline

If the resolution (R) is less than 3.0, adjust the mobile phase or replace the column.

(D) *SPF standard assay*—(*1*) The SPF standard is diluted to the same concentration as the HPLC reference standard according to the following steps:

(*i*) *Step 1*. Weigh 1.0 g of the SPF standard (described in paragraph (i)(2)(i) of this section) into a 50-mL volumetric flask.

(*ii*) *Step 2*. Add approximately 30 mL of isopropanol and heat with swirling until contents are evenly dispersed.

(*iii*) *Step 3*. Cool to room temperature (15 to 30 °C) and dilute to volume with isopropanol. Mix well.

(*iv*) *Step 4*. Pipet 5.0 mL of the preparation into a 50-mL volumetric flask and dilute to volume with isopropanol. Mix well.

(*2*)(*i*) Inject 10-microliter of diluted SPF standard from paragraph (i)(2)(D)(*1*) of this section and calculate the amount of oxybenzone and padimate O as follows:

$$\text{Percent Oxybenzone} = \frac{\text{Peak area of oxybenzone in sunscreen standard}}{\text{Peak area of oxybenzone in HPLC reference standard}} * 100$$

$$\text{Percent Padimate O} = \frac{\text{Peak area of padimate O in sunscreen standard}}{\text{Peak area of padimate O in HPLC reference standard}} * 100$$

(*ii*) The percent of oxybenzone and padimate O in the SPF standard should be between 95 and 105.

(*3*) *Test subjects*—(i) *Number of subjects*. A test panel should include enough subjects to produce a minimum of 10 valid test results. A maximum of three subjects may be rejected from this panel based on paragraph (i)(5)(v)) of this section.

(ii) *Medical history*. (A) Obtain a medical history from each subject with emphasis on the effects of sunlight on the subject's skin. Determine that each subject is in good general health with skin type I, II, or III as follows:

(*1*) Always burns easily; never tans (sensitive).

(*2*) Always burns easily; tans minimally (sensitive).

(*3*) Burns moderately; tans gradually (light brown) (normal).

(*4*) Burns minimally; always tans well (moderate brown) (normal).

(*5*) Rarely burns; tans profusely (dark brown) (insensitive).

(*6*) Never burns; deeply pigmented (insensitive).

(B) Skin type is based on first 30 to 45 minutes of sun exposure after a winter season of no sun exposure. Determine that each subject is not taking topical or systemic medication that is known

to alter responses to UV radiation. Determine that each subject has no history of sensitivities to topical products and/or abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(iii) *Physical examination.* Conduct a physical examination to determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. A suitable source of low power UVA, such as a Woods lamp, is helpful in this process. If any of these conditions are present, the subject is not qualified to participate in the study. The presence of nevi, blemishes, or moles will be acceptable if, in the physician's judgment, they will neither compromise the study nor jeopardize a subject's safety. Subjects with dysplastic nevi should not be enrolled. Excess hair on the back is acceptable if the hair is clipped. Shaving is unacceptable because it may remove a significant portion of the stratum corneum and temporarily alter the skin's response to UV radiation.

(iv) *Informed consent.* Obtain legally effective written informed consent from all test subjects.

(4) *Sunscreen application.* (i) *Test site.* Test sites are locations on each subject's back, between the beltline and the shoulder blades (scapulae) and lateral to the midline, where skin responses to UV radiation are determined. Responses on unprotected skin (no test material applied) and protected skin (sunscreen test product(s) or SPF standard applied) are determined at separate unprotected and protected test sites, respectively. Test sites should be randomly located in a blinded manner. Each test site should be a minimum of 30 square centimeters and outlined with indelible ink.

(ii) *Test subsite.* Test subsites are the locations to which UV radiation is administered within a test site. At least five test subsites should receive UV doses within each test site. Test subsites should be at least 0.5 square centimeters (cm^2) in area and should be separated from each other by at least 0.8 cm. Each test subsite should be outlined with indelible ink.

(iii) *Applying test materials.* Apply the sunscreen test product and the SPF standard at 2 milligrams per square centimeter (mg/cm^2) to their respective test sites. Use a finger cot compatible with the sunscreen to spread the product as evenly as possible.

(iv) *Waiting period.* Wait at least 15 minutes after applying a sunscreen product before exposing the test sites to UV radiation as described in paragraph (i)(5)) of this section. For water resistant sunscreen products, proceed with the water resistance testing procedure described in paragraph (i)(7) of this section after waiting at least 15 minutes.

(5) *UV exposure*—(i) *Definition of minimal erythema dose (MED).* The minimal erythema dose (MED) is the smallest UV dose that produces perceptible redness of the skin (erythema) with clearly defined borders at 16 to 24 hours after UV exposure. The MED for unprotected skin (MED_u) is determined on a test site that does not have sunscreen applied. The MED for protected skin (MED_p) is determined on a test site that has sunscreen applied. An MED_p is determined for the SPF standard ($ssMED_p$). An MED_p is determined for the sunscreen test product ($tpMED_p$).

(ii) *UV exposure for initial* MED_u. For each test subject, administer a series of UV radiation doses expressed as J/m^2-eff (as determined according to paragraph (a)(2) of this section) to the test subsites within an unprotected test site using an accurately calibrated solar simulator. Select doses that are a geometric series represented by 1.25^n (*i.e.*, each dose is 25 percent greater than the previous dose).

(iii) *UV exposure for final* MED_u, $ssMED_p$, *and* $tpMED_p$. For each subject, determine the final MED_u, $ssMED_p$, and $tpMED_p$ by administering a series of five UV doses to the appropriate test sites. The middle dose (X) in each of these dose series (*i.e.*, the third dose) should equal the initial MED_u times the expected SPF. Note that the expected SPF equals 1 and 16.3 for the final MED_u and $ssMED_p$, respectively. The remaining UV doses in the series depend upon the expected SPF value of the sunscreen test product(s).

For products with an expected SPF less than 8, administer UV doses that increase by 25 percent with each successive dose (*i.e.*, 0.64X, 0.80X, 1.00X,

1.25X, and 1.56X). For products with an expected SPF from 8 to 15, administer UV doses that increase by 20 percent with each successive dose (*i.e.*, 0.69X, 0.83X, 1.00X, 1.20X, and 1.44X). For products with an expected SPF higher than 15, administer UV doses that increase by 15 percent with each successive dose (*i.e.*, 0.76X, 0.87X, 1.00X, 1.15X, and 1.32X).

(iv) *Evaluation of test subsites.* In order that the person who evaluates the test subsites is not biased, he/she should not be the same person who applied the sunscreen drug product to the test site or administered the UV doses. After UV doses are administered, all immediate responses should be recorded. These may include an immediate darkening or tanning, typically grayish or purplish in color, which fades in 30 to 60 minutes; an immediate reddening at the subsite, due to heating of the skin, which fades rapidly; and an immediate generalized heat response, spreading beyond the subsite, which fades in 30 to 60 minutes. After the immediate responses are noted, each subject should shield the exposed area from further UV radiation until the MED is determined. Determine the MED 16 to 24 hours after UV exposure. Because erythema is evaluated 16 to 24 hours after UV exposure, the final MED_u, $ssMED_p$, and $tpMED_p$ are typically determined the day following determination of the initial MED_u. Evaluate the erythema responses of each test subsite using either tungsten or warm white fluorescent lighting that provides at least 450 lux of illumination at the test site. For the evaluation, the test subject should be in the same position as when the test site was irradiated.

(v) *Invalid test data.* Reject test data for a test subject if erythema is not present on either the unprotected or protected test sites; or erythema is present at all subsites; or the responses are inconsistent with the series of UV doses administered; or the subject was noncompliant (*e.g.*, the subject withdraws from the test due to illness or work conflicts or does not shield the exposed testing sites from further UV radiation until the MED is determined).

(6) *Determination of SPF.* (i) Calculate an SPF value for each test subject (SPF_i) as follows:

$$SPFi = \frac{MEDp}{MEDu}$$

(ii) Calculate the mean

$$SPF\ (\overline{SPF})$$

and the standard deviation (s) from the SPF_i values. Calculate the standard error (SE), which equals $s/\sqrt{n}$ (where n equals the number of subjects who provided valid test results). Obtain the t value from Student's t distribution table corresponding to the upper 5-percent point with n—1 degrees of freedom. Determine the labeled SPF value, which equals the largest whole number less than

$$\overline{SPF} - (t * SE).$$

In order for the SPF determination of a test product to be considered valid, the SPF value of the SPF standard should fall within the standard deviation range of the expected SPF (*i.e.*, 16.3 ±3.43).

(7) *Determination of water resistance.* The following procedure should be performed in an indoor fresh water pool, whirlpool, and/or hot tub maintained at 23 to 32 °C. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity should be recorded.

(i) *Water resistance (40 minutes).* The labeled SPF should be determined after 40 minutes of water immersion using the following procedure:

(A) Step 1: Apply the sunscreen as described in paragraph (d) of this section.

(B) Step 2: Perform moderate activity in water for 20 minutes.

(C) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(D) Step 4: Perform moderate activity in water for 20 minutes.

(E) Step 5: Allow test sites to dry completely without toweling.

(F) Step 6: Apply the SPF standard as described in paragraph (d) of this section.

Step 1. Expose test sites to UV doses as described in paragraph (e) of this section.

(ii) *Water resistance (80 minutes)*. The labeled SPF should be determined after 80 minutes of water immersion using the following procedure:

(A) Step 1: Apply the sunscreen as described in paragraph (d) of this section.

(B) Step 2: Perform moderate activity in water for 20 minutes.

(C) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(D) Step 4: Perform moderate activity in water for 20 minutes.

(E) Step 5: Rest out of water for 15 minutes. Do not towel test site(s).

(F) Step 6: Perform moderate activity in water for 20 minutes.

(G) Step 7: Rest out of water for 15 minutes. Do not towel test site(s).

(H) Step 8: Perform moderate activity in water for 20 minutes.

(I) Step 9: Allow test sites to dry completely without toweling.

(J) Step 10: Apply the SPF standard as described in paragraph (d) of this section.

(K) Step 11: Expose test sites to UV doses as described in paragraph (e) of this section.

(j) *Broad spectrum test procedure*—(1) *UV Spectrometry*. (i) *Plate*. Use optical-grade polymethylmethacrylate (PMMA) plates suitable for UV transmittance measurements. The plate should be roughened on one side to a three dimensional surface topography measure (Sa) between 2 and 7 micrometers and must have a rectangular application area of at least 16 square centimeters (with no side shorter than 4 cm).

(ii) *Sample holder*. The sample holder should hold the PMMA plate in a horizontal position to avoid flowing of the sunscreen drug product from one edge of the PMMA plate to the other. It should be mounted as close as possible to the input optics of the spectrometer to maximize capture of forward scattered radiation. The sample holder should be a thin, flat plate with a suitable aperture through which UV radiation can pass. The PMMA plate should be placed on the upper surface of the sample holder with the roughened side facing up.

(iii) *Light source*. The light source should produce a continuous spectral distribution of UV radiation from 290 to 400 nanometers.

(iv) *Input optics*. Unless the spectrometer is equipped with an integrating sphere, an ultraviolet radiation diffuser should be placed between the sample and the input optics of the spectrometer. The diffuser will be constructed from any UV radiation transparent material (*e.g.*, Teflon® or quartz). The diffuser ensures that the radiation received by the spectrometer is not collimated. The spectrometer input slits should be set to provide a bandwidth that is less than or equal to 1 nanometer.

(v) *Dynamic range of the spectrometer*. The dynamic range of the spectrometer should be sufficient to measure transmittance accurately through a highly absorbing sunscreen product at all terrestrial solar UV wavelengths (290 to 400 nm).

(2) *Sunscreen product application to PMMA plate*. The accuracy of the test depends upon the application of a precisely controlled amount of sunscreen product with a uniform distribution over the PMMA plate. The product is applied at 0.75 mg per square centimeter to the roughened side of the PMMA plate. The sunscreen product should be applied in a series of small dots over the entire PMMA plate and then spread evenly using a gloved finger. Spreading should be done with a very light spreading action for approximately 30 seconds followed by spreading with greater pressure for approximately 30 seconds. The plate should then be allowed to equilibrate for 15 minutes in the dark before the pre-irradiation described in paragraph (c) of this section.

(3) *Sunscreen product pre-irradiation*. To account for lack of photostability, apply the sunscreen product to the PMMA plate as described in paragraph (b) of this section and then irradiate with a solar simulator described in section 352.70(b) of this chapter. The irradiation dose should be 4 MEDs which is equivalent to an erythemal effective dose of 800 J/m^2 (*i.e.*, 800 J/m^2-eff).

(4) *Calculation of mean transmittance values*. After pre-irradiation described in paragraph (c) of this section, mean transmittance values should be determined for each wavelength λ over the full UV spectrum (290 to 400 nanometers). The transmittance values

should be measured at 1 nanometer intervals. Measurements of spectral irradiance transmitted for each wavelength λ through control PMMA plates coated with 15 microliters of glycerin (no sunscreen product) should be obtained from at least 5 different locations on the PMMA plate [C1(λ), C2(λ), C3(λ), C4(λ), and C5(λ)]. In addition, a minimum of 5 measurements of spectral irradiance transmitted for each wavelength λ through the PMMA plate covered with the sunscreen product will be similarly obtained after pre-irradiation of the sunscreen product [P1(λ), P2(λ), P3(λ), P4(λ), and P5(λ)].

The mean transmittance for each wavelength,

$$\overline{T(\lambda)},$$

is the ratio of the mean of the C(λ) values to the mean of the P(λ) values, as follows:

$$\overline{T(\lambda)} = \frac{\sum_1^n P(\lambda)/n}{\sum_1^n C(\lambda)/n}$$

Where n ≥5

(5) *Calculation of mean absorbance values*. (i) Mean transmittance values,

$$\overline{T(\lambda)},$$

are converted into mean absorbance values,

$$\overline{A(\lambda)},$$

at each wavelength by taking the negative logarithm of the mean transmittance value as follows:

$$\overline{A(\lambda)} = -\log \overline{T(\lambda)}$$

(ii) The calculation yields 111 monochromatic absorbance values in 1 nanometer increments from 290 to 400 nanometers.

(6) *Number of plates*. For each sunscreen product, mean absorbance values should be determined from at least three individual PMMA plates. Because paragraph (d) of this section requires at least 5 measurements per plate, there should be a total of at least 15 measurements.

(7) *Calculation of the critical wavelength*. The critical wavelength is identified as the wavelength at which the integral of the spectral absorbance curve reaches 90 percent of the integral over the UV spectrum from 290 to 400 nm. The following equation defines the critical wavelength:

$$\int_{290}^{\lambda c} A(\lambda)d\lambda = 0.9 \int_{290}^{400} A(\lambda)d\lambda$$

Where λc = critical wavelength
A(λ) = mean absorbance at each wavelength
dλ = wavelength interval between measurements

A mean critical wavelength of 370 nm or greater is classified as broad spectrum protection.

[76 FR 35660, June 17, 2011, as amended at 76 FR 38975, July 5, 2011]

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

I. SECTION 201.66 STANDARD LABELING FORMAT

A. Overall

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

B. Typeface and size

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

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the ''Drug Facts'' box (or similar

enclosure), providing separation between each of the headings.

2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the ''Drug Facts'' box (or similar enclosure), immediately following the title and immediately preceding the subheadings.

3. A 0.5-point horizontal hairline follows the title, immediately preceding the heading, when a heading appears on a subsequent panel immediately after the ''Drug Facts (continued)'' title.

D. Box or Enclosure

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

II. SECTION 201.66 MODIFIED LABELING FORMAT

A. Overall

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

B. Typeface and size

1. ''Drug Facts'' is set in 9 point Helvetica Bold Italic, left justified.

2. The headings (e.g., ''Directions'') are set in 8 point Helvetica Bold Italic, left justified.

3. The subheadings (e.g., ''Ask a doctor or pharmacist before use if you are'') are set in 6 point Helvetica Bold, left justified.

4. The information is set in 6 point Helvetica Regular with 6.5 point leading, left justified.

5. The heading ''Purpose'' is right justified.

6. The bullet is a 5-point solid square.

7. Bulleted information may start on same line as headings (except for the ''Warnings'' heading) and subheadings, with 2 em spacing separating bullets, and need not be vertically aligned.

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the ''Drug Facts'' box (or similar enclosure), providing separation between each of the headings.

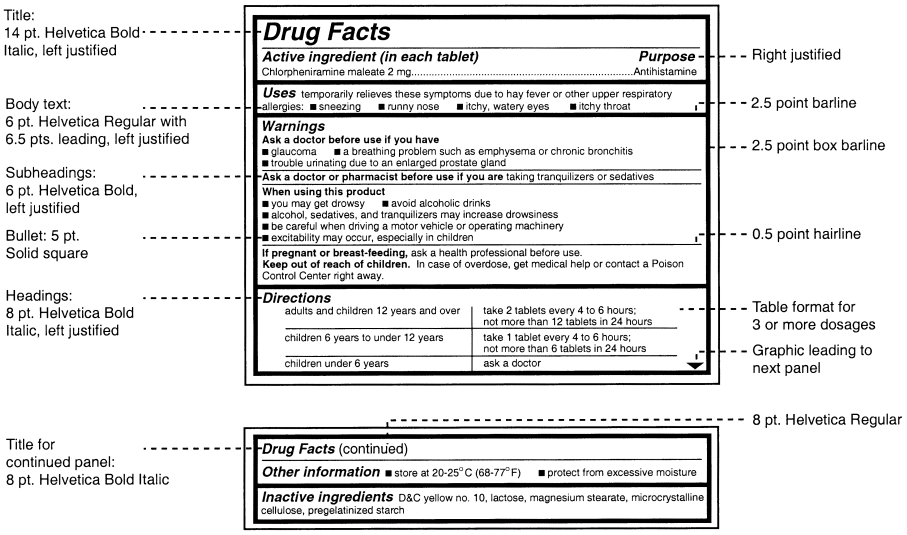
2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the ''Drug Facts'' box (or similar enclosure), immediately following the title and immediately preceding the subheadings.

D. Box or Enclosure

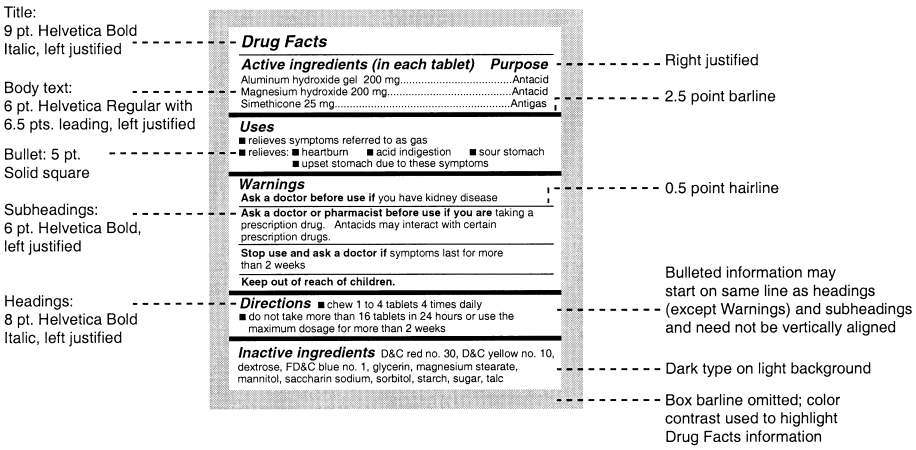
1. All information is set off by color contrast. No barline is used.

III. EXAMPLES OF §201.66 STANDARD LABELING AND MODIFIED LABELING FORMATS

A. SECTION 201.66 STANDARD LABELING FORMAT



B. SECTION 201.66 MODIFIED LABELING FORMAT



PART 202—PRESCRIPTION DRUG ADVERTISING

AUTHORITY: 21 U.S.C. 321, 331, 352, 355, 360b, 371.

§ 202.1 Prescription-drug advertisements.

(a)(1) The ingredient information required by section 502(n) 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.

(2) The order of listing of ingredients in the advertisement shall be the same as the order of listing of ingredients on the label of the product, and the information presented in the advertisement concerning the quantity of each such ingredient shall be the same as the corresponding information on the label of the product.

(3) The advertisement shall not employ a fanciful proprietary name for the drug or any 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 advertisement shall not feature inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.

(5) The advertisement shall not designate 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.

(b)(1) If an advertisement for 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 in the advertisement for the drug; but, except as provided below in this subparagraph, the established name need not be used with the proprietary name or designation in the running text of the advertisement. On any page of an advertisement 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 the 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 advertisement 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.

(c) In the case of a prescription drug containing two or more active ingredients, if the advertisement 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 in the advertisement by section 502(n) 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.

(d)(1) If the advertisement employs one proprietary name or designation to refer to a combination of active ingredients present in more than one preparation (the individual preparations differing from each other as to quantities of active ingredients and/or the form of the finished preparation) and there is no established name corresponding to such proprietary name or designation, a listing showing the established names of the active ingredients shall be placed in direct conjunction with the most prominent display of such proprietary name or designation. The prominence of this listing of active ingredients shall bear a reasonable relationship to the prominence of the proprietary name and the relationship between such proprietary name or designation, and the listing of active ingredients shall be made clear by use of such phrase as ''brand of'', preceding the listing of active ingredients.

(2) The advertisement shall prominently display the name of at least one specific dosage form and shall have the quantitative ingredient information required by section 502(n) of the act in direct conjunction with such display. If other dosage forms are listed in the advertisement, the quantitative ingredient information for such dosage forms shall appear in direct conjunction and in equal prominence with the most prominent listing of the names of such dosage forms.

(e) True statement of information in brief summary relating to side effects, contraindications, and effectiveness:

(1) *When required.* All advertisements for any prescription drug (''prescription drug'' as used in this section means drugs defined in section 503(b)(1) of the act and § 201.105, applicable to drugs for use by man and veterinary

drugs, respectively), except advertisements described in paragraph (e)(2) of this section, shall present a true statement of information in brief summary relating to side effects, contraindications (when used in this section ''side effects, contraindications'' include side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc.) and effectiveness. Advertisements broadcast through media such as radio, television, or telephone communications systems shall include information relating to the major side effects and contraindications of the advertised drugs in the audio or audio and visual parts of the presentation and unless adequate provision is made for dissemination of the approved or permitted package labeling in connection with the broadcast presentation shall contain a brief summary of all necessary information related to side effects and contraindications.

(2) *Exempt advertisements.* The following advertisements are exempt from the requirements of paragraph (e)(1) of this section under the conditions specified:

(i) *Reminder advertisements.* Reminder advertisements are those which call attention to the name of the drug product but do not include indications or dosage recommendations for use of the drug product. These reminder advertisements shall contain only the proprietary name of the drug product, if any; the established name of the drug product, if any; the established name of each active ingredient in the drug product; and, optionally, information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, the name and address of the manufacturer, packer, or distributor or other written, printed, or graphic matter containing no representation or suggestion relating to the advertised drug product. If the Commissioner finds that there is evidence of significant incidence of fatalities or serious injury associated with the use of a particular prescription drug, he may withdraw this exemption by so notifying the manufacturer, packer, or distributor of the drug by letter. Reminder advertisements, other than those solely intended to convey price information including, but not limited to, those subject to the requirements of § 200.200 of this chapter, are not permitted for a prescription drug product whose labeling contains a boxed warning relating to a serious hazard associated with the use of the drug product. Reminder advertisements which are intended to provide consumers with information concerning the price charged for a prescription for a drug product are exempt from the requirements of this section if they meet all of the conditions contained in § 200.200 of this chapter. Reminder advertisements, other than those subject to the requirements of § 200.200 of this chapter, are not permitted for a drug for which an announcement has been published pursuant to a review on the labeling claims for the drug by the National Academy of Sciences/National Research Council (NAS/NRC), Drug Efficacy Study Group, and for which no claim has been evaluated as higher than ''possibly effective.'' If the Commissioner finds the circumstances are such that a reminder advertisement may be misleading to prescribers of drugs subject to NAS/NRC evaluation, such advertisements will not be allowed and the manufacturer, packer, or distributor will be notified either in the publication of the conclusions on the effectiveness of the drug or by letter.

(ii) *Advertisements of bulk-sale drugs.* Advertisements of bulk-sale drugs that promote sale of the drug in bulk packages in accordance with the practice of the trade solely to be processed, manufactured, labeled, or repackaged in substantial quantities and that contain no claims for the therapeutic safety or effectiveness of the drug.

(iii) *Advertisements of prescription-compounding drugs.* Advertisements of prescription-compounding drugs that promote sale of a drug for use as a prescription chemical or other compound for use by registered pharmacists in compounding prescriptions if the drug otherwise complies with the conditions for the labeling exemption contained in § 201.120 and the advertisement contains no claims for the therapeutic safety or effectiveness of the drug.

(3) *Scope of information to be included; applicability to the entire advertisement.* (i) The requirement of a true statement of information relating to side effects, contraindications, and effectiveness applies to the entire advertisement. Untrue or misleading information in any part of the advertisement will not be corrected by the inclusion in another distinct part of the advertisement of a brief statement containing true information relating to side effects, contraindications, and effectiveness of the drug. If any part or theme of the advertisement would make the advertisement false or misleading by reason of the omission of appropriate qualification or pertinent information, that part or theme shall include the appropriate qualification or pertinent information, which may be concise if it is supplemented by a prominent reference on each page to the presence and location elsewhere in the advertisement of a more complete discussion of such qualification or information.

(ii) The information relating to effectiveness is not required to include information relating to all purposes for which the drug is intended but may optionally be limited to a true statement of the effectiveness of the drug for the selected purpose(s) for which the drug is recommended or suggested in the advertisement. The information relating to effectiveness shall include specific indications for use of the drug for purposes claimed in the advertisement; for example, when an advertisement contains a broad claim that a drug is an antibacterial agent, the advertisement shall name a type or types of infections and microorganisms for which the drug is effective clinically as specifically as required, approved, or permitted in the drug package labeling.

(iii) The information relating to side effects and contraindications shall disclose each specific side effect and contraindication (which include side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc.; see paragraph (e)(1) of this section) contained in required, approved, or permitted labeling for the advertised drug dosage form(s): *Provided, however,*

(*a*) The side effects and contraindications disclosed may be limited to those pertinent to the indications for which the drug is recommended or suggested in the advertisement to the extent that such limited disclosure has previously been approved or permitted in drug labeling conforming to the provisions of §§ 201.100 or 201.105; and

(*b*) The use of a single term for a group of side effects and contraindications (for example, ''blood dyscrasias'' for disclosure of ''leukopenia,'' ''agranulocytosis,'' and ''neutropenia'') is permitted only to the extent that the use of such a single term in place of disclosure of each specific side effect and contraindication has been previously approved or permitted in drug labeling conforming to the provisions of §§ 201.100 or 201.105.

(4) *Substance of information to be included in brief summary.* (i)(*a*) An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the act after October 10, 1962, or a prescription drug covered by a new animal drug application approved pursuant to section 512 of the act after August 1, 1969, or any approved supplement thereto, or for a prescription drug listed in the index pursuant to section 572 of the act, or any granted modification thereto, shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement, new animal drug application or supplement, or new animal drug index listing or modification. The advertisement shall present information from labeling required, approved, permitted, or granted in a new-drug or new animal drug application or new animal drug index listing relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

(*b*) If a prescription drug was covered by a new-drug application or a supplement thereto that became effective prior to October 10, 1962, an advertisement may recommend or suggest:

(*1*) Uses contained in the labeling accepted in such new-drug application

and any effective, approved, or permitted supplement thereto.

(*2*) Additional uses contained in labeling in commercial use on October 9, 1962, to the extent that such uses did not cause the drug to be an unapproved ''new drug'' as ''new drug'' was defined in section 201(p) of the act as then in force, and to the extent that such uses would be permitted were the drug subject to paragraph (e)(4)(iii) of this section.

(*3*) Additional uses contained in labeling in current commercial use to the extent that such uses do not cause the drug to be an unapproved ''new drug'' as defined in section 201(p) of the act as amended or a ''new animal drug'' as defined in section 201(v) of the act as amended.

The advertisement shall present information from labeling required, approved, or permitted in a new-drug application relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

(ii) In the case of an advertisement for a prescription drug other than a drug the labeling of which causes it to be an unapproved ''new drug'' and other than drugs covered by paragraph (e)(4)(i) of this section, an advertisement may recommend and suggest the drug only for those uses contained in the labeling thereof:

(*a*) For which the drug is generally recognized as safe and effective among experts qualified by scientific training and experience to evaluate the safety and effectiveness of such drugs; or

(*b*) For which there exists substantial evidence of safety and effectiveness, consisting of adequate and well-controlled investigations, including clinical investigations (as used in this section ''clinical investigations,'' ''clinical experience,'' and ''clinical significance'' mean in the case of drugs intended for administration to man, investigations, experience, or significance in humans, and in the case of drugs intended for administration to other animals, investigations, experience, or significance in the specie or species for which the drug is advertised), by experts qualified by scientific training and experience to evaluate the safety and effectiveness of the drug involved, on the basis of which it can fairly and responsibly be concluded by such experts that the drug is safe and effective for such uses; or

(*c*) For which there exists substantial clinical experience (as used in this section this means substantial clinical experience adequately documented in medical literature or by other data (to be supplied to the Food and Drug Administration, if requested)), on the basis of which it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective for such uses; or

(*d*) For which safety is supported under any of the preceding clauses in paragraphs (e)(4)(iii) (*a*), (*b*), and (*c*) of this section and effectiveness is supported under any other of such clauses.

The advertisement shall present information relating to each specific side effect and contraindication that is required, approved, or permitted in the package labeling by §§ 201.100 or 201.105 of this chapter of the drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

(5) *''True statement'' of information.* An advertisement does not satisfy the requirement that it present a ''true statement'' of information in brief summary relating to side effects, contraindications, and effectiveness if:

(i) It is false or misleading with respect to side effects, contraindications, or effectiveness; or

(ii) It fails to present a fair balance between information relating to side effects and contraindications and information relating to effectiveness of the drug in that the information relating to effectiveness is presented in greater scope, depth, or detail than is required by section 502(n) of the act and this information is not fairly balanced by a presentation of a summary of true information relating to side effects and contraindications of the drug; *Provided, however,* That no advertisement shall be considered to be in violation of this section if the presentation of true information relating to side effects and contraindications is comparable in depth and detail with the claims for effectiveness or safety.

(iii) It fails to reveal facts material in the light of its representations or material with respect to consequences that may result from the use of the drug as recommended or suggested in the advertisement.

(6) *Advertisements that are false, lacking in fair balance, or otherwise misleading.* An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act, among other reasons, if it:

(i) Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients (as used in this section *patients* means humans and in the case of veterinary drugs, other animals), safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience (as described in paragraphs (e)(4)(ii) (*b*) and (*c*) of this section) whether or not such representations are made by comparison with other drugs or treatments, and whether or not such a representation or suggestion is made directly or through use of published or unpublished literature, quotations, or other references.

(ii) Contains a drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience.

(iii) Contains favorable information or opinions about a drug previously regarded as valid but which have been rendered invalid by contrary and more credible recent information, or contains literature references or quotations that are significantly more favorable to the drug than has been demonstrated by substantial evidence or substantial clinical experience.

(iv) Contains a representation or suggestion that a drug is safer than it has been demonstrated to be by substantial evidence or substantial clinical experience, by selective presentation of information from published articles or other references that report no side effects or minimal side effects with the drug or otherwise selects information from any source in a way that makes a drug appear to be safer than has been demonstrated.

(v) Presents information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does.

(vi) Contains references to literature or studies that misrepresent the effectiveness of a drug by failure to disclose that claimed results may be due to concomitant therapy, or by failure to disclose the credible information available concerning the extent to which claimed results may be due to placebo effect (information concerning placebo effect is not required unless the advertisement promotes the drug for use by man).

(vii) Contains favorable data or conclusions from nonclinical studies of a drug, such as in laboratory animals or in vitro, in a way that suggests they have clinical significance when in fact no such clinical significance has been demonstrated.

(viii) Uses a statement by a recognized authority that is apparently favorable about a drug but fails to refer to concurrent or more recent unfavorable data or statements from the same authority on the same subject or subjects.

(ix) Uses a quote or paraphrase out of context to convey a false or misleading idea.

(x) Uses literature, quotations, or references that purport to support an advertising claim but in fact do not support the claim or have relevance to the claim.

(xi) Uses literature, quotations, or references for the purpose of recommending or suggesting conditions of drug use that are not approved or permitted in the drug package labeling.

(xii) Offers a combination of drugs for the treatment of patients suffering from a condition amenable to treatment by any of the components rather than limiting the indications for use to patients for whom concomitant therapy as provided by the fixed combination drug is indicated, unless such condition is included in the uses permitted under paragraph (e)(4) of this section.

(xiii) Uses a study on normal individuals without disclosing that the subjects were normal, unless the drug is intended for use on normal individuals.

(xiv) Uses ''statistics'' on numbers of patients, or counts of favorable results or side effects, derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such ''statistics'' are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case.

(xv) Uses erroneously a statistical finding of ''no significant difference'' to claim clinical equivalence or to deny or conceal the potential existence of a real clinical difference.

(xvi) Uses statements or representations that a drug differs from or does not contain a named drug or category of drugs, or that it has a greater potency per unit of weight, in a way that suggests falsely or misleadingly or without substantial evidence or substantial clinical experience that the advertised drug is safer or more effective than such other drug or drugs.

(xvii) Uses data favorable to a drug derived from patients treated with dosages different from those recommended in approved or permitted labeling if the drug advertised is subject to section 505 of the act, or, in the case of other drugs, if the dosages employed were different from those recommended in the labeling and generally recognized as safe and effective. This provision is not intended to prevent citation of reports of studies that include some patients treated with dosages different from those authorized, if the results in such patients are not used.

(xviii) Uses headline, subheadline, or pictorial or other graphic matter in a way that is misleading.

(xix) Represents or suggests that drug dosages properly recommended for use in the treatment of certain classes of patients or disease conditions are safe and effective for the treatment of other classes of patients or disease conditions when such is not the case.

(xx) Presents required information relating to side effects or contraindications by means of a general term for a group in place of disclosing each specific side effect and contraindication (for example employs the term *blood dyscrasias* instead of ''leukopenia,'' ''agranulocytosis,'' ''neutropenia,'' etc.) unless the use of such general term conforms to the provisions of paragraph (e)(3)(iii) of this section.

Provided, however, That any provision of this paragraph shall be waived with respect to a specified advertisement as set forth in a written communication from the Food and Drug Administration on a petition for such a waiver from a person who would be adversely affected by the enforcement of such provision on the basis of a showing that the advertisement is not false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act. A petition for such a waiver shall set forth clearly and concisely the petitioner's interest in the advertisement, the specific provision of this paragraph from which a waiver is sought, a complete copy of the advertisement, and a showing that the advertisement is not false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act.

(7) *Advertisements that may be false, lacking in fair balance, or otherwise misleading.* An advertisement may be false, lacking in fair balance, or otherwise misleading or otherwise violative of section 502(n) of the act if it:

(i) Contains favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions.

(ii) Uses the concept of ''statistical significance'' to support a claim that has not been demonstrated to have clinical significance or validity, or fails to reveal the range of variations around the quoted average results.

(iii) Uses statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations.

(iv) Uses tables or graphs to distort or misrepresent the relationships, trends, differences, or changes among the variables or products studied; for example, by failing to label abscissa

and ordinate so that the graph creates a misleading impression.

(v) Uses reports or statements represented to be statistical analyses, interpretations, or evaluations that are inconsistent with or violate the established principles of statistical theory, methodology, applied practice, and inference, or that are derived from clinical studies the design, data, or conduct of which substantially invalidate the application of statistical analyses, interpretations, or evaluations.

(vi) Contains claims concerning the mechanism or site of drug action that are not generally regarded as established by scientific evidence by experts qualified by scientific training and experience without disclosing that the claims are not established and the limitations of the supporting evidence.

(vii) Fails to provide sufficient emphasis for the information relating to side effects and contraindications, when such information is contained in a distinct part of an advertisement, because of repetition or other emphasis in that part of the advertisement of claims for effectiveness or safety of the drug.

(viii) Fails to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis.

(ix) Fails to provide adequate emphasis (for example, by the use of color scheme, borders, headlines, or copy that extends across the gutter) for the fact that two facing pages are part of the same advertisement when one page contains information relating to side effects and contraindications.

(x) In an advertisement promoting use of the drug in a selected class of patients (for example, geriatric patients or depressed patients), fails to present with adequate emphasis the significant side effects and contraindications or the significant dosage considerations, when dosage recommendations are included in an advertisement, especially applicable to that selected class of patients.

(xi) Fails to present on a page facing another page (or on another full page) of an advertisement on more than one page, information relating to side effects and contraindications when such information is in a distinct part of the advertisement.

(xii) Fails to include on each page or spread of an advertisement the information relating to side effects and contraindications or a prominent reference to its presence and location when it is presented as a distinct part of an advertisement.

(xiii) Contains information from published or unpublished reports or opinions falsely or misleadingly represented or suggested to be authentic or authoritative.

(f)–(i) [Reserved]

(j)(1) No advertisement concerning a particular prescription drug may be disseminated without prior approval by the Food and Drug Administration if:

(i) The sponsor or the Food and Drug Administration has received information that has not been widely publicized in medical literature that the use of the drug may cause fatalities or serious damage;

(ii) The Commissioner (or in his absence the officer acting as Commissioner), after evaluating the reliability of such information, has notified the sponsor that the information must be a part of the advertisements for the drug; and

(iii) The sponsor has failed within a reasonable time as specified in such notification to present to the Food and Drug Administration a program, adequate in light of the nature of the information, for assuring that such information will be publicized promptly and adequately to the medical profession in subsequent advertisements.

If the Commissioner finds that the program presented is not being followed, he will notify the sponsor that prior approval of all advertisements for the particular drug will be required. Nothing in this paragraph is to be construed as limiting the Commissioner's or the Secretary's rights, as authorized by law, to issue publicity, to suspend any new-drug application, to decertify any

antibiotic, or to recommend any regulatory action.

(2) Within a reasonable time after information concerning the possibility that a drug may cause fatalities or serious damage has been widely publicized in medical literature, the Food and Drug Administration shall notify the sponsor of the drug by mail that prior approval of advertisements for the drug is no longer necessary.

(3) Dissemination of an advertisement not in compliance with this paragraph shall be deemed to be an act that causes the drug to be misbranded under section 502(n) of the act.

(4) Any advertisement may be submitted to the Food and Drug Administration prior to publication for comment. If the advertiser is notified that the submitted advertisement is not in violation and, at some subsequent time, the Food and Drug Administration changes its opinion, the advertiser will be so notified and will be given a reasonable time for correction before any regulatory action is taken under this section. Notification to the advertiser that a proposed advertisement is or is not considered to be in violation shall be in written form.

(5) The sponsor shall have an opportunity for a regulatory hearing before the Food and Drug Administration pursuant to part 16 of this chapter with respect to any determination that prior approval is required for advertisements concerning a particular prescription drug, or that a particular advertisement is not approvable.

(k) An advertisement issued or caused to be issued by the manufacturer, packer, or distributor of the drug promoted by the advertisement and which is not in compliance with section 502(n) of the act and the applicable regulations thereunder shall cause stocks of such drug in possession of the person responsible for issuing or causing the issuance of the advertisement, and stocks of the drug distributed by such person and still in the channels of commerce, to be misbranded under section 502(n) of the act.

(l)(1) Advertisements subject to section 502(n) of the act include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.

(2) Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the ''Physicians Desk Reference'') for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act.

[40 FR 14016, Mar. 27, 1975, as amended at 40 FR 58799, Dec. 18, 1975; 41 FR 48266, Nov. 2, 1976; 42 FR 15674, Mar. 22, 1977; 60 FR 38480, July 27, 1995; 72 FR 69119, Dec. 6, 2007]

EFFECTIVE DATE NOTE: At 44 FR 37467, June 26, 1979, § 202.1(e)(6) (ii) and (vii) were revised. At 44 FR 74817, Dec. 18, 1979, paragraphs (e)(6) (ii) and (vii) were stayed indefinitely. At 64 FR 400, Jan. 5, 1999, these paragraphs were amended. For the convenience of the user, paragraphs (e)(6) (ii) and (vii), published at 44 FR 37467, are set forth below:

§ 202.1 Prescription-drug advertisements.

* * * * *

(e) * * *

(6) * * *

(ii) Represents or suggests that a prescription drug is safer or more effective than another drug in some particular when the difference has not been demonstrated by substantial evidence. An advertisement for a prescription drug may not, either directly or by implication, e.g., by use of comparative test data or reference to published reports, represent that the drug is safer or more effective than another drug, nor may an advertisement contain a quantitative statement of safety or effectiveness (*a*) unless the representation has been approved as part of the labeling in a new drug application or biologic license, or (*b*) if the drug is not a new drug or biologic, unless the representation of safety or effectiveness is supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.111 (a)(5)(ii) of this chapter, or unless the requirement for adequate and well-controlled

studies is waived as provided in § 314.111(a)(5)(ii) of this chapter.

* * * * *

(vii) Suggests, on the basis of favorable data or conclusions from nonclinical studies of a prescription drug, such as studies in laboratory animals or in vitro, that the studies have clinical significance, if clinical significance has not been demonstrated. Data that demonstrate activity or effectiveness for a prescription drug in animal or in vitro tests and have not been shown by adequate and well-controlled clinical studies to pertain to clinical use may be used in advertising except that (*a*), in the case of anti-infective drugs, in vitro data may be included in the advertisement, if data are immediately preceded by the statement ''The following in vitro data are available but their clinical significance is unknown'' and (b), in the case of other drug classes, in vitro and animal data that have not been shown to pertain to clinical use by adequate and well-controlled clinical studies as defined in § 314.111(a)(5)(ii) of this chapter may not be used unless the requirement for adequate and well-controlled studies is waived as provided in § 314.111(a)(5)(ii) of this chapter.

* * * * *

PART 203—PRESCRIPTION DRUG MARKETING

Subpart A—General Provisions

Sec.
203.1 Scope.
203.2 Purpose.
203.3 Definitions.

Subpart B—Reimportation

203.10 Restrictions on reimportation.
203.11 Applications for reimportation to provide emergency medical care.
203.12 An appeal from an adverse decision by the district office.

Subpart C—Sales Restrictions

203.20 Sales restrictions.
203.22 Exclusions.
203.23 Returns.

Subpart D—Samples

203.30 Sample distribution by mail or common carrier.
203.31 Sample distribution by means other than mail or common carrier (direct delivery by a representative or detailer).
203.32 Drug sample storage and handling requirements.
203.33 Drug sample forms.
203.34 Policies and procedures; administrative systems.
203.35 Standing requests.
203.36 Fulfillment houses, shipping and mailing services, comarketing agreements, and third-party recordkeeping.
203.37 Investigation and notification requirements.
203.38 Sample lot or control numbers; labeling of sample units.
203.39 Donation of drug samples to charitable institutions.

Subpart E—Wholesale Distribution

203.50 Requirements for wholesale distribution of prescription drugs.

Subpart F—Request and Receipt Forms, Reports, and Records

203.60 Request and receipt forms, reports, and records.

Subpart G—Rewards

203.70 Application for a reward.

AUTHORITY: 21 U.S.C. 331, 333, 351, 352, 353, 360, 371, 374, 381.

SOURCE: 64 FR 67756, Dec. 3, 1999, unless otherwise noted.

Subpart A—General Provisions

§ 203.1 Scope.

This part sets forth procedures and requirements pertaining to the reimportation and wholesale distribution of prescription drugs, including both bulk drug substances and finished dosage forms; the sale, purchase, or trade of (or the offer to sell, purchase, or trade) prescription drugs, including bulk drug substances, that were purchased by hospitals or health care entities, or donated to charitable organizations; and the distribution of prescription drug samples. Blood and blood components intended for transfusion are excluded from the restrictions in and the requirements of the Prescription Drug Marketing Act of 1987 and the Prescription Drug Amendments of 1992.

§ 203.2 Purpose.

The purpose of this part is to implement the Prescription Drug Marketing Act of 1987 and the Prescription Drug Amendments of 1992, except for those sections relating to State licensing of

wholesale distributors (see part 205 of this chapter), to protect the public health, and to protect the public against drug diversion by establishing procedures, requirements, and minimum standards for the distribution of prescription drugs and prescription drug samples.

§ 203.3 Definitions.

(a) *The act* means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 *et seq.*).

(b) *Authorized distributor of record* means a distributor with whom a manufacturer has established an ongoing relationship to distribute such manufacturer's products.

(c) *Blood* means whole blood collected from a single donor and processed either for transfusion or further manufacturing.

(d) *Blood component* means that part of a single-donor unit of blood separated by physical or mechanical means.

(e) *Bulk drug substance* means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

(f) *Charitable institution* or *charitable organization* means a nonprofit hospital, health care entity, organization, institution, foundation, association, or corporation that has been granted an exemption under section 501(c)(3) of the Internal Revenue Code of 1954, as amended.

(g) *Common control* means the power to direct or cause the direction of the management and policies of a person or an organization, whether by ownership of stock, voting rights, by contract, or otherwise.

(h) *Distribute* means to sell, offer to sell, deliver, or offer to deliver a drug to a recipient, except that the term ''distribute'' does not include:

(1) Delivering or offering to deliver a drug by a common carrier in the usual course of business as a common carrier; or

(2) Providing of a drug sample to a patient by:

(i) A practitioner licensed to prescribe such drug;

(ii) A health care professional acting at the direction and under the supervision of such a practitioner; or

(iii) The pharmacy of a hospital or of another health care entity that is acting at the direction of such a practitioner and that received such sample in accordance with the act and regulations.

(i) *Drug sample* means a unit of a prescription drug that is not intended to be sold and is intended to promote the sale of the drug.

(j) *Drug coupon* means a form that may be redeemed, at no cost or at reduced cost, for a drug that is prescribed in accordance with section 503(b) of the act.

(k) *Electronic record* means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

(l) *Electronic signature* means any computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

(m) *Emergency medical reasons* include, but are not limited to, transfers of a prescription drug between health care entities or from a health care entity to a retail pharmacy to alleviate a temporary shortage of a prescription drug arising from delays in or interruption of regular distribution schedules; sales to nearby emergency medical services, i.e., ambulance companies and fire fighting organizations in the same State or same marketing or service area, or nearby licensed practitioners, of drugs for use in the treatment of acutely ill or injured persons; provision of minimal emergency supplies of drugs to nearby nursing homes for use in emergencies or during hours of the day when necessary drugs cannot be obtained; and transfers of prescription drugs by a retail pharmacy to another retail pharmacy to alleviate a temporary shortage; but do not include regular and systematic sales to licensed practitioners of prescription

drugs that will be used for routine office procedures.

(n) *FDA* means the U.S. Food and Drug Administration.

(o) *Group purchasing organization* means any entity established, maintained, and operated for the purchase of prescription drugs for distribution exclusively to its members with such membership consisting solely of hospitals and health care entities bound by written contract with the entity.

(p) *Handwritten signature* means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

(q) *Health care entity* means any person that provides diagnostic, medical, surgical, or dental treatment, or chronic or rehabilitative care, but does not include any retail pharmacy or any wholesale distributor. Except as provided in § 203.22(h) and (i), a person cannot simultaneously be a ''health care entity'' and a retail pharmacy or wholesale distributor.

(r) *Licensed practitioner* means any person licensed or authorized by State law to prescribe drugs.

(s) *Manufacturer* means any person who is a manufacturer as defined by § 201.1 of this chapter.

(t) *Nonprofit affiliate* means any not-for-profit organization that is either associated with or a subsidiary of a charitable organization as defined in section 501(c)(3) of the Internal Revenue Code of 1954.

(u) *Ongoing relationship* means an association that exists when a manufacturer and a distributor enter into a written agreement under which the distributor is authorized to distribute the manufacturer's products for a period of time or for a number of shipments. If the distributor is not authorized to distribute a manufacturer's entire product line, the agreement must identify the specific drug products that the distributor is authorized to distribute.

(v) *PDA* means the Prescription Drug Amendments of 1992.

(w) *PDMA* means the Prescription Drug Marketing Act of 1987.

(x) *Person* includes any individual, partnership, corporation, or association.

(y) *Prescription drug* means any drug (including any biological product, except for blood and blood components intended for transfusion or biological products that are also medical devices) required by Federal law (including Federal regulation) to be dispensed only by a prescription, including finished dosage forms and bulk drug substances subject to section 503(b) of the act.

(z) *Representative* means an employee or agent of a drug manufacturer or distributor who promotes the sale of prescription drugs to licensed practitioners and who may solicit or receive written requests for the delivery of drug samples. A detailer is a representative.

(aa) *Sample unit* means a packet, card, blister pack, bottle, container, or other single package comprised of one or more dosage units of a prescription drug sample, intended by the manufacturer or distributor to be provided by a licensed practitioner to a patient in an unbroken or unopened condition.

(bb) *Unauthorized distributor* means a distributor who does not have an ongoing relationship with a manufacturer to sell or distribute its products.

(cc) *Wholesale distribution* means distribution of prescription drugs to persons other than a consumer or patient, but does not include:

(1) Intracompany sales;

(2) The purchase or other acquisition by a hospital or other health care entity that is a member of a group purchasing organization of a drug for its own use from the group purchasing organization or from other hospitals or health care entities that are members of such organizations;

(3) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug by a charitable organization to a nonprofit affiliate of the organization to the extent otherwise permitted by law;

(4) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug among hospitals or other

health care entities that are under common control;

(5) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug for emergency medical reasons;

(6) The sale, purchase, or trade of a drug, an offer to sell, purchase, or trade a drug, or the dispensing of a drug under a prescription executed in accordance with section 503(b) of the act;

(7) The distribution of drug samples by manufacturers' and authorized distributors' representatives;

(8) The sale, purchase, or trade of blood or blood components intended for transfusion;

(9) Drug returns, when conducted by a hospital, health care entity, or charitable institution in accordance with § 203.23; or

(10) The sale of minimal quantities of drugs by retail pharmacies to licensed practitioners for office use.

(dd) *Wholesale distributor* means any person engaged in wholesale distribution of prescription drugs, including, but not limited to, manufacturers; repackers; own-label distributors; private-label distributors; jobbers; brokers; warehouses, including manufacturers' and distributors' warehouses, chain drug warehouses, and wholesale drug warehouses; independent wholesale drug traders; and retail pharmacies that conduct wholesale distributions.

[64 FR 67756, Dec. 3, 1999, as amended at 73 FR 59500, Oct. 9, 2008]

Subpart B—Reimportation

§ 203.10 Restrictions on reimportation.

No prescription drug or drug composed wholly or partly of insulin that was manufactured in a State and exported from the United States may be reimported by anyone other than its manufacturer, except that FDA may grant permission to a person other than the manufacturer to reimport a prescription drug or insulin-containing drug if it determines that such reimportation is required for emergency medical care.

§ 203.11 Applications for reimportation to provide emergency medical care.

(a) Applications for reimportation for emergency medical care shall be submitted to the director of the FDA District Office in the district where reimportation is sought (addresses found in part 5, subpart M of this chapter).

(b) Applications for reimportation to provide emergency medical care shall be reviewed and approved or disapproved by each district office.

[64 FR 67756, Dec. 3, 1999, as amended at 69 FR 17292, Apr. 2, 2004]

§ 203.12 An appeal from an adverse decision by the district office.

An appeal from an adverse decision by the district office involving insulin-containing drugs or prescription human drugs, other than biological products, may be made to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002. An appeal from an adverse decision by the district office involving prescription human biological products may be made to the Office of Compliance and Biologics Quality (HFM–600), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852 or the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002, depending on the Center responsible for regulating the product.

[64 FR 67756, Dec. 3, 1999, as amended at 69 FR 48775, Aug. 11, 2004; 70 FR 14980, Mar. 24, 2005; 74 FR 13112, Mar. 26, 2009]

Subpart C—Sales Restrictions

§ 203.20 Sales restrictions.

Except as provided in § 203.22 or § 203.23, no person may sell, purchase, or trade, or offer to sell, purchase, or trade any prescription drug that was:

(a) Purchased by a public or private hospital or other health care entity; or

(b) Donated or supplied at a reduced price to a charitable organization.

§ 203.22 Exclusions.

Section 203.20 does not apply to:

(a) The purchase or other acquisition of a drug for its own use by a hospital or other health care entity that is a member of a group purchasing organization from the group purchasing organization or from other hospitals or health care entities that are members of the organization.

(b) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug by a charitable organization to a nonprofit affiliate of the organization to the extent otherwise permitted by law.

(c) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug among hospitals or other health care entities that are under common control.

(d) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug for emergency medical reasons.

(e) The sale, purchase, or trade of a drug, an offer to sell, purchase, or trade a drug, or the dispensing of a drug under a valid prescription.

(f) The sale, purchase, or trade of a drug or the offer to sell, purchase, or trade a drug by hospitals or health care entities owned or operated by Federal, State, or local governmental units to other hospitals or health care entities owned or operated by Federal, State, or local governmental units.

(g) The sale, purchase, or trade of, or the offer to sell, purchase, or trade blood or blood components intended for transfusion.

(h) The sale, purchase, or trade of, or the offer to sell, purchase, or trade, by a registered blood establishment that qualifies as a health care entity any:

(1) Drug indicated for a bleeding or clotting disorder, or anemia;

(2) Blood collection container approved under section 505 of the act; or

(3) Drug that is a blood derivative (or a recombinant or synthetic form of a blood derivative); as long as all of the health care services that the establishment provides are related to its activities as a registered blood establishment or the health care services consist of collecting, processing, storing, or administering human hematopoietic stem/progenitor cells or performing diagnostic testing of specimens provided that these specimens are tested together with specimens undergoing routine donor testing. Blood establishments relying on the exclusion in this paragraph must satisfy all other requirements of the act and this part applicable to a wholesale distributor or retail pharmacy.

(i) The sale, purchase, or trade of, or the offer to sell, purchase, or trade, by a comprehensive hemophilia diagnostic treatment center that is receiving a grant under section 501(a)(2) of the Social Security Act and that qualifies as a health care entity, any drug indicated for a bleeding or clotting disorder, or anemia, or any drug that is a blood derivative (or a recombinant or synthetic form of a blood derivative). Comprehensive hemophilia diagnostic treatment centers relying on the exclusion in this paragraph must satisfy all other requirements of the act and this part applicable to a wholesale distributor or retail pharmacy.

[64 FR 67756, Dec. 3, 1999, as amended at 73 FR 59500, Oct. 9, 2008]

§ 203.23 Returns.

The return of a prescription drug purchased by a hospital or health care entity or acquired at a reduced price by or donated to a charitable institution is exempt from the prohibitions in § 203.20, provided that:

(a) The hospital, health care entity, or charitable institution documents the return by filling out a credit memo specifying:

(1) The name and address of the hospital, health care entity, or charitable institution;

(2) The name and address of the manufacturer or wholesale distributor from which it was acquired;

(3) The product name and lot or control number;

(4) The quantity returned; and

(5) The date of the return.

(b) The hospital, health care entity, or charitable institution forwards a copy of each credit memo to the manufacturer and retains a copy of each credit memo for its records;

(c) Any drugs returned to a manufacturer or wholesale distributor are kept under proper conditions for storage, handling, and shipping, and written documentation showing that proper conditions were maintained is provided

to the manufacturer or wholesale distributor to which the drugs are returned.

Subpart D—Samples

§ 203.30 Sample distribution by mail or common carrier.

(a) *Requirements for drug sample distribution by mail or common carrier.* A manufacturer or authorized distributor of record may distribute a drug sample to a practitioner licensed to prescribe the drug that is to be sampled or, at the written request of a licensed practitioner, to the pharmacy of a hospital or other health care entity, by mail or common carrier, provided that:

(1) The licensed practitioner executes and submits a written request to the manufacturer or authorized distributor of record, as set forth in paragraph (b) of this section, before the delivery of the drug sample;

(2) The manufacturer or authorized distributor of record verifies with the appropriate State authority that the practitioner requesting the drug sample is licensed or authorized under State law to prescribe the drug product;

(3) The recipient executes a written receipt, as set forth in paragraph (c) of this section, when the drug sample is delivered; and

(4) The receipt is returned to the manufacturer or distributor from which the drug sample was received.

(b) *Contents of the written request form for delivery of samples by mail or common carrier.* (1) A written request for a drug sample to be delivered by mail or common carrier to a licensed practitioner is required to contain the following:

(i) The name, address, professional title, and signature of the practitioner making the request;

(ii) The practitioner's State license or authorization number or, where a scheduled drug product is requested, the practitioner's Drug Enforcement Administration number.

(iii) The proprietary or established name and the strength of the drug sample requested;

(iv) The quantity requested;

(v) The name of the manufacturer and the authorized distributor of record, if the drug sample is requested from an authorized distributor of record; and

(vi) The date of the request.

(2) A written request for a drug sample to be delivered by mail or common carrier to the pharmacy of a hospital or other health care entity is required to contain, in addition to all of the information in paragraph (b)(1) of this section, the name and address of the pharmacy of the hospital or other health care entity to which the drug sample is to be delivered.

(c) *Contents of the receipt to be completed upon delivery of a drug sample.* The receipt is to be on a form designated by the manufacturer or distributor, and is required to contain the following:

(1) If the drug sample is delivered to the licensed practitioner who requested it, the receipt is required to contain the name, address, professional title, and signature of the practitioner or the practitioner's designee who acknowledges delivery of the drug sample; the proprietary or established name and strength of the drug sample and the quantity of the drug sample delivered; and the date of the delivery.

(2) If the drug sample is delivered to the pharmacy of a hospital or other health care entity at the request of a licensed practitioner, the receipt is required to contain the name and address of the requesting licensed practitioner; the name and address of the hospital or health care entity pharmacy designated to receive the drug sample; the name, address, professional title, and signature of the person acknowledging delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

§ 203.31 Sample distribution by means other than mail or common carrier (direct delivery by a representative or detailer).

(a) *Requirements for drug sample distribution by means other than mail or common carrier.* A manufacturer or authorized distributor of record may distribute by means other than mail or common carrier, by a representative or detailer, a drug sample to a practitioner licensed to prescribe the drug to

be sampled or, at the written request of such a licensed practitioner, to the pharmacy of a hospital or other health care entity, provided that:

(1) The manufacturer or authorized distributor of record receives from the licensed practitioner a written request signed by the licensed practitioner before the delivery of the drug sample;

(2) The manufacturer or authorized distributor of record verifies with the appropriate State authority that the practitioner requesting the drug sample is licensed or authorized under State law to prescribe the drug product;

(3) A receipt is signed by the recipient, as set forth in paragraph (c) of this section, when the drug sample is delivered;

(4) The receipt is returned to the manufacturer or distributor; and

(5) The requirements of paragraphs (d) through (e) of this section are met.

(b) *Contents of the written request forms for delivery of samples by a representative.* (1) A written request for delivery of a drug sample by a representative to a licensed practitioner is required to contain the following:

(i) The name, address, professional title, and signature of the practitioner making the request;

(ii) The practitioner's State license or authorization number, or, where a scheduled drug product is requested, the practitioner's Drug Enforcement Administration number;

(iii) The proprietary or established name and the strength of the drug sample requested;

(iv) The quantity requested;

(v) The name of the manufacturer and the authorized distributor of record, if the drug sample is requested from an authorized distributor of record; and

(vi) The date of the request.

(2) A written request for delivery of a drug sample by a representative to the pharmacy of a hospital or other health care entity is required to contain, in addition to all of the information in paragraph (b) of this section, the name and address of the pharmacy of the hospital or other health care entity to which the drug sample is to be delivered.

(c) *Contents of the receipt to be completed upon delivery of a drug sample.* The receipt is to be on a form designated by the manufacturer or distributor, and is required to contain the following:

(1) If the drug sample is received at the address of the licensed practitioner who requested it, the receipt is required to contain the name, address, professional title, and signature of the practitioner or the practitioner's designee who acknowledges delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

(2) If the drug sample is received by the pharmacy of a hospital or other health care entity at the request of a licensed practitioner, the receipt is required to contain the name and address of the requesting licensed practitioner; the name and address of the hospital or health care entity pharmacy designated to receive the drug sample; the name, address, professional title, and signature of the person acknowledging delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

(d) *Inventory and reconciliation of drug samples of manufacturers' and distributors' representatives.* Each drug manufacturer or authorized distributor of record that distributes drug samples by means of representatives shall conduct, at least annually, a complete and accurate physical inventory of all drug samples. All drug samples in the possession or control of each manufacturer's and distributor's representatives are required to be inventoried and the results of the inventory are required to be recorded in an inventory record, as specified in paragraph (d)(1) of this section. In addition, manufacturers and distributors shall reconcile the results of the physical inventory with the most recently completed prior physical inventory and create a report documenting the reconciliation process, as specified in paragraph (d)(2) of this section.

(1) The inventory record is required to identify all drug samples in a representative's stock by the proprietary or established name, dosage strength, and number of units.

(2) The reconciliation report is required to include:

(i) The inventory record for the most recently completed prior inventory;

(ii) A record of each drug sample shipment received since the most recently completed prior inventory, including the sender and date of the shipment, and the proprietary or established name, dosage strength, and number of sample units received;

(iii) A record of drug sample distributions since the most recently completed inventory showing the name and address of each recipient of each sample unit shipped, the date of the shipment, and the proprietary or established name, dosage strength, and number of sample units shipped. For the purposes of this paragraph and paragraph (d)(2)(v) of this section, ''distributions'' includes distributions to health care practitioners or designated hospital or health care entity pharmacies, transfers or exchanges with other firm representatives, returns to the manufacturer or authorized distributor, destruction of drug samples by a sales representative, and other types of drug sample dispositions. The specific type of distribution must be specified in the record;

(iv) A record of drug sample thefts or significant losses reported by the representative since the most recently completed prior inventory, including the approximate date of the occurrence and the proprietary or established name, dosage strength, and number of sample units stolen or lost; and

(v) A record summarizing the information required by paragraphs (d)(2)(ii) through (d)(2)(iv) of this section. The record must show, for each type of sample unit (i.e., sample units having the same established or proprietary name and dosage strength), the total number of sample units received, distributed, lost, or stolen since the most recently completed prior inventory. For example, a typical entry in this record may read ''50 units risperidone (1 mg) returned to manufacturer'' or simply ''Risperidone (1 mg)/50/returned to manufacturer.''

(3) Each drug manufacturer or authorized distributor of record shall take appropriate internal control measures to guard against error and possible fraud in the conduct of the physical inventory and reconciliation, and in the preparation of the inventory record and reconciliation report.

(4) A manufacturer or authorized distributor of record shall carefully evaluate any apparent discrepancy or significant loss revealed through the inventory and reconciliation process and shall fully investigate any such discrepancy or significant loss that cannot be justified.

(e) *Lists of manufacturers' and distributors' representatives.* Each drug manufacturer or authorized distributor of record who distributes drug samples by means of representatives shall maintain a list of the names and addresses of its representatives who distribute drug samples and of the sites where drug samples are stored.

§ 203.32 Drug sample storage and handling requirements.

(a) *Storage and handling conditions.* Manufacturers, authorized distributors of record, and their representatives shall store and handle all drug samples under conditions that will maintain their stability, integrity, and effectiveness and ensure that the drug samples are free of contamination, deterioration, and adulteration.

(b) *Compliance with compendial and labeling requirements.* Manufacturers, authorized distributors of record, and their representatives can generally comply with this section by following the compendial and labeling requirements for storage and handling of a particular prescription drug in handling samples of that drug.

§ 203.33 Drug sample forms.

A sample request or receipt form may be delivered by mail, common carrier, or private courier or may be transmitted photographically or electronically (i.e., by telephoto, wirephoto, radiophoto, facsimile transmission (FAX), xerography, or electronic data transfer) or by any other system, provided that the method for

transmission meets the security requirements set forth in § 203.60(c).

§ 203.34 Policies and procedures; administrative systems.

Each manufacturer or authorized distributor of record that distributes drug samples shall establish, maintain, and adhere to written policies and procedures describing its administrative systems for the following:

(a) Distributing drug samples by mail or common carrier, including methodology for reconciliation of requests and receipts;

(b) Distributing drug samples by means other than mail or common carrier including the methodology for:

(1) Reconciling requests and receipts, identifying patterns of nonresponse, and the manufacturer's or distributor's response when such patterns are found;

(2) Conducting the annual physical inventory and preparation of the reconciliation report;

(3) Implementing a sample distribution security and audit system, including conducting random and for-cause audits of sales representatives by personnel independent of the sales force; and

(4) Storage of drug samples by representatives;

(c) Identifying any significant loss of drug samples and notifying FDA of the loss; and

(d) Monitoring any loss or theft of drug samples.

§ 203.35 Standing requests.

Manufacturers or authorized distributors of record shall not distribute drug samples on the basis of open-ended or standing requests, but shall require separate written requests for each drug sample or group of samples. An arrangement by which a licensed practitioner requests in writing that a specified number of drug samples be delivered over a period of not more than 6 months, with the actual delivery dates for parts of the order to be set by subsequent oral communication or electronic transmission, is not considered to be a standing request.

§ 203.36 Fulfillment houses, shipping and mailing services, comarketing agreements, and third-party recordkeeping.

(a) *Responsibility for creating and maintaining forms, reports, and records.* Any manufacturer or authorized distributor of record that uses a fulfillment house, shipping or mailing service, or other third party, or engages in a comarketing agreement with another manufacturer or distributor to distribute drug samples or to meet any of the requirements of PDMA, PDA, or this part, remains responsible for creating and maintaining all requests, receipts, forms, reports, and records required under PDMA, PDA, and this part.

(b) *Responsibility for producing requested forms, reports, or records.* A manufacturer or authorized distributor of record that contracts with a third party to maintain some or all of its records shall produce requested forms, reports, records, or other required documents within 2 business days of a request by an authorized representative of FDA or another Federal, State, or local regulatory or law enforcement official.

§ 203.37 Investigation and notification requirements.

(a) *Investigation of falsification of drug sample records.* A manufacturer or authorized distributor of record that has reason to believe that any person has falsified drug sample requests, receipts, or records, or is diverting drug samples, shall:

(1) Notify FDA, by telephone or in writing, within 5 working days;

(2) Immediately initiate an investigation; and

(3) Provide FDA with a complete written report, including the reason for and the results of the investigation, not later than 30 days after the date of the initial notification in paragraph (a)(1) of this section.

(b) *Significant loss or known theft of drug samples.* A manufacturer or authorized distributor of record that distributes drug samples or a charitable institution that receives donated drug samples from a licensed practitioner shall:

(1) Notify FDA, by telephone or in writing, within 5 working days of becoming aware of a significant loss or known theft;

(2) Immediately initiate an investigation into the significant loss or known theft; and

(3) Provide FDA with a complete written report, including the reason for and the results of the investigation, not later than 30 days after the date of the initial notification in paragraph (b)(1) of this section.

(c) *Conviction of a representative.* (1) A manufacturer or authorized distributor of record that distributes drug samples shall notify FDA, by telephone or in writing, within 30 days of becoming aware of the conviction of one or more of its representatives for a violation of section 503(c)(1) of the act or any State law involving the sale, purchase, or trade of a drug sample or the offer to sell, purchase, or trade a drug sample.

(2) A manufacturer or authorized distributor of record shall provide FDA with a complete written report not later than 30 days after the date of the initial notification.

(d) *Selection of individual responsible for drug sample information.* A manufacturer or authorized distributor of record that distributes drug samples shall inform FDA in writing within 30 days of selecting the individual responsible for responding to a request for information about drug samples of that individual's name, business address, and telephone number.

(e) *Whom to notify at FDA.* Notifications and reports concerning prescription human drugs and biological products regulated by the Center for Drug Evaluation and Research shall be made to the Division of Compliance Risk Management and Surveillance, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002. Notifications and reports concerning prescription human biological products regulated by the Center for Biologics Evaluation and Research shall be made to the Division of Inspections and Surveillance (HFM–650), Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852.

[64 FR 67756, Dec. 3, 1999, as amended at 69 FR 48775, Aug. 11, 2004; 70 FR 14981, Mar. 24, 2005; 74 FR 13112, Mar. 26, 2009]

§ 203.38 Sample lot or control numbers; labeling of sample units.

(a) *Lot or control number required on drug sample labeling and sample unit label.* The manufacturer or authorized distributor of record of a drug sample shall include on the label of the sample unit and on the outside container or packaging of the sample unit, if any, an identifying lot or control number that will permit the tracking of the distribution of each drug sample unit.

(b) *Records containing lot or control numbers required for all drug samples distributed.* A manufacturer or authorized distributor of record shall maintain for all samples distributed records of drug sample distribution containing lot or control numbers that are sufficient to permit the tracking of sample units to the point of the licensed practitioner.

(c) *Labels of sample units.* Each sample unit shall bear a label that clearly denotes its status as a drug sample, e.g., ''sample,'' ''not for sale,'' ''professional courtesy package.''

(1) A drug that is labeled as a drug sample is deemed to be a drug sample within the meaning of the act.

(2) A drug product dosage unit that bears an imprint identifying the dosage form as a drug sample is deemed to be a drug sample within the meaning of the act.

(3) Notwithstanding paragraphs (c)(1) and (c)(2) of this section, any article that is a drug sample as defined in section 503(c)(1) of the act and § 203.3(i) that fails to bear the label required in this paragraph (c) is a drug sample.

§ 203.39 Donation of drug samples to charitable institutions.

A charitable institution may receive a drug sample donated by a licensed practitioner or another charitable institution for dispensing to a patient of the charitable institution, or donate a drug sample to another charitable institution for dispensing to its patients, provided that the following requirements are met:

(a) A drug sample donated by a licensed practitioner or donating charitable institution shall be received by a charitable institution in its original, unopened packaging with its labeling intact.

(b) Delivery of a donated drug sample to a recipient charitable institution shall be completed by mail or common carrier, collection by an authorized agent or employee of the recipient charitable institution, or personal delivery by a licensed practitioner or an agent or employee of the donating charitable institution. Donated drug samples shall be placed by the donor in a sealed carton for delivery to or collection by the recipient charitable institution.

(c) A donated drug sample shall not be dispensed to a patient or be distributed to another charitable institution until it has been examined by a licensed practitioner or registered pharmacist at the recipient charitable institution to confirm that the donation record accurately describes the drug sample delivered and that no drug sample is adulterated or misbranded for any reason, including, but not limited to, the following:

(1) The drug sample is out of date;

(2) The labeling has become mutilated, obscured, or detached from the drug sample packaging;

(3) The drug sample shows evidence of having been stored or shipped under conditions that might adversely affect its stability, integrity, or effectiveness;

(4) The drug sample is for a prescription drug product that has been recalled or is no longer marketed; or

(5) The drug sample is otherwise possibly contaminated, deteriorated, or adulterated.

(d) The recipient charitable institution shall dispose of any drug sample found to be unsuitable by destroying it or by returning it to the manufacturer. The charitable institution shall maintain complete records of the disposition of all destroyed or returned drug samples.

(e) The recipient charitable institution shall prepare at the time of collection or delivery of a drug sample a complete and accurate donation record, a copy of which shall be retained by the recipient charitable institution for at least 3 years, containing the following information:

(1) The name, address, and telephone number of the licensed practitioner (or donating charitable institution);

(2) The manufacturer, brand name, quantity, and lot or control number of the drug sample donated; and

(3) The date of the donation.

(f) Each recipient charitable institution shall maintain complete and accurate records of donation, receipt, inspection, inventory, dispensing, redistribution, destruction, and returns sufficient for complete accountability and auditing of drug sample stocks.

(g) Each recipient charitable institution shall conduct, at least annually, an inventory of prescription drug sample stocks and shall prepare a report reconciling the results of each inventory with the most recent prior inventory. Drug sample inventory discrepancies and reconciliation problems shall be investigated by the charitable institution and reported to FDA.

(h) A recipient charitable institution shall store drug samples under conditions that will maintain the sample's stability, integrity, and effectiveness, and will ensure that the drug samples will be free of contamination, deterioration, and adulteration.

(i) A charitable institution shall notify FDA within 5 working days of becoming aware of a significant loss or known theft of prescription drug samples.

Subpart E—Wholesale Distribution

§ 203.50 Requirements for wholesale distribution of prescription drugs.

(a) *Identifying statement for sales by unauthorized distributors.* Before the completion of any wholesale distribution by a wholesale distributor of a prescription drug for which the seller is not an authorized distributor of record to another wholesale distributor or retail pharmacy, the seller shall provide to the purchaser a statement identifying each prior sale, purchase, or trade of such drug. This identifying statement shall include:

(1) The proprietary and established name of the drug;

(2) Dosage;

(3) Container size;

(4) Number of containers;

(5) The drug's lot or control number(s);

(6) The business name and address of all parties to each prior transaction involving the drug, starting with the manufacturer; and

(7) The date of each previous transaction.

(b) The drug origin statement is subject to the record retention requirements of § 203.60 and must be retained by all wholesale distributors involved in the distribution of the drug product, whether authorized or unauthorized, for 3 years.

(c) *Identifying statement not required when additional manufacturing processes are completed.* A manufacturer that subjects a drug to any additional manufacturing processes to produce a different drug is not required to provide to a purchaser a statement identifying the previous sales of the component drug or drugs.

(d) *List of authorized distributors of record.* Each manufacturer shall maintain at the corporate offices a current written list of all authorized distributors of record.

(1) Each manufacturer's list of authorized distributors of record shall specify whether each distributor listed thereon is authorized to distribute the manufacturer's full product line or only particular, specified products.

(2) Each manufacturer shall update its list of authorized distributors of record on a continuing basis.

(3) Each manufacturer shall make its list of authorized distributors of record available on request to the public for inspection or copying. A manufacturer may impose reasonable copying charges for such requests from members of the public.

Subpart F—Request and Receipt Forms, Reports, and Records

§ 203.60 Request and receipt forms, reports, and records.

(a) *Use of electronic records, electronic signatures, and handwritten signatures executed to electronic records.* (1) Provided the requirements of part 11 of this chapter are met, electronic records, electronic signatures, and handwritten signatures executed to electronic records may be used as an alternative to paper records and handwritten signatures executed on paper to meet any of the record and signature requirements of PDMA, PDA, or this part.

(2) Combinations of paper records and electronic records, electronic records and handwritten signatures executed on paper, or paper records and electronic signatures or handwritten signatures executed to electronic records, may be used to meet any of the record and signature requirements of PDMA, PDA, or this part, provided that:

(i) The requirements of part 11 of this chapter are met for the electronic records, electronic signatures, or handwritten signatures executed to electronic records; and

(ii) A reasonably secure link between the paper-based and electronic components exists such that the combined records and signatures are trustworthy and reliable, and to ensure that the signer cannot readily repudiate the signed records as not genuine.

(3) For the purposes of this paragraph (a), the phrase ''record and signature requirements of PDMA, PDA, or this part'' includes drug sample request and receipt forms, reports, records, and other documents, and their associated signatures required by PDMA, PDA, and this part.

(b) *Maintenance of request and receipt forms, reports, records, and other documents created on paper.* Request and receipt forms, reports, records, and other documents created on paper may be maintained on paper or by photographic imaging (i.e., photocopies or microfiche), provided that the security and authentication requirements described in paragraph (c) of this section are followed. Where a required document is created on paper and electronically scanned into a computer, the resulting record is an electronic record that must meet the requirements of part 11 of this chapter.

(c) *Security and authentication requirements for request and receipt forms, reports, records, and other documents created on paper.* A request or receipt form, report, record, or other document, and any signature appearing thereon, that is created on paper and

that is maintained by photographic imaging, or transmitted electronically (i.e., by facsimile) shall be maintained or transmitted in a form that provides reasonable assurance of being:

(1) Resistant to tampering, revision, modification, fraud, unauthorized use, or alteration;

(2) Preserved in accessible and retrievable fashion; and

(3) Available to permit copying for purposes of review, analysis, verification, authentication, and reproduction by the person who executed the form or created the record, by the manufacturer or distributor, and by authorized personnel of FDA and other regulatory and law enforcement agencies.

(d) *Retention of request and receipt forms, reports, lists, records, and other documents.* Any person required to create or maintain reports, lists, or other records under PDMA, PDA, or this part, including records relating to the distribution of drug samples, shall retain them for at least 3 years after the date of their creation.

(e) *Availability of request and receipt forms, reports, lists, and records.* Any person required to create or maintain request and receipt forms, reports, lists, or other records under PDMA, PDA, or this part shall make them available, upon request, in a form that permits copying or other means of duplication, to FDA or other Federal, State, or local regulatory and law enforcement officials for review and reproduction. The records shall be made available within 2 business days of a request.

Subpart G—Rewards

§ 203.70 Application for a reward.

(a) *Reward for providing information leading to the institution of a criminal proceeding against, and conviction of, a person for the sale, purchase, or trade of a drug sample.* A person who provides information leading to the institution of a criminal proceeding against, and conviction of, a person for the sale, purchase, or trade of a drug sample, or the offer to sell, purchase, or trade a drug sample, in violation of section 503(c)(1) of the act, is entitled to one-half the criminal fine imposed and collected for such violation, but not more than $125,000.

(b) *Procedure for making application for a reward for providing information leading to the institution of a criminal proceeding against, and conviction of, a person for the sale, purchase, or trade of a drug sample.* A person who provides information leading to the institution of a criminal proceeding against, and conviction of, a person for the sale, purchase, or trade of a drug sample, or the offer to sell, purchase, or trade a drug sample, in violation of section 503(c)(1) of the act, may apply for a reward by making written application to:

(1) Director, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002; or

(2) Director, Office of Compliance and Biologics Quality (HFM–600), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, as appropriate.

[64 FR 67756, Dec. 3, 1999, as amended at 69 FR 48775, Aug. 11, 2004; 74 FR 13112, Mar. 26, 2009]

PART 205—GUIDELINES FOR STATE LICENSING OF WHOLESALE PRESCRIPTION DRUG DISTRIBUTORS

Sec.

205.1 Scope.
205.2 Purpose.
205.3 Definitions.
205.4 Wholesale drug distributor licensing requirement.
205.5 Minimum required information for licensure.
205.6 Minimum qualifications.
205.7 Personnel.
205.8 Violations and penalties.
205.50 Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

AUTHORITY: 21 U.S.C. 351, 352, 353, 371, 374.

SOURCE: 55 FR 38023, Sept. 14, 1990, unless otherwise noted.

§ 205.1 Scope.

This part applies to any person, partnership, corporation, or business firm in a State engaging in the wholesale

distribution of human prescription drugs in interstate commerce.

§ 205.2 Purpose.

The purpose of this part is to implement the Prescription Drug Marketing Act of 1987 by providing minimum standards, terms, and conditions for the licensing by State licensing authorities of persons who engage in wholesale distributions in interstate commerce of prescription drugs.

§ 205.3 Definitions.

(a) *Blood* means whole blood collected from a single donor and processed either for transfusion or further manufacturing.

(b) *Blood component* means that part of blood separated by physical or mechanical means.

(c) *Drug sample* means a unit of a prescription drug that is not intended to be sold and is intended to promote the sale of the drug.

(d) *Manufacturer* means anyone who is engaged in manufacturing, preparing, propagating, compounding, processing, packaging, repackaging, or labeling of a prescription drug.

(e) *Prescription drug* means any human drug required by Federal law or regulation to be dispensed only by a prescription, including finished dosage forms and active ingredients subject to section 503(b) of the Federal Food, Drug, and Cosmetic Act.

(f) *Wholesale distribution* and *wholesale distribution* means distribution of prescription drugs to persons other than a consumer or patient, but does not include:

(1) Intracompany sales;

(2) The purchase or other acquisition by a hospital or other health care entity that is a member of a group purchasing organization of a drug for its own use from the group purchasing organization or from other hospitals or health care entities that are members of such organizations;

(3) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug by a charitable organization described in section 501(c)(3) of the Internal Revenue Code of 1954 to a nonprofit affiliate of the organization to the extent otherwise permitted by law;

(4) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug among hospitals or other health care entities that are under common control; for purposes of this section, *common control* means the power to direct or cause the direction of the management and policies of a person or an organization, whether by ownership of stock, voting rights, by contract, or otherwise;

(5) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug for emergency medical reasons; for purposes of this section, *emergency medical reasons* includes transfers of prescription drugs by a retail pharmacy to another retail pharmacy to alleviate a temporary shortage;

(6) The sale, purchase, or trade of a drug, an offer to sell, purchase, or trade a drug, or the dispensing of a drug pursuant to a prescription;

(7) The distribution of drug samples by manufacturers' representatives or distributors' representatives; or

(8) The sale, purchase, or trade of blood and blood components intended for transfusion.

(9) Drug returns, when conducted by a hospital, health care entity, or charitable institution in accordance with § 203.23 of this chapter; or

(10) The sale of minimal quantities of drugs by retail pharmacies to licensed practitioners for office use.

(g) *Wholesale distributor* means any one engaged in wholesale distribution of prescription drugs, including, but not limited to, manufacturers; repackers; own-label distributors; private-label distributors; jobbers; brokers; warehouses, including manufacturers' and distributors' warehouses, chain drug warehouses, and wholesale drug warehouses; independent wholesale drug traders; and retail pharmacies that conduct wholesale distributions.

(h) *Health care entity* means any person that provides diagnostic, medical, surgical, or dental treatment, or chronic or rehabilitative care, but does not include any retail pharmacy or any wholesale distributor. Except as provided in § 203.22(h) and (i) of this chapter, a person cannot simultaneously be

a ''health care entity'' and a retail pharmacy or wholesale distributor.

[55 FR 38023, Sept. 14, 1990, as amended at 64 FR 67762, Dec. 3, 1999, 73 FR 59501, Oct. 9, 2008]

§ 205.4 Wholesale drug distributor licensing requirement.

Every wholesale distributor in a State who engages in wholesale distributions of prescription drugs in interstate commerce must be licensed by the State licensing authority in accordance with this part before engaging in wholesale distributions of prescription drugs in interstate commerce.

§ 205.5 Minimum required information for licensure.

(a) The State licensing authority shall require the following minimum information from each wholesale drug distributor as part of the license described in § 205.4 and as part of any renewal of such license:

(1) The name, full business address, and telephone number of the licensee;

(2) All trade or business names used by the licensee;

(3) Addresses, telephone numbers, and the names of contact persons for all facilities used by the licensee for the storage, handling, and distribution of prescription drugs;

(4) The type of ownership or operation (i.e., partnership, corporation, or sole proprietorship); and

(5) The name(s) of the owner and/or operator of the licensee, including:

(i) If a person, the name of the person;

(ii) If a partnership, the name of each partner, and the name of the partnership;

(iii) If a corporation, the name and title of each corporate officer and director, the corporate names, and the name of the State of incorporation; and

(iv) If a sole proprietorship, the full name of the sole proprietor and the name of the business entity.

(b) The State licensing authority may provide for a single license for a business entity operating more than one facility within that State, or for a parent entity with divisions, subsidiaries, and/or affiliate companies within that State when operations are conducted at more than one location and there exists joint ownership and control among all the entities.

(c) Changes in any information in paragraph (a) of this section shall be submitted to the State licensing authority as required by such authority.

(Approved by the Office of Management and Budget under control number 0910–0251)

§ 205.6 Minimum qualifications.

(a) The State licensing authority shall consider, at a minimum, the following factors in reviewing the qualifications of persons who engage in wholesale distribution of prescription drugs within the State:

(1) Any convictions of the applicant under any Federal, State, or local laws relating to drug samples, wholesale or retail drug distribution, or distribution of controlled substances;

(2) Any felony convictions of the applicant under Federal, State, or local laws;

(3) The applicant's past experience in the manufacture or distribution of prescription drugs, including controlled substances;

(4) The furnishing by the applicant of false or fraudulent material in any application made in connection with drug manufacturing or distribution;

(5) Suspension or revocation by Federal, State, or local government of any license currently or previously held by the applicant for the manufacture or distribution of any drugs, including controlled substances;

(6) Compliance with licensing requirements under previously granted licenses, if any;

(7) Compliance with requirements to maintain and/or make available to the State licensing authority or to Federal, State, or local law enforcement officials those records required under this section; and

(8) Any other factors or qualifications the State licensing authority considers relevant to and consistent with the public health and safety.

(b) The State licensing authority shall have the right to deny a license to an applicant if it determines that the granting of such a license would not be in the public interest.

§ 205.7 Personnel.

The State licensing authority shall require that personnel employed in wholesale distribution have appropriate education and/or experience to assume responsibility for positions related to compliance with State licensing requirements.

§ 205.8 Violations and penalties.

(a) State licensing laws shall provide for the suspension or revocation of licenses upon conviction of violations of Federal, State, or local drug laws or regulations, and may provide for fines, imprisonment, or civil penalties.

(b) State licensing laws shall provide for suspension or revocation of licenses, where appropriate, for violations of its provisions.

§ 205.50 Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

The State licensing law shall include the following minimum requirements for the storage and handling of prescription drugs, and for the establishment and maintenance of prescription drug distribution records by wholesale drug distributors and their officers, agents, representatives, and employees:

(a) *Facilities.* All facilities at which prescription drugs are stored, warehoused, handled, held, offered, marketed, or displayed shall:

(1) Be of suitable size and construction to facilitate cleaning, maintenance, and proper operations;

(2) Have storage areas designed to provide adequate lighting, ventilation, temperature, sanitation, humidity, space, equipment, and security conditions;

(3) Have a quarantine area for storage of prescription drugs that are outdated, damaged, deteriorated, misbranded, or adulterated, or that are in immediate or sealed, secondary containers that have been opened;

(4) Be maintained in a clean and orderly condition; and

(5) Be free from infestation by insects, rodents, birds, or vermin of any kind.

(b) *Security.* (1) All facilities used for wholesale drug distribution shall be secure from unauthorized entry.

(i) Access from outside the premises shall be kept to a minimum and be well-controlled.

(ii) The outside perimeter of the premises shall be well-lighted.

(iii) Entry into areas where prescription drugs are held shall be limited to authorized personnel.

(2) All facilities shall be equipped with an alarm system to detect entry after hours.

(3) All facilities shall be equipped with a security system that will provide suitable protection against theft and diversion. When appropriate, the security system shall provide protection against theft or diversion that is facilitated or hidden by tampering with computers or electronic records.

(c) *Storage.* All prescription drugs shall be stored at appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the United States Pharmacopeia/National Formulary (USP/NF).

(1) If no storage requirements are established for a prescription drug, the drug may be held at ''controlled'' room temperature, as defined in an official compendium, to help ensure that its identity, strength, quality, and purity are not adversely affected.

(2) Appropriate manual, electromechanical, or electronic temperature and humidity recording equipment, devices, and/or logs shall be utilized to document proper storage of prescription drugs.

(3) The recordkeeping requirements in paragraph (f) of this section shall be followed for all stored drugs.

(d) *Examination of materials.* (1) Upon receipt, each outside shipping container shall be visually examined for identity and to prevent the acceptance of contaminated prescription drugs or prescription drugs that are otherwise unfit for distribution. This examination shall be adequate to reveal container damage that would suggest possible contamination or other damage to the contents.

(2) Each outgoing shipment shall be carefully inspected for identity of the prescription drug products and to ensure that there is no delivery of prescription drugs that have been damaged in storage or held under improper conditions.

(3) The recordkeeping requirements in paragraph (f) of this section shall be followed for all incoming and outgoing prescription drugs.

(e) *Returned, damaged, and outdated prescription drugs.* (1) Prescription drugs that are outdated, damaged, deteriorated, misbranded, or adulterated shall be quarantined and physically separated from other prescription drugs until they are destroyed or returned to their supplier.

(2) Any prescription drugs whose immediate or sealed outer or sealed secondary containers have been opened or used shall be identified as such, and shall be quarantined and physically separated from other prescription drugs until they are either destroyed or returned to the supplier.

(3) If the conditions under which a prescription drug has been returned cast doubt on the drug's safety, identity, strength, quality, or purity, then the drug shall be destroyed, or returned to the supplier, unless examination, testing, or other investigation proves that the drug meets appropriate standards of safety, identity, strength, quality, and purity. In determining whether the conditions under which a drug has been returned cast doubt on the drug's safety, identity, strength, quality, or purity, the wholesale drug distributor shall consider, among other things, the conditions under which the drug has been held, stored, or shipped before or during its return and the condition of the drug and its container, carton, or labeling, as a result of storage or shipping.

(4) The recordkeeping requirements in paragraph (f) of this section shall be followed for all outdated, damaged, deteriorated, misbranded, or adulterated prescription drugs.

(f) *Recordkeeping.* (1) Wholesale drug distributors shall establish and maintain inventories and records of all transactions regarding the receipt and distribution or other disposition of prescription drugs. These records shall include the following information:

(i) The source of the drugs, including the name and principal address of the seller or transferor, and the address of the location from which the drugs were shipped;

(ii) The identity and quantity of the drugs received and distributed or disposed of; and

(iii) The dates of receipt and distribution or other disposition of the drugs.

(2) Inventories and records shall be made available for inspection and photocopying by authorized Federal, State, or local law enforcement agency officials for a period of 3 years after the date of their creation.

(3) Records described in this section that are kept at the inspection site or that can be immediately retrieved by computer or other electronic means shall be readily available for authorized inspection during the retention period. Records kept at a central location apart from the inspection site and not electronically retrievable shall be made available for inspection within 2 working days of a request by an authorized official of a Federal, State, or local law enforcement agency.

(g) *Written policies and procedures.* Wholesale drug distributors shall establish, maintain, and adhere to written policies and procedures, which shall be followed for the receipt, security, storage, inventory, and distribution of prescription drugs, including policies and procedures for identifying, recording, and reporting losses or thefts, and for correcting all errors and inaccuracies in inventories. Wholesale drug distributors shall include in their written policies and procedures the following:

(1) A procedure whereby the oldest approved stock of a prescription drug product is distributed first. The procedure may permit deviation from this requirement, if such deviation is temporary and appropriate.

(2) A procedure to be followed for handling recalls and withdrawals of prescription drugs. Such procedure shall be adequate to deal with recalls and withdrawals due to:

(i) Any action initiated at the request of the Food and Drug Administration or other Federal, State, or

local law enforcement or other government agency, including the State licensing agency;

(ii) Any voluntary action by the manufacturer to remove defective or potentially defective drugs from the market; or

(iii) Any action undertaken to promote public health and safety by replacing of existing merchandise with an improved product or new package design.

(3) A procedure to ensure that wholesale drug distributors prepare for, protect against, and handle any crisis that affects security or operation of any facility in the event of strike, fire, flood, or other natural disaster, or other situations of local, State, or national emergency.

(4) A procedure to ensure that any outdated prescription drugs shall be segregated from other drugs and either returned to the manufacturer or destroyed. This procedure shall provide for written documentation of the disposition of outdated prescription drugs. This documentation shall be maintained for 2 years after disposition of the outdated drugs.

(h) *Responsible persons*. Wholesale drug distributors shall establish and maintain lists of officers, directors, managers, and other persons in charge of wholesale drug distribution, storage, and handling, including a description of their duties and a summary of their qualifications.

(i) *Compliance with Federal, State, and local law*. Wholesale drug distributors shall operate in compliance with applicable Federal, State, and local laws and regulations.

(1) Wholesale drug distributors shall permit the State licensing authority and authorized Federal, State, and local law enforcement officials to enter and inspect their premises and delivery vehicles, and to audit their records and written operating procedures, at reasonable times and in a reasonable manner, to the extent authorized by law.

(2) Wholesale drug distributors that deal in controlled substances shall register with the appropriate State controlled substance authority and with the Drug Enforcement Administration (DEA), and shall comply with all applicable State, local, and DEA regulations.

(j) *Salvaging and reprocessing*. Wholesale drug distributors shall be subject to the provisions of any applicable Federal, State, or local laws or regulations that relate to prescription drug product salvaging or reprocessing, including parts 207, 210, and 211 of this chapter.

(Approved by the Office of Management and Budget under control number 0910–0251)

[55 FR 38023, Sept. 14, 1990, as amended at 64 FR 67763, Dec. 3, 1999]

PART 206—IMPRINTING OF SOLID ORAL DOSAGE FORM DRUG PRODUCTS FOR HUMAN USE

Sec.
206.1 Scope.
206.3 Definitions.
206.7 Exemptions.
206.10 Code imprint required.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 355, 371; 42 U.S.C. 262.

SOURCE: 58 FR 47958, Sept. 13, 1993, unless otherwise noted.

§ 206.1 Scope.

This part applies to all solid oral dosage form human drug products, including prescription drug products, over-the-counter drug products, biological drug products, and homeopathic drug products, unless otherwise exempted under § 206.7.

§ 206.3 Definitions.

The following definitions apply to this part:

The act means the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et seq.*).

Debossed means imprinted with a mark below the dosage form surface.

Drug product means a finished dosage form, e.g., a tablet or capsule that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Embossed means imprinted with a mark raised above the dosage form surface.

Engraved means imprinted with a code that is cut into the dosage form surface after it has been completed.

Imprinted means marked with an identification code by means of embossing, debossing, engraving, or printing with ink.

Manufacturer means the manufacturer as described in §§ 201.1 and 600.3(t) of this chapter.

Solid oral dosage form means capsules, tablets, or similar drug products intended for oral use.

§ 206.7 Exemptions.

(a) The following classes of drug products are exempt from requirements of this part:

(1) Drug products intended for use in a clinical investigation under section 505(i) of the act, but not including drugs distributed under a treatment IND under part 312 of this chapter or distributed as part of a nonconcurrently controlled study. Placebos intended for use in a clinical investigation are exempt from the requirements of this part if they are designed to copy the active drug products used in that investigation.

(2) Drugs, other than reference listed drugs, intended for use in bioequivalence studies.

(3) Drugs that are extemporaneously compounded by a licensed pharmacist, upon receipt of a valid prescription for an individual patient from a practitioner licensed by law to prescribe or administer drugs, to be used solely by the patient for whom they are prescribed.

(4) Radiopharmaceutical drug products.

(b) Exemption of drugs because of size or unique physical characteristics:

(1) For a drug subject to premarket approval, FDA may provide an exemption from the requirements of § 206.10 upon a showing that the product's size, shape, texture, or other physical characteristics make imprinting technologically infeasible or impossible.

(i) Exemption requests for products with approved applications shall be made in writing to the appropriate review division in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 5901–B Ammendale Rd., Beltsville, MD 20705–1266 or the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. If FDA denies the request, the holder of the approved application will have 1 year after the date of an agency denial to imprint the drug product.

(ii) Exemption requests for products that have not yet received approval shall be made in writing to the appropriate review division in CDER or CBER.

(2) Any product not subject to premarket approval is exempt from the requirement of § 206.10 if, based on the product's size, shape, texture, or other physical characteristics, the manufacturer or distributor of the product is prepared to demonstrate that imprinting the dosage form is technologically infeasible or impossible.

(c) For drugs that are administered solely in controlled health care settings and not provided to patients for self-administration, sponsors may submit requests for exemptions from the requirements of this rule. Controlled settings include physicians' offices and other health care facilities. Exemption requests should be submitted in writing to the appropriate review division in CDER or CBER.

[58 FR 47958, Sept. 13, 1993, as amended at 70 FR 14981, Mar. 24, 2005; 74 FR 13112, Mar. 26, 2009]

§ 206.10 Code imprint required.

(a) Unless exempted under § 206.7, no drug product in solid oral dosage form may be introduced or delivered for introduction into interstate commerce unless it is clearly marked or imprinted with a code imprint that, in conjunction with the product's size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product. Identification of the drug product requires identification of its active ingredients and its dosage strength. Inclusion of a letter or number in the imprint, while not required, is encouraged as a more effective means of identification than a symbol or logo by itself. Homeopathic drug products are required only to bear an imprint that identifies the manufacturer and their homeopathic nature.

(b) A holder of an approved application who has, under § 314.70 (b) of this chapter, supplemented its application

to provide for a new imprint is not required to bring its product into compliance with this section during the pendency of the agency's review. Once the review is complete, the drug product is subject to the requirements of the rule.

(c) A solid oral dosage form drug product that does not meet the requirement for imprinting in paragraph (a) of this section and is not exempt from the requirement may be considered adulterated and misbranded and may be an unapproved new drug.

(d) For purposes of this section, *code imprint* means any single letter or number or any combination of letters and numbers, including, e.g., words, company name, and National Drug Code, or a mark, symbol, logo, or monogram, or a combination of letters, numbers, and marks or symbols, assigned by a drug firm to a specific drug product.

[58 FR 47958, Sept. 13, 1993, as amended at 60 FR 19846, Apr. 21, 1995; 69 FR 18763, Apr. 8, 2004]

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

Subpart A—General

Sec.
207.3 Definitions.
207.7 Establishment registration and product listing for human blood and blood products and for medical devices.

Subpart B—Exemptions

207.10 Exemptions for establishments.

Subpart C—Procedures for Domestic Drug Establishments

207.20 Who must register and submit a drug list.
207.21 Times for registration and drug listing.
207.22 How and where to register and list drugs.
207.25 Information required in registration and drug listing.
207.26 Amendments to registration.
207.30 Updating drug listing information.
207.31 Additional drug listing information.
207.35 Notification of registrant; drug establishment registration number and drug listing number.
207.37 Inspection of registrations and drug listings.
207.39 Misbranding by reference to registration or to registration number.

Subpart D—Procedure for Foreign Drug Establishments

207.40 Establishment registration and drug listing requirements for foreign establishments.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360b, 371, 374, 381, 393; 42 U.S.C. 262, 264, 271.

SOURCE: 45 FR 38043, June 6, 1980, unless otherwise noted.

Subpart A—General

§ 207.3 Definitions.

(a) The following definitions apply to this part:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act approved June 25, 1938 (52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 301–392)), except as otherwise provided.

(2) *Advertising* and *labeling* include the promotional material described in § 202.1(l) (1) and (2) respectively.

(3) *Any material change* includes but is not limited to any change in the name of the drug, any change in the identity or quantity of the active ingredient(s), any change in the identity or quantity of the inactive ingredient(s) where quantitative listing of all ingredients is required by § 207.31(a)(2), any significant change in the labeling of a prescription drug, and any significant change in the label or package insert of an over-the-counter drug. Changes that are not significant include changes in arrangement or printing or changes of an editorial nature.

(4) *Bulk drug substance* means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

(5) *Commercial distribution* means any distribution of a human drug except for investigational use under part 312 of this chapter, and any distribution of an animal drug or animal feed bearing or containing an animal drug for noninvestigational uses, but the term does not include internal or interplant

transfer of a bulk drug substance between registered establishments within the same parent, subsidiary, and/or affiliate company. For foreign establishments, the term ''commercial distribution'' shall have the same meaning except that the term shall not include distribution of any drug that is neither imported nor offered for import into the United States.

(6) *Drug product salvaging* means the act of segregating drug products that may have been subjected to improper storage conditions, such as extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation, for the purpose of returning some or all of the products to the marketplace.

(7) *Establishment* means a place of business under one management at one general physical location. The term includes, among others, independent laboratories that engage in control activities for a registered drug establishment (e.g., *consulting* laboratories), manufacturers of medicated feeds and of vitamin products that are drugs in accordance with section 201(g) of the act, human blood donor centers, and animal facilities used for the production or control testing of licensed biologicals, and establishments engaged in drug product salvaging.

(8) *Manufacturing or processing* means the *manufacture, preparation, propagation, compounding, or processing of a drug or drugs* as used in section 510 of the act and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

(9) *Representative sampling of advertisements* means typical advertising material (excluding labeling as determined in § 202.1(l) (1) and (2)) that gives a balanced picture of the promotional claims used for the drug, e.g., if more than one medical journal advertisement is used but the promotional content is essentially identical, only one need be submitted.

(10) *Representative sampling of any other labeling* means typical labeling material (excluding labels and package inserts) that gives a balanced picture of the promotional claims used for the drug, e.g., if more than one brochure is used but the promotional content is essentially identical, only one need be submitted.

(11) *United States agent* means a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent. This definition excludes mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment's agent is not physically present.

(b) The definitions and interpretations of terms in sections 201, 502(e), and 510 of the act apply to the use of terms in this part.

[45 FR 38043, June 6, 1980, as amended at 55 FR 11576, Mar. 29, 1990; 66 FR 59156, Nov. 27, 2001]

§ 207.7 Establishment registration and product listing for human blood and blood products and for medical devices.

(a) Owners and operators of human blood and blood product establishments shall register and list their products with the Center for Biologics Evaluation and Research (HFM–375), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, on Form FDA–2830 (Blood Establishment Registration and Product Listing), in accordance with part 607 of this chapter. Such owners and operators who also manufacture or process other drug products at the same establishment shall, in addition, register and list all such other drug products with the Drug Listing Branch in accordance with this part.

(b) [Reserved]

(c) Owners and operators of establishments engaged in manufacture or processing of medical devices shall register and list their products with the Center for Devices and Radiological Health, FDA, on Form FDA–2891 (Initial Registration of Device Establishments), FDA–2891a (Registration of Device Establishment), and FDA–2892 (Medical

Device Listing), in accordance with part 807.

(d) Owners and operators of establishments engaged in the manufacture or processing at the same establishment of both drug products and medical devices shall (1) register with the Records Repository Team (HFD–143), Center for Drug Evaluation and Research, FDA, and list their drug products in accordance with this part, and (2) register with the Center for Devices and Radiological Health and list their medical devices in accordance with part 807.

[45 FR 38043, June 6, 1980, as amended at 50 FR 8995, Mar. 6, 1985; 55 FR 11576, Mar. 29, 1990; 66 FR 59156, Nov. 27, 2001; 69 FR 48775, Aug. 11, 2004]

Subpart B—Exemptions

§ 207.10 Exemptions for establishments.

The following classes of persons are exempt from registration and drug listing in accordance with this part under section 510(g)(1), (g)(2), and (g)(3) of the act, or because FDA has found, under section 510(g)(5) of the act, that their registration is not necessary for the protection of the public health. The exemptions in paragraphs (a) and (b) of this section are limited to pharmacies, hospitals, clinics, and public health agencies located in any State as defined in section 201(a)(1) of the act.

(a) Pharmacies that operate under applicable local laws regulating dispensing of prescription drugs and that do not manufacture or process drugs for sale other than in the regular course of the practice of the profession of pharmacy, including dispensing and selling drugs at retail. The supplying of prescription drugs by these pharmacies to a practitioner licensed to administer these drugs for his or her use in the course of professional practice or to other pharmacies to meet temporary inventory shortages are not acts that require pharmacies to register.

(b) Hospitals, clinics, and public health agencies that maintain establishments in conformance with any applicable local laws regulating the practices of pharmacy or medicine and that regularly engage in dispensing prescription drugs, other than human blood or blood products, upon prescription of practitioners licensed by law to administer these drugs to patients under their professional care.

(c) Practitioners who are licensed by law to prescribe or administer drugs and who manufacture or process drugs solely for use in their professional practice.

(d) Persons who manufacture or process drugs not for sale but solely for use in research, teaching, or chemical analysis.

(e) Manufacturers of harmless inactive ingredients that are excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs, and who otherwise would not be required to register under this part.

(f) Persons who only manufacture the following:

(1) Type B or Type C medicated feed using Category I, Type A medicated articles or Category I, Type B or Type C medicated feeds, and/or;

(2) Type B or Type C medicated feed using Category II, Type B or Type C medicated feeds.

(3) Persons who manufacture free-choice feeds, as defined in § 510.455 of this chapter, or medicated liquid feeds, as defined in § 558.5 of this chapter, where a medicated feed mill license is required are not exempt.

(g) Any manufacturer of a virus, serum, toxin, or analogous product intended for treatment of domestic animals who holds an unsuspended and unrevoked license issued by the Secretary of Agriculture under the animal virus-serum-toxin law of March 4, 1913 (37 Stat. 832 (21 U.S.C. 151 *et seq.*)), provided that this exemption from registration applies only to the manufacture or processing of that animal virus, serum, toxin, or analogous product.

(h) Carriers, in their receipt, carriage, holding, or delivery of drugs in the usual course of business as carriers.

[45 FR 38043, June 6, 1980, as amended at 51 FR 7389, Mar. 3, 1986; 64 FR 63203, Nov. 19, 1999; 66 FR 59156, Nov. 27, 2001]

Subpart C—Procedures for Domestic Drug Establishments

§ 207.20 Who must register and submit a drug list.

(a) Owners or operators of all drug establishments, not exempt under section 510(g) of the act or subpart B of this part 207, that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs shall register and submit a list of every drug in commercial distribution (except that registration and listing information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments). Drug listing is not required for the manufacturing, preparation, propagation, compounding, or processing of an animal feed bearing or containing an animal drug (i.e., a Type B or Type C medicated feed), nor is drug listing required for establishments engaged in drug product salvaging. Drug products manufactured, prepared, propagated, compounded, or processed in any State as defined in section 201(a)(1) of the act must be listed whether or not the output of such establishments or any particular drug so listed enters interstate commerce. No owner or operator may register an establishment if any part of the establishment is registered by any other owner or operator.

(b) Owners or operators of establishments not otherwise required to register under section 510 of the act that distribute under their own label or trade name a drug manufactured or processed by a registered establishment may elect to submit listing information directly to FDA and to obtain a Labeler Code. A distributor who submits drug listing information shall include the registration number of the drug establishment that manufactured, prepared, propagated, compounded, or processed each drug listed. All distributors who submit drug listing information to FDA assume full responsibility for compliance with all of the requirements of this part. Each such distributor at the time of submitting or updating drug listing information as required under § 207.30 shall certify to the registered establishment that the submission has been made by providing a signed copy of Form FDA–2656 (Registration of Drug Establishment) to the registered establishment that manufactures or processes the drug. Each such distributor shall submit the original of Form FDA–2656 showing this certification to FDA, and shall accompany the certification with a list showing the National Drug Code number that the distributor has assigned to each drug product. If a distributor does not elect to submit drug listing information directly to FDA and to obtain a Labeler Code, the registered establishment shall submit the drug listing information. Distributors or registered establishments shall use Form FDA–2658 (Registered Establishments' Report of Private Label Distributors) to submit drug listing information or to request a Labeler Code, or both.

(c) Before beginning manufacture or processing of a drug subject to one of the following applications, an owner or operator of an establishment is required to register before the agency approves or grants it: A new drug application, an abbreviated new drug application, a new animal drug application, an abbreviated new animal drug application, a medicated feed mill license application, a biologics license application, or a request for addition to the index.

(d) No registration fee is required.

(e) Registration and listing do not constitute an admission, or agreement, or determination that a product is a drug as defined in section 201(g) of the act.

(f) Owners and operators of establishments or persons engaged in the recovery, screening, testing, processing, storage, or distribution of human cells, tissues, and cellular and tissue-based products, as defined in § 1271.3(d) of this chapter, that are regulated under section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act must register and list those human cells, tissues, and cellular and tissue-based products with the Center for Biologics Evaluation and Research on Form FDA 3356 following the procedures set out in subpart B of part 1271 of this chapter, instead of the

procedures for registration and listing contained in this part, except that the additional listing information requirements in § 207.31 remain applicable.

[45 FR 38043, June 6, 1980, as amended at 45 FR 32293, May 16, 1980; 52 FR 2682, Jan. 26, 1987; 55 FR 11576, Mar. 29, 1990; 64 FR 400, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 64 FR 63203, Nov. 19, 1999; 66 FR 5466, Jan. 19, 2001; 66 FR 59157, Nov. 27, 2001; 66 FR 5447, Jan. 19, 2001; 72 FR 69120, Dec. 6, 2007]

§ 207.21 Times for registration and drug listing.

(a) The owner or operator of an establishment entering into the manufacture or processing of a drug or drugs shall register the establishment within 5 days after the beginning of the operation and shall submit a list of every drug in commercial distribution at that time. If the owner or operator of the establishment has not previously entered into such an operation, the owner or operator shall register within 5 days after submitting a new drug application, abbreviated new drug application, new animal drug application, abbreviated new animal drug application, request for addition to the index, medicated feed mill license application, or a biologics license application. Owners or operators shall renew their registration information annually.

The schedule is as follows:

First letter of company name	Date FDA will mail forms
A or B	January
C, D, or E	February
F, G, or H	March
I, J, K, L. or M	April
N, O, P, Q, or R	May
S or T	June
U, V, W, X, Y, or Z	July

(b) Owners and operators of all registered establishments shall update their drug listing information every June and December.

[45 FR 38043, June 6, 1980, as amended at 55 FR 11576, Mar. 29, 1990; 64 FR 400, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 64 FR 63203, Nov. 19, 1999; 66 FR 59157, Nov. 27, 2001; 72 FR 69120, Dec. 6, 2007]

§ 207.22 How and where to register and list drugs.

(a) An establishment shall register the first time on Form FDA–2656 (Registration of Drug Establishment), obtainable on request from the Records Repository Team (HFD–143), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or from FDA district offices. An establishment whose drug registration for that year was validated under § 207.35 shall make subsequent annual registration on Form FDA–2656 as described in § 207.21(a) by mailing the completed form to the above address within 30 days after receipt from FDA.

(b) The first list of drugs and later June and December updatings shall be on Form FDA–2657 (Drug Product Listing), obtainable upon request as described in paragraph (a) of this section. An establishment may submit, in lieu of Form FDA–2657, tapes for computer inputs containing the information specified in Form FDA–2657 if formats proposed for this use were reviewed and approved by the Records Repository Team (HFD–143), Center for Drug Evaluation and Research, FDA.

[45 FR 38043, June 6, 1980, as amended at 50 FR 8995, Mar. 6, 1985; 55 FR 11576, Mar. 29, 1990; 69 FR 48775, Aug. 11, 2004]

§ 207.25 Information required in registration and drug listing.

(a) Form FDA–2656 (Registration of Drug Establishment) provides for furnishing or confirming information required by the act. This information includes, for each establishment, the name and full address of the drug establishment; all trade names used by the establishment; the kind of ownership or operation (that is, individually owned, partnership or corporation); and the name of the owner or operator of the establishment. The term *name of the owner or operator* includes in the case of a partnership the name of each partner, and in the case of a corporation the name and title of each corporate officer and director and the name of the State of incorporation.

(b) Form FDA–2657 (Drug Product Listing) provides that information required by the act be furnished as follows:

(1) A list of drugs, including bulk drug substances and Type A articles for use in the manufacture of animal feeds as well as finished dosage forms, by established name and by proprietary

name, that are being manufactured or processed for commercial distribution and that have not been included in any list previously submitted to FDA on Form FDA–2657 or in conjunction with the FDA voluntary inventory on Form FDA–2422 (Survey Report of Marketed Drugs), or Form FDA–2250 (National Drug Code Directory Input).

(2) For each drug listed that the registrant regards as subject to section 505 or 512 of the act, the new drug application number, abbreviated new drug application number, new animal drug application number, or abbreviated new animal drug application number and a copy of all current labeling, except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement.

(3) For each drug listed that the registrant regards as subject to section 351 of the Public Health Service Act, the license number of the manufacturer.

(4) For each human prescription drug listed that the registrant regards as not subject to section 505 of the act or 351 of the Public Health Service Act, and that is not manufactured by a registered blood bank, a copy of all current labeling (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement) and a representative sampling of advertisements.

(5) For each human over-the-counter drug listed, or each animal drug listed, that the registrant regards as not subject to section 505 or 512 of the act or 351 of the Public Health Service Act, a copy of the label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), the package insert, and a representative sampling of any other labeling.

(6) For each prescription or over-the-counter drug so listed that the registrant regards as not subject to section 505 or 512 of the act or 351 of the Public Health Service Act, and that is not manufactured by a registered blood bank, a quantitative listing of the active ingredient(s). Unless the quantitative listing is expressed as a percentage in the offical compendium or the ingredient is a nonantibiotic ingredient in a Type A medicated article for use in the manufacture of animal feeds, the quantity of an ingredient shall be expressed in terms of the amount, not the percent, of that ingredient in each dosage unit or, if the drug is not in unit dosage form, the amount of the ingredient in a specific unit of weight or measure of the drug. For a drug formulation that is a Type A medicated article subject to § 207.35(b)(2)(iii), the registrant may limit the quantitative listing of ingredients to each variation of level of active drug ingredient.

(7) For each drug listed, the registration number of every drug establishment within the parent company at which it is manufactured or processed.

(8) For each drug listed, the National Drug Code (NDC) number. If FDA has not assigned an NDC Labeler Code, the registrant shall include a Product Code and Package Code and FDA will assign a Labeler Code as described in § 207.35(b)(2)(i).

(c) For each drug product listed that is subject to the imprinting requirements of part 206 of this chapter, including products that are exempted under § 206.7(b), drug companies must submit a document that provides the name of the product, its active ingredient(s), dosage strength, National Drug Code number, the name of its manufacturer or distributor, its size, shape, color, and code imprint (if any), and any other characteristic that identifies the product as unique.

[45 FR 38043, June 6, 1980, as amended at 52 FR 2682, Jan. 26, 1987; 55 FR 11577, Mar. 29, 1990; 58 FR 47959, Sept. 13, 1993; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999; 66 FR 59157, Nov. 27, 2001]

§ 207.26 Amendments to registration.

Changes in individual ownership, corporate or partnership structure location or drug-handling activity, shall be submitted by Form FDA–2656 (Registration of Drug Establishment) as amendment to registration within 5 days of such changes. A change in a registered establishment's firm name within 6 months of the registration of the establishment is required to be supported by a signed statement of the establishment's owner or operator that the change is not made for the purpose

of changing the name of the manufacturer of a drug product under § 201.1 of this chapter. Changes in the names of officers and directors of the corporations do not require such amendment but must be shown at time of annual registration.

[45 FR 25777, Apr. 15, 1980, as amended at 55 FR 11577, Mar. 29, 1990]

§ 207.30 Updating drug listing information.

(a) After submitting the initial drug listing information, every person who is required to list drugs under § 207.20 shall submit on Form FDA–2657 (Drug Product Listing) during each subsequent June and December, or at the discretion of the registrant when the change occurs, the following information:

(1) A list of each drug introduced by the registrant for commerical distribution which has not been included in any list previously submitted. The registrant shall provide all of the information required by § 207.25(b) for each such drug.

(2) A list of each drug formerly listed in accordance with § 207.25(b) for which commercial distribution has been discontinued, including for each drug so listed the National Drug Code (NDC) number, the identity by established name and by proprietary name, and date of discontinuance. It is requested but not required that the reason for discontinuance of distribution be included with this information.

(3) A list of each drug for which a notice of discontinuance was submitted under paragraph (a)(2) of this section and for which commercial distribution has been resumed, including for each drug so listed the NDC number, the identity by established name and by proprietary name, the date of resumption, and any other information required by § 207.25(b) not previously submitted.

(4) Any material change in any information previously submitted.

(b) When no changes have occurred since the previously submitted list, no report is required.

§ 207.31 Additional drug listing information.

(a) In addition to the information routinely required by §§ 207.25 and 207.30, FDA may require submission of the following information by letter or by FEDERAL REGISTER notice:

(1) For a particular prescription drug so listed that the registrant regards as not subject to section 505 of the act, upon request by FDA for good cause, a copy of all advertisements.

(2) For a particular drug product so listed that the registrant regards as not subject to section 505 or 512 of the act, upon a finding by FDA that it is necessary to carry out the purposes of the act, a quantitative listing of all ingredients.

(3) For a particular drug product, upon request by FDA, a brief statement of the basis for the registrant's belief that the drug product is not subject to section 505 or 512 of the act.

(4) For each registrant, upon a finding by FDA that it is necessary to carry out the purposes of the act, a list of each listed drug product containing a particular ingredient.

(b) It is requested but not required that a qualitative listing of the inactive ingredients be submitted for all listed drugs in the format prescribed in Form FDA–2657 (Drug Product Listing).

(c) It is requested but not required that a quantitative listing of the active ingredients be submitted for all drugs listed that are subject to section 505 or 512 of the act or section 351 of the Public Health Service Act.

[45 FR 38043, June 6, 1980, as amended at 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999]

§ 207.35 Notification of registrant; drug establishment registration number and drug listing number.

(a) FDA will provide to the registrant a validated copy of Form FDA–2656 (Registration of Drug Establishment) as evidence of registration. This validated copy will be sent to the mailing address shown on the form. FDA will assign a permanent registration number to each drug establishment registered in accordance with these regulations.

(b) Using the National Drug Code (NDC) numbering system, FDA assigns

a drug listing number to each drug or class of drugs listed as follows:

(1) If a drug is already listed in the National Drug Code System or in the National Health Related Items Code System, the number is the same as that assigned under those codes. FDA adds a lead zero to the first three characters of the code, which identifies the manufacturer or distributor, to expand the ''Labeler Code'' segment to four characters. The National Drug Code, Product Code, and Package Code configurations used to describe these drugs, or any drugs added to the product line, remain the same, i.e., a four-character Product Code and a two-character Package Code. A manufacturer or distributor may either retain alphanumeric characters that are already used in the Product Code and Package Code segments of the National Drug Code or convert these alphanumeric characters to all numeric digits. The manufacturer or distributor shall inform FDA of a decision to convert the alphanumeric characters to all numeric digits.

(2) If a registered establishment or distributor has not previously participated in the National Drug Code System or in the National Health Related Items Code System, FDA uses the National Drug Code numbering system in assigning a number, as follows (only numerals are used):

(i) The first 5 numeric characters of the 10-character code identify the manufacturer or distributor and are known as the Labeler Code. FDA will expand the Labeler Code from five to six numeric characters when the available five-character code combinations are exhausted. FDA will assign Labeler Code numbers and provide them to the registrant along with the validated copy of Form FDA–2656. Any registered firm that does not have an assigned Labeler Code will be assigned one when registration and listing information are submitted.

(ii) The last 5 numeric characters of the 10-character code identify the drug and the trade package size and type. The segment that identifies the drug formulation is known as the Product Code and the segment that identifies the trade package size and type is known as the Package Code. The manufacturer or distributor will assign the Product Code and the Package Code before drug listing and include these codes in Form FDA–2657 (Drug Product Listing). The manufacturer or distributor may use either of two methods in assigning the Product and Package Codes: a 3–2 Product-Package Code configuration (e.g., 542–12) or a 4–1 Product-Package Code configuration (e.g., 5421–2). A manufacturer or distributor with a given Labeler Code shall use only one such Product-Package Code configuration and shall use this same configuration in assigning the Product-Package Codes for all drugs included in the drug listing. The manufacturer or distributor shall report to FDA the Product-Package Code configuration used in assigning these codes.

(iii) If the drug formulation is a Type A medicated article intended for use in the manufacture of an animal feed, FDA assigns a separate Product Code only for each variation of level of active drug ingredient.

(3) FDA requests but does not require that the NDC number appear on all drug labels and in other drug labeling, including the label of any prescription drug container furnished to a consumer. If the NDC number is shown on a drug label, it shall be placed as follows:

(i) The NDC number shall appear prominently in the top third of the principal display panel of the label on the immediate container and of any outside container or wrapper. Instead of appearing in the top third of the label, the NDC number may appear as part of and contiguous to any bar-code symbol for any drug product if two conditions are met. First, the symbol appears prominently on the immediate container and on any outside container or wrapper and in a conspicuous location; this condition is not satisfied by the appearance of the symbol only on the natural bottom of a container or wrapper. Second, the bar-code symbol is compatible with the NDC, i.e., the symbol provides a format capable of encoding the numeric characters of an NDC Number. The term *principal display panel*, as used in this paragraph, means that part of a label most likely to be displayed, presented, shown, or examined under customary conditions

of display to the consumer (for over-the-counter drug products) or to the dispenser (for prescription drug products).

(ii) The NDC number shall be preceded by the prefix ''NDC'' or ''N'' when it is used on a label or in labeling. The prefix used for a drug product shall be used consistently on the label of the immediate container, outside container, or wrapper, if any, and on other labeling for that drug product.

(iii) The Product-Package Code configuration shall be indicated and the segments of the number shall be separated by a dash, e.g., NDC 15643–542–12 or N 15643–542–12.

(iv) All 10 characters shall appear and the leading zeros in any segment of the NDC number shall be shown, except that leading zeros may be omitted from any segment of the NDC number when the NDC number is used for product identification by direct imprinting on dosage forms or in the case of containers too small or otherwise unable to accommodate a label with sufficent space to bear both required and optional labeling information.

(v) The placing of the assigned NDC number on a label or in other labeling does not require the submission of a supplemental new drug application, supplemental new animal drug application, or a modification to an index listing.

(4)(i) If any change occurs in those product characteristics that clearly distinguish one drug product version from another, the registrant shall assign a new NDC number to the new product version and submit that information to FDA. Such a change includes, but is not limited to, a change in active ingredient(s); strength or concentration of active ingredient(s); dosage form; route of administration, if it also includes a change in product formulation; product name; and a change in marketing status from prescription to over-the-counter or over-the-counter to prescription. If, by notice in the FEDERAL REGISTER, FDA requires a change in drug product characteristics and determines the change will require assignment of a new product code to the reformulated product, FDA will announce its determination in the FEDERAL REGISTER publication that requires the change, setting forth its reasoning and justification for its determination. If a change only in the trade package is involved, the registrant may revise the trade package code without the assignment of a new product code segment, but shall inform FDA of the new code for the trade package and the characteristics of the new trade package.

(ii) When a registrant has discontinued a drug product, its product code may be reassigned to another drug product 5 years after the expiration date of the discontinued product, or, if there is no expiration date, 5 years after the last shipment of the discontinued product into commercial distribution. Reuse of product codes may occur, under the specified conditions, regardless of the NDC, Product Code, and Package Code configuration used.

(c) Although registration and drug listing are required to engage in the drug activities described in § 207.20, validation of registration and the assignment of a drug listing number do not, in themselves, establish that the holder of the registration is legally qualified to deal in such drugs.

[45 FR 38043, June 6, 1980, as amended at 48 FR 54007, Nov. 30, 1983; 52 FR 2682, Jan. 26, 1987; 55 FR 11577, Mar. 29, 1990; 64 FR 400, Jan. 5, 1999; 72 FR 69120, Dec. 6, 2007]

§ 207.37 Inspection of registrations and drug listings.

(a) A copy of the Form FDA–2656 (Registration of Drug Establishment) filed by the registrant will be available for inspection in accordance with section 510(f) of the act, at the Records Repository Team (HFD–143), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. In addition, copies of these forms for establishments located within a particular geographic area are available for inspection at FDA district offices responsible for that geographical area. Copies of forms submitted by foreign drug establishments are available for inspection at the Division of Manufacturing and Product Quality, Foreign Inspection Team (HFD–325), Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Upon request and receipt of a stamped, self-addressed envelope, the Records Repository Team, the Foreign Inspection Team, or the appropriate FDA district office will verify registration numbers or provide the location of a registered establishment. The mailing address for the Foreign Inspection Team is: Division of Manufacturing and Product Quality, Office of Compliance, Center for Drug Evaluation and Research (HFD–325), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(1) The following types of information submitted under the drug listing requirements will be available for public disclosure when compiled:

(i) A list of all drug products.

(ii) A list of all drug products arranged by labeled indications or pharmacological category.

(iii) A list of all drug products arranged by manufacturer.

(iv) A list of a drug product's active ingredients.

(v) A list of drug products newly marketed or for which marketing is resumed.

(vi) A list of drug products discontinued.

(vii) Labeling.

(viii) Advertising.

(ix) Information that has become a matter of public knowledge.

(x) A list of drug products containing a particular active ingredient.

(xi) A list of all code imprints.

(2) The following types of information submitted in accordance with the drug listing requirements will not be available for public disclosure (except that any of the information will be available for public disclosure if it has become a matter of public knowledge or if FDA finds that confidentiality would be inconsistent with protection of the public health):

(i) Any information submitted as the basis upon which it has been determined that a particular drug product is not subject to section 505 or 512 of the act.

(ii) A list of a drug product's inactive ingredients.

(iii) A list of drugs containing a particular inactive ingredient.

(b) Requests for information about registrations and drug listings of an establishment should be directed to the Information Management Team (HFD–095), Office of Information Technology, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 or, with respect to the information described in paragraph (a) of this section, to the FDA district office responsible for the geographic area in which the establishment is located.

[45 FR 38043, June 6, 1980, as amended at 50 FR 8996, Mar. 6, 1985; 55 FR 11577, Mar. 29, 1990; 58 FR 47959, Sept. 13, 1993; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999; 66 FR 59157, Nov. 27, 2001; 69 FR 48775, Aug. 11, 2004]

§ 207.39 Misbranding by reference to registration or to registration number.

Registration of a drug establishment or drug wholesaler, or assignment of a registration number, or assignment of a NDC number does not in any way denote approval of the firm or its products. Any representation that creates an impression of official approval because of registration or possession of registration number or NDC number is misleading and constitutes misbranding.

Subpart D—Procedure for Foreign Drug Establishments

§ 207.40 Establishment registration and drug listing requirements for foreign establishments.

(a) Foreign drug establishments whose drugs are imported or offered for import into the United States shall comply with the establishment registration and drug listing requirements in subpart C of this part, unless exempt under subpart B of this part or unless the drugs enter a foreign trade zone and are re-exported from that foreign trade zone without having entered U. S. commerce.

(b) No drug may be imported or offered for import into the United States unless it is listed as required in subpart C of this part and manufactured, prepared, propagated, compounded, or processed at a registered foreign drug establishment; however, this restriction does not apply to a drug imported or offered for import under the investigational use provisions in part 312 of

this chapter, or the investigational new animal drug use provisions in part 511 of this chapter, or to a component of a drug imported under section 801(d)(3) of the act. Foreign drug establishments shall submit all listing information, including labels and labeling, and registration information in the English language.

(c) Each foreign drug establishment required to register under paragraph (a) of this section shall submit the name, address, and phone number of its United States agent as part of its initial and updated registration information in accordance with subpart C of this part. Each foreign drug establishment shall designate only one United States agent.

(1) The United States agent shall reside or maintain a place of business in the United States.

(2) Upon request from FDA, the United States agent shall assist FDA in communications with the foreign drug establishment, respond to questions concerning the foreign drug establishment's products that are imported or offered for import into the United States, and assist FDA in scheduling inspections of the foreign drug establishment. If the agency is unable to contact the foreign drug establishment directly or expeditiously, FDA may provide information or documents to the United States agent, and such an action shall be considered to be equivalent to providing the same information or documents to the foreign drug establishment.

(3) The foreign drug establishment or the United States agent shall report changes in the United States agent's name, address, or phone number to FDA within 10-business days of the change.

[66 FR 59157, Nov. 27, 2001]

PART 208—MEDICATION GUIDES FOR PRESCRIPTION DRUG PRODUCTS

Subpart A—General Provisions

Sec.
208.1 Scope and purpose.
208.3 Definitions.

Subpart B—General Requirements for a Medication Guide

208.20 Content and format of a Medication Guide.
208.24 Distributing and dispensing a Medication Guide.
208.26 Exemptions and deferrals.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360, 371, 374; 42 U.S.C. 262.

SOURCE: 63 FR 66396, Dec. 1, 1998, unless otherwise noted.

Subpart A—General Provisions

§ 208.1 Scope and purpose.

(a) This part sets forth requirements for patient labeling for human prescription drug products, including biological products, that the Food and Drug Administration (FDA) determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information. It applies primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional. This part shall apply to new prescriptions and refill prescriptions.

(b) The purpose of patient labeling for human prescription drug products required under this part is to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products.

(c) Patient labeling will be required if the FDA determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

§ 208.3 Definitions.

For the purposes of this part, the following definitions shall apply:

(a) *Authorized dispenser* means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide drug products on prescription in the course of professional practice.

(b) *Dispense to patients* means the act of delivering a prescription drug product to a patient or an agent of the patient either:

(1) By a licensed practitioner or an agent of a licensed practitioner, either directly or indirectly, for self-administration by the patient, or the patient's agent, or outside the licensed practitioner's direct supervision; or

(2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a licensed practitioner.

(c) *Distribute* means the act of delivering, other than by dispensing, a drug product to any person.

(d) *Distributor* means a person who distributes a drug product.

(e) *Drug product* means a finished dosage form, e.g., tablet, capsule, or solution, that contains an active drug ingredient, generally, but not necessarily, in association with inactive ingredients. For purposes of this part, drug product also means biological product within the meaning of section 351(a) of the Public Health Service Act.

(f) *Licensed practitioner* means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to prescribe drug products in the course of professional practice.

(g) *Manufacturer* means for a drug product that is not also a biological product, both the manufacturer as described in § 201.1 and the applicant as described in § 314.3(b) of this chapter, and for a drug product that is also a biological product, the manufacturer as described in § 600.3(t) of this chapter.

(h) *Medication Guide* means FDA-approved patient labeling conforming to the specifications set forth in this part and other applicable regulations.

(i) *Packer* means a person who packages a drug product.

(j) *Patient* means any individual with respect to whom a drug product is intended to be, or has been, used.

(k) *Serious risk or serious adverse effect* means an adverse drug experience, or the risk of such an experience, as that term is defined in §§ 310.305, 312.32, 314.80, and 600.80 of this chapter.

Subpart B—General Requirements for a Medication Guide

§ 208.20 Content and format of a Medication Guide.

(a) A Medication Guide shall meet all of the following conditions:

(1) The Medication Guide shall be written in English, in nontechnical, understandable language, and shall not be promotional in tone or content.

(2) The Medication Guide shall be scientifically accurate and shall be based on, and shall not conflict with, the approved professional labeling for the drug product under § 201.57 of this chapter, but the language of the Medication Guide need not be identical to the sections of approved labeling to which it corresponds.

(3) The Medication Guide shall be specific and comprehensive.

(4) The letter height or type size shall be no smaller than 10 points (1 point = 0.0138 inches) for all sections of the Medication Guide, except the manufacturer's name and address and the revision date.

(5) The Medication Guide shall be legible and clearly presented. Where appropriate, the Medication Guide shall also use boxes, bold or underlined print, or other highlighting techniques to emphasize specific portions of the text.

(6) The words ''Medication Guide'' shall appear prominently at the top of the first page of a Medication Guide. The verbatim statement ''This Medication Guide has been approved by the U.S. Food and Drug Administration'' shall appear at the bottom of a Medication Guide.

(7) The brand and established or proper name of the drug product shall appear immediately below the words ''Medication Guide.'' The established or proper name shall be no less than one-half the height of the brand name.

(b) A Medication Guide shall contain those of the following headings relevant to the drug product and to the need for the Medication Guide in the

specified order. Each heading shall contain the specific information as follows:

(1) The brand name (e.g., the trademark or proprietary name), if any, and established or proper name. Those products not having an established or proper name shall be designated by their active ingredients. The Medication Guide shall include the phonetic spelling of either the brand name or the established name, whichever is used throughout the Medication Guide.

(2) The heading, ''What is the most important information I should know about (name of drug)?'' followed by a statement describing the particular serious and significant public health concern that has created the need for the Medication Guide. The statement should describe specifically what the patient should do or consider because of that concern, such as, weighing particular risks against the benefits of the drug, avoiding particular behaviors (e.g., activities, drugs), observing certain events (e.g., symptoms, signs) that could prevent or mitigate a serious adverse effect, or engaging in particular behaviors (e.g., adhering to the dosing regimen).

(3) The heading, ''What is (name of drug)?'' followed by a section that identifies a drug product's indications for use. The Medication Guide may not identify an indication unless the indication is identified in the indications and usage section of the professional labeling for the product required under § 201.57 of this chapter. In appropriate circumstances, this section may also explain the nature of the disease or condition the drug product is intended to treat, as well as the benefit(s) of treating the condition.

(4) The heading, ''Who should not take (name of drug)?'' followed by information on circumstances under which the drug product should not be used for its labeled indication (its contraindications). The Medication Guide shall contain directions regarding what to do if any of the contraindications apply to a patient, such as contacting the licensed practitioner or discontinuing use of the drug product.

(5) The heading, ''How should I take (name of drug)?'' followed by information on the proper use of the drug product, such as:

(i) A statement stressing the importance of adhering to the dosing instructions, if this is particularly important;

(ii) A statement describing any special instructions on how to administer the drug product, if they are important to the drug's safety or effectiveness;

(iii) A statement of what patients should do in case of overdose of the drug product; and

(iv) A statement of what patients should do if they miss taking a scheduled dose(s) of the drug product, where there are data to support the advice, and where the wrong behavior could cause harm or lack of effect.

(6) The heading ''What should I avoid while taking (name of drug)?'' followed by a statement or statements of specific, important precautions patients should take to ensure proper use of the drug, including:

(i) A statement that identifies activities (such as driving or sunbathing), and drugs, foods, or other substances (such as tobacco or alcohol) that patients should avoid when using the medication;

(ii) A statement of the risks to mothers and fetuses from the use of the drug during pregnancy, if specific, important risks are known;

(iii) A statement of the risks of the drug product to nursing infants, if specific, important risks are known;

(iv) A statement about pediatric risks, if the drug product has specific hazards associated with its use in pediatric patients;

(v) A statement about geriatric risks, if the drug product has specific hazards associated with its use in geriatric patients; and

(vi) A statement of special precautions, if any, that apply to the safe and effective use of the drug product in other identifiable patient populations.

(7) The heading, ''What are the possible or reasonably likely side effects of (name of drug)?'' followed by:

(i) A statement of the adverse reactions reasonably likely to be caused by the drug product that are serious or occur frequently.

(ii) A statement of the risk, if there is one, of patients' developing dependence on the drug product.

(iii) For drug products approved under section 505 of the act, the following verbatim statement: ''Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.''

(8) General information about the safe and effective use of prescription drug products, including:

(i) The verbatim statement that ''Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide'' followed by a statement that patients should ask health professionals about any concerns, and a reference to the availability of professional labeling;

(ii) A statement that the drug product should not be used for a condition other than that for which it is prescribed, or given to other persons;

(iii) The name and place of business of the manufacturer, packer, or distributor of a drug product that is not also a biological product, or the name and place of business of the manufacturer or distributor of a drug product that is also a biological product, and in any case the name and place of business of the dispenser of the product may also be included; and

(iv) The date, identified as such, of the most recent revision of the Medication Guide placed immediately after the last section.

(9) Additional headings and subheadings may be interspersed throughout the Medication Guide, if appropriate.

[63 FR 66396, Dec. 1, 1998, as amended at 73 FR 404, Jan. 3, 2008]

§ 208.24 Distributing and dispensing a Medication Guide.

(a) The manufacturer of a drug product for which a Medication Guide is required under this part shall obtain FDA approval of the Medication Guide before the Medication Guide may be distributed.

(b) Each manufacturer who ships a container of drug product for which a Medication Guide is required under this part is responsible for ensuring that Medication Guides are available for distribution to patients by either:

(1) Providing Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product; or

(2) Providing the means to produce Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product.

(c) Each distributor or packer that receives Medication Guides, or the means to produce Medication Guides, from a manufacturer under paragraph (b) of this section shall provide those Medication Guides, or the means to produce Medication Guides, to each authorized dispenser to whom it ships a container of drug product.

(d) The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.

(e) Each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part shall, when the product is dispensed to a patient (or to a patient's agent), provide a Medication Guide directly to each patient (or to the patient's agent) unless an exemption applies under § 208.26.

(f) An authorized dispenser or wholesaler is not subject to section 510 of the Federal Food, Drug, and Cosmetic Act, which requires the registration of producers of drugs and the listing of drugs in commercial distribution, solely because of an act performed by the authorized dispenser or wholesaler under this part.

§ 208.26 Exemptions and deferrals.

(a) FDA on its own initiative, or in response to a written request from an applicant, may exempt or defer any Medication Guide content or format requirement, except those requirements in § 208.20 (a)(2) and (a)(6), on the basis that the requirement is inapplicable,

unnecessary, or contrary to patients' best interests. Requests from applicants should be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product, or for a biological product, to the application division in the office with product responsibility.

(b) If the licensed practitioner who prescribes a drug product subject to this part determines that it is not in a particular patient's best interest to receive a Medication Guide because of significant concerns about the effect of a Medication Guide, the licensed practitioner may direct that the Medication Guide not be provided to the particular patient. However, the authorized dispenser of a prescription drug product subject to this part shall provide a Medication Guide to any patient who requests information when the drug product is dispensed regardless of any such direction by the licensed practitioner.

PART 209—REQUIREMENT FOR AUTHORIZED DISPENSERS AND PHARMACIES TO DISTRIBUTE A SIDE EFFECTS STATEMENT

Subpart A—General Provisions

Sec.
209.1 Scope and purpose.
209.2 Definitions.

Subpart B—Requirements

209.10 Content and format of the side effects statement.
209.11 Dispensing and distributing the side effects statement.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 371; 42 U.S.C. 241.

SOURCE: 73 FR 404, Jan. 3, 2008, unless otherwise noted.

Subpart A—General Provisions

§ 209.1 Scope and purpose.

(a) This part sets forth requirements for human prescription drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act and dispensed by authorized dispensers and pharmacies to consumers. This part requires distribution of a side effects statement and applies to new and refill prescriptions. This part is not intended to apply to authorized dispensers dispensing or administering prescription drug products to inpatients in a hospital or health care facility under an order of a licensed practitioner, or as part of supervised home health care.

(b) The purpose of providing the side effects statement is to enable consumers to report side effects of prescription drug products to FDA.

§ 209.2 Definitions.

For the purposes of this part, the following definitions apply:

Act means the Federal Food, Drug, and Cosmetic Act (sections 201–907 (21 U.S.C. 301–397)).

Authorized dispenser means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide drug products on prescription in the course of professional practice.

Consumer medication information means written information voluntarily provided to consumers by dispensing pharmacists as part of patient medication counseling activities.

Medication Guide means FDA-approved patient labeling conforming to the specifications set forth in part 208 of this chapter and other applicable regulations.

Pharmacy includes, but is not limited to, a retail, mail order, Internet, hospital, university, or clinic pharmacy, or a public health agency, regularly and lawfully engaged in dispensing prescription drugs.

Side effects statement means the following verbatim statement: ''Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.''

Subpart B—Requirements

§ 209.10 Content and format of the side effects statement.

(a) *Content*. The side effects statement provided with each prescription drug product approved under section 505 of the act must read: ''Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.''

(b) *Format*. The side effects statement must be in a single, clear, easy-to-read type style. The letter height or type

size used for the side effects statement in accordance with paragraphs (b)(1) and (b)(2) of § 209.11 must be no smaller than 6 points (1 point = 0.0138 inch). The letter height or type size for the side effects statement under paragraphs (b)(3), (b)(4), and (b)(5) of § 209.11 must be no smaller than 10 points.

§ 209.11 Dispensing and distributing the side effects statement.

(a) Each authorized dispenser or pharmacy must distribute the side effects statement with each prescription drug product approved under section 505 of the act and dispensed. The side effects statement must be distributed with new and refill prescriptions.

(b) An authorized dispenser or pharmacy must choose one or more of the following options to distribute the side effects statement:

(1) Distribute the side effects statement on a sticker attached to the unit package, vial, or container of the drug product;

(2) Distribute the side effects statement on a preprinted pharmacy prescription vial cap;

(3) Distribute the side effects statement on a separate sheet of paper;

(4) Distribute the side effects statement in consumer medication information; or

(5) Distribute the appropriate FDA-approved Medication Guide that contains the side effects statement.

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

Sec.

210.1 Status of current good manufacturing practice regulations.
210.2 Applicability of current good manufacturing practice regulations.
210.3 Definitions.

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

SOURCE: 43 FR 45076, Sept, 29, 1978, unless otherwise noted.

§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

(c) Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labeling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in § 1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor-eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211, 225, and 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211, 225, and 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.

[43 FR 45076, Sept. 29, 1978, as amended at 69 FR 29828, May 25, 2004; 74 FR 65431, Dec. 10, 2009]

§ 210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211, 225, and 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part, in parts 211, 225, and 226 of this chapter, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

(c) An investigational drug for use in a phase 1 study, as described in § 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in § 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.

[69 FR 29828, May 25, 2004, as amended at 73 FR 40462, July 15, 2008; 74 FR 65431, Dec. 10, 2009]

§ 210.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in parts 211, 225, and 226 of this chapter.

(b) The following definitions of terms apply to this part and to parts 211, 225, and 226 of this chapter.

(1) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 *et seq.*).

(2) *Batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

(4) *Drug product* means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

(5) *Fiber* means any particulate contaminant with a length at least three times greater than its width.

(6) *Nonfiber releasing filter* means any filter, which after appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered.

(7) *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 man or other animals. 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.

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

(9) *In-process material* means any material fabricated, compounded, blended, or derived by chemical reaction that is

produced for, and used in, the preparation of the drug product.

(10) *Lot* means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

(11) *Lot number, control number, or batch number* means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.

(12) *Manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of drug products.

(13) The term *medicated feed* means any Type B or Type C medicated feed as defined in § 558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of part 225 of this chapter.

(14) The term *medicated premix* means a Type A medicated article as defined in § 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of part 226 of this chapter.

(15) *Quality control unit* means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

(16) *Strength* means:

(i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or

(ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

(17) *Theoretical yield* means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

(18) *Actual yield* means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.

(19) *Percentage of theoretical yield* means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.

(20) *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(21) *Representative sample* means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

(22) Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

[43 FR 45076, Sept. 29, 1978, as amended at 51 FR 7389, Mar. 3, 1986; 58 FR 41353, Aug. 3, 1993; 73 FR 51931, Sept. 8, 2008; 74 FR 65431, Dec. 10, 2009]

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Subpart A—General Provisions

Sec.
211.1 Scope.
211.3 Definitions.

Subpart B—Organization and Personnel

211.22 Responsibilities of quality control unit.
211.25 Personnel qualifications.

211.28 Personnel responsibilities.
211.34 Consultants.

Subpart C—Buildings and Facilities

211.42 Design and construction features.
211.44 Lighting.
211.46 Ventilation, air filtration, air heating and cooling.
211.48 Plumbing.
211.50 Sewage and refuse.
211.52 Washing and toilet facilities.
211.56 Sanitation.
211.58 Maintenance.

Subpart D—Equipment

211.63 Equipment design, size, and location.
211.65 Equipment construction.
211.67 Equipment cleaning and maintenance.
211.68 Automatic, mechanical, and electronic equipment.
211.72 Filters.

Subpart E—Control of Components and Drug Product Containers and Closures

211.80 General requirements.
211.82 Receipt and storage of untested components, drug product containers, and closures.
211.84 Testing and approval or rejection of components, drug product containers, and closures.
211.86 Use of approved components, drug product containers, and closures.
211.87 Retesting of approved components, drug product containers, and closures.
211.89 Rejected components, drug product containers, and closures.
211.94 Drug product containers and closures.

Subpart F—Production and Process Controls

211.100 Written procedures; deviations.
211.101 Charge-in of components.
211.103 Calculation of yield.
211.105 Equipment identification.
211.110 Sampling and testing of in-process materials and drug products.
211.111 Time limitations on production.
211.113 Control of microbiological contamination.
211.115 Reprocessing.

Subpart G—Packaging and Labeling Control

211.122 Materials examination and usage criteria.
211.125 Labeling issuance.
211.130 Packaging and labeling operations.
211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.
211.134 Drug product inspection.
211.137 Expiration dating.

Subpart H—Holding and Distribution

211.142 Warehousing procedures.
211.150 Distribution procedures.

Subpart I—Laboratory Controls

211.160 General requirements.
211.165 Testing and release for distribution.
211.166 Stability testing.
211.167 Special testing requirements.
211.170 Reserve samples.
211.173 Laboratory animals.
211.176 Penicillin contamination.

Subpart J—Records and Reports

211.180 General requirements.
211.182 Equipment cleaning and use log.
211.184 Component, drug product container, closure, and labeling records.
211.186 Master production and control records.
211.188 Batch production and control records.
211.192 Production record review.
211.194 Laboratory records.
211.196 Distribution records.
211.198 Complaint files.

Subpart K—Returned and Salvaged Drug Products

211.204 Returned drug products.
211.208 Drug product salvaging.

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

SOURCE: 43 FR 45077, Sept. 29, 1978, unless otherwise noted.

Subpart A—General Provisions

§211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs) for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts 600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use; and in part 1271 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of

the act or under a biological product license application under section 351 of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, or in parts 600 through 680 of this chapter, or in part 1271 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(c) Pending consideration of a proposed exemption, published in the FEDERAL REGISTER of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 of this chapter, and where applicable, parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.

[43 FR 45077, Sept. 29, 1978, as amended at 62 FR 66522, Dec. 19, 1997; 69 FR 29828, May 25, 2004; 74 FR 65431, Dec. 10, 2009]

§ 211.3 Definitions.

The definitions set forth in § 210.3 of this chapter apply in this part.

Subpart B—Organization and Personnel

§ 211.22 Responsibilities of quality control unit.

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

§ 211.25 Personnel qualifications.

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

§ 211.28 Personnel responsibilities.

(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

(b) Personnel shall practice good sanitation and health habits.

(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

§ 211.34 Consultants.

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

§ 211.42 Design and construction features.

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures, and labeling before disposition;

(3) Storage of released components, drug product containers, closures, and labeling;

(4) Storage of in-process materials;

(5) Manufacturing and processing operations;

(6) Packaging and labeling operations;

(7) Quarantine storage before release of drug products;

(8) Storage of drug products after release;

(9) Control and laboratory operations;

(10) Aseptic processing, which includes as appropriate:

(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;

(iv) A system for monitoring environmental conditions;

(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;

(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

§ 211.44 Lighting.

Adequate lighting shall be provided in all areas.

§ 211.46 Ventilation, air filtration, air heating and cooling.

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

§ 211.48 Plumbing.

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards shall not be permitted in the potable water system.

(b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

[43 FR 45077, Sept. 29, 1978, as amended at 48 FR 11426, Mar. 18, 1983]

§ 211.50 Sewage and refuse.

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

§ 211.52 Washing and toilet facilities.

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accesible to working areas.

§ 211.56 Sanitation.

(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

(b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

§ 211.58 Maintenance.

Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Subpart D—Equipment

§ 211.63 Equipment design, size, and location.

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

§ 211.65 Equipment construction.

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

§ 211.67 Equipment cleaning and maintenance.

(a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§ 211.180 and 211.182.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51931, Sept. 8, 2008]

§ 211.68 Automatic, mechanical, and electronic equipment.

(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated

processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

(c) Such automated equipment used for performance of operations addressed by §§ 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections relating to the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section, and one person checks that the equipment properly performed the operation.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995; 73 FR 51932, Sept. 8, 2008]

§ 211.72 Filters.

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may be used when it is not possible to manufacture such products without the use of these filters. If use of a fiber-releasing filter is necessary, an additional nonfiber-releasing filter having a maximum nominal pore size rating of 0.2 micron (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. The use of an asbestos-containing filter is prohibited.

[73 FR 51932, Sept. 8, 2008]

Subpart E—Control of Components and Drug Product Containers and Closures

§ 211.80 General requirements.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

§ 211.82 Receipt and storage of untested components, drug product containers, and closures.

(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, whichever is appropriate, and released. Storage within the area shall conform to the requirements of § 211.80.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.84 Testing and approval or rejection of components, drug product containers, and closures.

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of

precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by § 211.170.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component.

(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.

(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

[43 FR 45077, Sept. 29, 1978, as amended at 63 FR 14356, Mar. 25, 1998; 73 FR 51932, Sept. 8, 2008]

§ 211.86 Use of approved components, drug product containers, and closures.

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

§ 211.87 Retesting of approved components, drug product containers, and closures.

Components, drug product containers, and closures shall be retested

or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with § 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure.

§ 211.89 Rejected components, drug product containers, and closures.

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

§ 211.94 Drug product containers and closures.

(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

Subpart F—Production and Process Controls

§ 211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

§ 211.101 Charge-in of components.

Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient.

(b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

(1) Component name or item code;

(2) Receiving or control number;

(3) Weight or measure in new container;

(4) Batch for which component was dispensed, including its product name, strength, and lot number.

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

(1) The component was released by the quality control unit;

(2) The weight or measure is correct as stated in the batch production records;

(3) The containers are properly identified. If the weighing, measuring, or subdividing operations are performed by automated equipment under § 211.68, only one person is needed to assure

paragraphs (c)(1), (c)(2), and (c)(3) of this section.

(d) Each component shall either be added to the batch by one person and verified by a second person or, if the components are added by automated equipment under §211.68, only verified by one person.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§211.103 Calculation of yield.

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person, or, if the yield is calculated by automated equipment under §211.68, be independently verified by one person.

[73 FR 51932, Sept. 8, 2008]

§211.105 Equipment identification.

(a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

(b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

§211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate;

(5) Clarity, completeness, or pH of solutions.

(6) Bioburden testing.

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§211.111 Time limitations on production.

When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

§ 211.113 Control of microbiological contamination.

(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.115 Reprocessing.

(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics.

(b) Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G—Packaging and Labeling Control

§ 211.122 Materials examination and usage criteria.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

(d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.

(e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

(f) Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.

(g) If cut labeling is used for immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons, packaging and labeling operations shall include one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different drug product;

(2) Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations; or

(3) Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

(4) Use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment.

(h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41353, Aug. 3, 1993; 77 FR 16163, Mar. 20, 2012]

§ 211.125 Labeling issuance.

(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.

(b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

(c) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with § 211.122(g)(2).

(d) All excess labeling bearing lot or control numbers shall be destroyed.

(e) Returned labeling shall be maintained and stored in a manner to prevent mixups and provide proper identification.

(f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

§ 211.130 Packaging and labeling operations.

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

§ 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(a) *General.* The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-evident packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

(b) *Requirements for tamper-evident package.* (1) Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale shall package the product in a tamper-evident package, if this product is accessible to the public while held for sale. A tamper-evident package is one having one or more indicators or barriers to entry which, if

breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term ''distinctive by design'' means the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-evident package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(2) In addition to the tamper-evident packaging feature described in paragraph (b)(1) of this section, any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.

(c) *Labeling.* (1) In order to alert consumers to the specific tamper-evident feature(s) used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampules, containers of compressed medical oxygen, or aerosol products that depend upon the power of a liquefied or compressed gas to expel the contents from the container) is required to bear a statement that:

(i) Identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section;

(ii) Is prominently placed on the package; and

(iii) Is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.

(2) If the tamper-evident feature chosen to meet the requirements in paragraph (b) of this section uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say ''For your protection, this bottle has an imprinted seal around the neck.''

(d) *Request for exemptions from packaging and labeling requirements.* A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under § 10.30 of this chapter and should be clearly identified on the envelope as a ''Request for Exemption from the Tamper-Evident Packaging Rule.'' The petition is required to contain the following:

(1) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.

(2) The reasons that the drug product's compliance with the tamper-evident packaging or labeling requirements of this section is unnecessary or cannot be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

(e) *OTC drug products subject to approved new drug applications.* Holders of approved new drug applications for OTC drug products are required under § 314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under § 314.70(c) of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under § 314.70(b) of this chapter.

(f) *Poison Prevention Packaging Act of 1970.* This section does not affect any requirements for ''special packaging''

as defined under § 310.3(l) of this chapter and required under the Poison Prevention Packaging Act of 1970.

(Approved by the Office of Management and Budget under OMB control number 0910–0149)

[54 FR 5228, Feb. 2, 1989, as amended at 63 FR 59470, Nov. 4, 1998]

§ 211.134 Drug product inspection.

(a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.

(b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.

(c) Results of these examinations shall be recorded in the batch production or control records.

§ 211.137 Expiration dating.

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in § 211.166.

(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in § 211.166.

(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(d) Expiration dates shall appear on labeling in accordance with the requirements of § 201.17 of this chapter.

(e) Homeopathic drug products shall be exempt from the requirements of this section.

(f) Allergenic extracts that are labeled ''No U.S. Standard of Potency'' are exempt from the requirements of this section.

(g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.

(h) Pending consideration of a proposed exemption, published in the FEDERAL REGISTER of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981; 60 FR 4091, Jan. 20, 1995]

Subpart H—Holding and Distribution

§ 211.142 Warehousing procedures.

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

§ 211.150 Distribution procedures.

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart I—Laboratory Controls

§ 211.160 General requirements.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be

drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.165 Testing and release for distribution.

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of shortlived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with § 211.194(a)(2).

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant critieria.

§ 211.166 Stability testing.

(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods;

(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;

(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.

(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergenic extracts that are labeled ''No U.S. Standard of Potency'' are exempt from the requirements of this section.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981]

§ 211.167 Special testing requirements.

(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

(c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

§ 211.170 Reserve samples.

(a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:

(1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

(2) For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the

expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.

(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under § 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with § 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.

(2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under § 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

[48 FR 13025, Mar. 29, 1983, as amended at 60 FR 4091, Jan. 20, 1995]

§ 211.173 Laboratory animals.

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

§ 211.176 Penicillin contamination.

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD–470), Center for Drug Evaluation and Research, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

[43 FR 45077, Sept. 29, 1978, as amended at 47 FR 9396, Mar. 5, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11577, Mar. 29, 1990; 66 FR 56035, Nov. 6, 2001; 69 FR 18803, Apr. 9, 2004]

Subpart J—Records and Reports

§ 211.180 General requirements.

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under § 211.137, 3 years after distribution of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under § 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.

(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under § 211.192 for each drug product.

(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under §§ 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

§ 211.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under § 211.68, just the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

[73 FR 51933, Sept. 8, 2008]

§ 211.184 Component, drug product container, closure, and labeling records.

These records shall include the following:

(a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in § 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.

(b) The results of any test or examination performed (including those performed as required by § 211.82(a), § 211.84(d), or § 211.122(a)) and the conclusions derived therefrom.

(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.

(d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with §§ 211.122(c) and 211.130(c).

(e) The disposition of rejected components, drug product containers, closure, and labeling.

§ 211.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

(6) A statement of theoretical weight or measure at appropriate phases of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to § 211.192 is required;

(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

§ 211.188 Batch production and control records.

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;

(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

(1) Dates;

(2) Identity of individual major equipment and lines used;

(3) Specific identification of each batch of component or in-process material used;

(4) Weights and measures of components used in the course of processing;

(5) In-process and laboratory control results;

(6) Inspection of the packaging and labeling area before and after use;

(7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(8) Complete labeling control records, including specimens or copies of all labeling used;

(9) Description of drug product containers and closures;

(10) Any sampling performed;

(11) Identification of the persons performing and directly supervising or checking each significant step in the operation, or if a significant step in the operation is performed by automated equipment under § 211.68, the identification of the person checking the significant step performed by the automated equipment.

(12) Any investigation made according to § 211.192.

(13) Results of examinations made in accordance with § 211.134.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51933, Sept. 8, 2008]

§ 211.192 Production record review.

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup.

§ 211.194 Laboratory records.

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

(2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, AOAC INTERNATIONAL, Book of Methods,[1] or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

(3) A statement of the weight or measure of sample used for each test, where appropriate.

(4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

(5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

(6) A statement of the results of tests and how the results compare with established standards of identity,

[1] Copies may be obtained from: AOAC INTERNATIONAL, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877.

strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

(7) The initials or signature of the person who performs each test and the date(s) the tests were performed.

(8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

(c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

(d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 211.160(b)(4).

(e) Complete records shall be maintained of all stability testing performed in accordance with § 211.166.

[43 FR 45077, Sept. 29, 1978, as amended at 55 FR 11577, Mar. 29, 1990; 65 FR 18889, Apr. 10, 2000; 70 FR 40880, July 15, 2005; 70 FR 67651, Nov. 8, 2005]

§ 211.196 Distribution records.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

(Approved by the Office of Management and Budget under control number 0910–0139)

[49 FR 9865, Mar. 16, 1984]

§ 211.198 Complaint files.

(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with § 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with §§ 310.305 and 514.80 of this chapter.

(b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under § 211.137, such written records shall be maintained for 3 years after distribution of the drug product.

(1) The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.

(2) Where an investigation under § 211.192 is conducted, the written record shall include the findings of the investigation and followup. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with § 211.180(c).

(3) Where an investigation under § 211.192 is not conducted, the written record shall include the reason that an

investigation was found not to be necessary and the name of the responsible person making such a determination.

[43 FR 45077, Sept. 29, 1978, as amended at 51 FR 24479, July 3, 1986; 68 FR 15364, Mar. 31, 2003]

Subpart K—Returned and Salvaged Drug Products

§ 211.204 Returned drug products.

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of § 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

§ 211.208 Drug product salvaging.

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

PART 212—CURRENT GOOD MANUFACTURING PRACTICE FOR POSITRON EMISSION TOMOGRAPHY DRUGS

Subpart A—General Provisions

Sec.
212.1 What are the meanings of the technical terms used in these regulations?
212.2 What is current good manufacturing practice for PET drugs?
212.5 To what drugs do the regulations in this part apply?

Subpart B—Personnel and Resources

212.10 What personnel and resources must I have?

Subpart C—Quality Assurance

212.20 What activities must I perform to ensure drug quality?

Subpart D—Facilities and Equipment

212.30 What requirements must my facilities and equipment meet?

Subpart E—Control of Components, Containers, and Closures

212.40 How must I control the components I use to produce PET drugs and the containers and closures I package them in?

Subpart F—Production and Process Controls

212.50 What production and process controls must I have?

Subpart G—Laboratory Controls

212.60 What requirements apply to the laboratories where I test components, in-process materials, and finished PET drug products?
212.61 What must I do to ensure the stability of my PET drug products through expiry?

Subpart H—Finished Drug Product Controls and Acceptance Criteria

212.70 What controls and acceptance criteria must I have for my finished PET drug products?
212.71 What actions must I take if a batch of PET drug product does not conform to specifications?

Subpart I—Packaging and Labeling

212.80 What are the requirements associated with labeling and packaging PET drug products?

Subpart J—Distribution

212.90 What actions must I take to control the distribution of PET drug products?

Subpart K—Complaint Handling

212.100 What do I do if I receive a complaint about a PET drug product produced at my facility?

Subpart L—Records

212.110 How must I maintain records of my production of PET drugs?

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 371, 374; Sec. 121, Pub. L. 105–115, 111 Stat. 2296.

SOURCE: 74 FR 65431, Dec. 10, 2009, unless otherwise noted.

Subpart A—General Provisions

§ 212.1 What are the meanings of the technical terms used in these regulations?

The following definitions apply to words and phrases as they are used in this part. Other definitions of these words may apply when they are used in other parts of this chapter.

Acceptance criteria means numerical limits, ranges, or other criteria for tests that are used for or in making a decision to accept or reject a unit, lot, or batch of a PET drug product.

Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 321 *et seq.*).

Active pharmaceutical ingredient means a substance that is intended for incorporation into a finished PET drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis or monitoring of a disease or a manifestation of a disease in humans, but does not include intermediates used in the synthesis of such substance.

Batch means a specific quantity of PET drug intended to have uniform character and quality, within specified limits, that is produced according to a single production order during the same cycle of production.

Batch production and control record means a unique record that references an accepted master production and control record and documents specific details on production, labeling, and quality control for a single batch of a PET drug.

Component means any ingredient intended for use in the production of a PET drug, including any ingredients that may not appear in the final PET drug product.

Conditional final release means a final release made prior to completion of a required finished-product test because of a malfunction involving analytical equipment.

Final release means the authoritative decision by a responsible person in a PET production facility to permit the use of a batch of a PET drug in humans.

Inactive ingredient means any intended component of the PET drug other than the active pharmaceutical ingredient.

In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and is used in, the preparation of a PET drug.

Lot means a batch, or a specifically identified portion of a batch, having uniform character and quality within specified limits. In the case of a PET drug produced by continuous process, a lot is a specifically identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.

Lot number, *control number*, or *batch number* means any distinctive combination of letters, numbers, or symbols from which the complete history of the production, processing, packing, holding, and distribution of a batch or lot of a PET drug can be determined.

Master production and control record means a compilation of instructions containing the procedures and specifications for the production of a PET drug.

Material release means the authoritative decision by a responsible person in a PET production facility to permit the use of a component, container and closure, in-process material, packaging material, or labeling in the production of a PET drug.

PET means positron emission tomography.

PET drug means a radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images. The definition includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug. ''PET drug'' includes a ''PET drug product'' as defined in this section.

PET drug product means a finished dosage form of a PET drug, whether or not in association with one or more other ingredients.

PET drug production facility means a facility that is engaged in the production of a PET drug.

Production means the manufacturing, compounding, processing, packaging, labeling, reprocessing, repacking, relabeling, and testing of a PET drug.

Quality assurance means a system for ensuring the quality of active ingredients, PET drugs, intermediates, components that yield an active pharmaceutical ingredient, analytical supplies, and other components, including container-closure systems and in-process materials, through procedures, tests, analytical methods, and acceptance criteria.

Receiving facility means any hospital, institution, nuclear pharmacy, imaging facility, or other entity or part of an entity that accepts a PET drug product that has been given final release, but does not include a common or contract carrier that transports a PET drug product from a PET production facility to a receiving facility.

Specifications means the tests, analytical procedures, and appropriate acceptance criteria to which a PET drug, PET drug product, component, container-closure system, in-process material, or other material used in PET drug production must conform to be considered acceptable for its intended use. Conformance to specifications means that a PET drug, PET drug product, component, container-closure system, in-process material, or other material used in PET drug production, when tested according to the described analytical procedures, meets the listed acceptance criteria.

Strength means the concentration of the active pharmaceutical ingredient (radioactivity amount per volume or weight at the time of calibration).

Sub-batch means a quantity of PET drug having uniform character and quality, within specified limits, that is produced during one succession of multiple irradiations, using a given synthesis and/or purification operation.

Verification means confirmation that an established method, process, or system meets predetermined acceptance criteria.

§ 212.2 What is current good manufacturing practice for PET drugs?

Current good manufacturing practice for PET drugs is the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality assurance, holding, or distribution of PET drugs intended for human use. Current good manufacturing practice is intended to ensure that each PET drug meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it is supposed to have.

§ 212.5 To what drugs do the regulations in this part apply?

(a) *Application solely to PET drugs.* The regulations in this part apply only to the production, quality assurance, holding, and distribution of PET drugs.

Any human drug that does not meet the definition of a PET drug must be manufactured in accordance with the current good manufacturing practice requirements in parts 210 and 211 of this chapter.

(b) *Investigational and research PET drugs.* For investigational PET drugs for human use produced under an investigational new drug application in accordance with part 312 of this chapter, and PET drugs produced with the approval of a Radioactive Drug Research Committee in accordance with part 361 of this chapter, the requirement under the act to follow current good manufacturing practice is met by complying with the regulations in this part or by producing PET drugs in accordance with Chapter 823, ''Radiopharmaceuticals for Positron Emission Tomography—Compounding,'' May 1, 2009, pp. 365–369, 32d ed. of the United States Pharmacopeia (USP) National Formulary (NF) (USP 32/NF 27) (2009). The Director of the Federal Register approves this incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain a copy from the United States Pharmacopeial Convention, Inc., 12601 Twinbrook Pkwy., Rockville, MD 20852, Geeta M. Tirumalai, 301–816–8352, e-mail: *gt@usp.org*, Internet address: *http://www.usp.org/USPNF/notices*. You may inspect a copy at the Food and Drug Administration Biosciences Library, 10903 New Hampshire Ave., Silver Spring, MD, 20993–0002, 301–796–3504, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

Subpart B—Personnel and Resources

§ 212.10 What personnel and resources must I have?

You must have a sufficient number of personnel with the necessary education, background, training, and experience to perform their assigned functions. You must have adequate resources, including facilities and equipment, to enable your personnel to perform their functions.

Subpart C—Quality Assurance

§ 212.20 What activities must I perform to ensure drug quality?

(a) *Production operations.* You must oversee production operations to ensure that each PET drug meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it is supposed to have.

(b) *Materials.* You must examine and approve or reject components, containers, closures, in-process materials, packaging materials, labeling, and finished dosage forms to ensure compliance with procedures and specifications affecting the identity, strength, quality, or purity of a PET drug.

(c) *Specifications and processes.* You must approve or reject, before implementation, any initial specifications, methods, processes, or procedures, and any proposed changes to existing specifications, methods, processes, or procedures, to ensure that they maintain the identity, strength, quality, and purity of a PET drug. You must demonstrate that any change does not adversely affect the identity, strength, quality, or purity of any PET drug.

(d) *Production records.* You must review production records to determine whether errors have occurred. If errors have occurred, or a production batch or any component of the batch fails to meet any of its specifications, you must determine the need for an investigation, conduct investigations when necessary, and take appropriate corrective actions.

(e) *Quality assurance.* You must establish and follow written quality assurance procedures.

Subpart D—Facilities and Equipment

§ 212.30 What requirements must my facilities and equipment meet?

(a) *Facilities.* You must provide adequate facilities to ensure the orderly handling of materials and equipment, the prevention of mix-ups, and the prevention of contamination of equipment or product by substances, personnel, or

environmental conditions that could reasonably be expected to have an adverse effect on product quality.

(b) *Equipment procedures.* You must implement procedures to ensure that all equipment that could reasonably be expected to adversely affect the identity, strength, quality, or purity of a PET drug, or give erroneous or invalid test results when improperly used or maintained, is clean, suitable for its intended purposes, properly installed, maintained, and capable of repeatedly producing valid results. You must document your activities in accordance with these procedures.

(c) *Equipment construction and maintenance.* Equipment must be constructed and maintained so that surfaces that contact components, in-process materials, or PET drugs are not reactive, additive, or absorptive so as to alter the quality of PET drugs.

Subpart E—Control of Components, Containers, and Closures

§ 212.40 How must I control the components I use to produce PET drugs and the containers and closures I package them in?

(a) *Written procedures.* You must establish, maintain, and follow written procedures describing the receipt, login, identification, storage, handling, testing, and acceptance and/or rejection of components and drug product containers and closures. The procedures must be adequate to ensure that the components, containers, and closures are suitable for their intended use.

(b) *Written specifications.* You must establish appropriate written specifications for the identity, quality, and purity of components and for the identity and quality of drug product containers and closures.

(c) *Examination and testing.* Upon receipt, each lot of components and containers and closures must be uniquely identified and tested or examined to determine whether the lot complies with your specifications. You must not use in PET drug production any lot that does not meet its specifications, including any expiration date if applicable, or that has not yet received its material release. Any incoming lot must be appropriately designated as quarantined, accepted, or rejected. You must use a reliable supplier as a source of each lot of each component, container, and closure.

(1)(i) If you conduct finished-product testing of a PET drug product that includes testing to ensure that the correct components have been used, you must determine that each lot of incoming components used in that PET drug product complies with written specifications by examining a certificate of analysis provided by the supplier. You are not required to perform a specific identity test on any of those components.

(ii) If you do not conduct finished-product testing of a PET drug product that ensures that the correct components have been used, you must conduct identity testing on each lot of a component that yields an active ingredient and each lot of an inactive ingredient used in that PET drug product. This testing must be conducted using tests that are specific to each component that yields an active ingredient and each inactive ingredient. For any other component, such as a solvent or reagent, that is not the subject of finished-product testing, you must determine that each lot complies with written specifications by examining a certificate of analysis provided by the supplier; if you use such a component to prepare an inactive ingredient on site, you must perform an identity test on the components used to make the inactive ingredient before the components are released for use. However, if you use as an inactive ingredient a product that is approved under section 505 of the act (21 U.S.C. 355) and is marketed as a finished drug product intended for intravenous administration, you need not perform a specific identity test on that ingredient.

(2) You must examine a representative sample of each lot of containers and closures for conformity to its written specifications. You must perform at least a visual identification of each lot of containers and closures.

(d) *Handling and storage.* You must handle and store components, containers, and closures in a manner that prevents contamination, mix-ups, and

deterioration and ensures that they are and remain suitable for their intended use.

(e) *Records.* You must keep a record for each shipment of each lot of components, containers, and closures that you receive. The record must include the identity and quantity of each shipment, the supplier's name and lot number, the date of receipt, the results of any testing performed, the disposition of rejected material, and the expiration date (where applicable).

Subpart F—Production and Process Controls

§ 212.50 What production and process controls must I have?

You must have adequate production and process controls to ensure the consistent production of a PET drug that meets the applicable standards of identity, strength, quality, and purity.

(a) *Written control procedures.* You must have written production and process control procedures to ensure and document that all key process parameters are controlled and that any deviations from the procedures are justified.

(b) *Master production and control records.* You must have master production and control records that document all steps in the PET drug production process. The master production and control records must include the following information:

(1) The name and strength of the PET drug;

(2) If applicable, the name and radioactivity or other measurement of each active pharmaceutical ingredient and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product, and a statement of the total radioactivity or other measurement of any dosage unit;

(3) A complete list of components designated by names and codes sufficiently specific to indicate any special quality characteristic;

(4) Identification of all major pieces of equipment used in production;

(5) An accurate statement of the weight or measurement of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations are permitted in the amount of component necessary if they are specified in the master production and control records;

(6) A statement of action limits on radiochemical yield, i.e., the minimum percentage of yield beyond which investigation and corrective action are required;

(7) Complete production and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed; and

(8) A description of the PET drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling.

(c) *Batch production and control records.* Each time a batch of a PET drug is produced, a unique batch production and control record must be created. The batch production record must include the following information:

(1) Name and strength of the PET drug;

(2) Identification number or other unique identifier of the specific batch that was produced;

(3) The name and radioactivity or other measure of each active pharmaceutical ingredient and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product;

(4) Each major production step (obtained from the approved appropriate master production and control record);

(5) Weights (or other measure of quantity) and identification codes of components;

(6) Dates of production steps and times of critical production steps;

(7) Identification of major pieces of equipment used in production of the batch;

(8) Testing results;

(9) Labeling;

(10) Initials or signatures of persons performing or checking each significant step in the operation; and

(11) Results of any investigations conducted.

(d) *Area and equipment checks.* The production area and all equipment in the production area must be checked to

ensure cleanliness and suitability immediately before use. A record of these checks must be kept.

(e) *In-process materials controls.* Process controls must include control of in-process materials to ensure that the materials are controlled until required tests or other verification activities have been completed or necessary approvals are received and documented.

(f) *Process verification.* (1) For a PET drug for which each entire batch undergoes full finished-product testing to ensure that the product meets all specifications, process verification, as described in paragraph (f)(2) of this section, is not required.

(2) When the results of the production of an entire batch of a PET drug are not fully verified through finished-product testing or when only the initial sub-batch in a series is tested, the PET drug producer must demonstrate that the process for producing the PET drug is reproducible and is capable of producing a drug product that meets the predetermined acceptance criteria. Process verification activities and results must be documented. Documentation must include the date and signature of the individual(s) performing the verification, the monitoring and control methods and data, and the major equipment qualified.

Subpart G—Laboratory Controls

§ 212.60 What requirements apply to the laboratories where I test components, in-process materials, and finished PET drug products?

(a) *Testing procedures.* Each laboratory used to conduct testing of components, in-process materials, and finished PET drug products must have and follow written procedures for the conduct of each test and for the documentation of the results.

(b) *Specifications and standards.* Each laboratory must have sampling and testing procedures designed to ensure that components, in-process materials, and PET drug products conform to appropriate standards, including established standards of identity, strength, quality, and purity.

(c) *Analytical methods.* Laboratory analytical methods must be suitable for their intended use and must be sufficiently sensitive, specific, accurate, and reproducible.

(d) *Materials.* The identity, purity, and quality of reagents, solutions, and supplies used in testing procedures must be adequately controlled. All solutions that you prepare must be properly labeled to show their identity and expiration date.

(e) *Equipment.* All equipment used to perform the testing must be suitable for its intended purposes and capable of producing valid results.

(f) *Equipment maintenance.* Each laboratory must have and follow written procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained, and that these activities are documented.

(g) *Test records.* Each laboratory performing tests related to the production of a PET drug must keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A suitable identification of the sample received for testing.

(2) A description of each method used in the testing of the sample, a record of all calculations performed in connection with each test, and a statement of the weight or measurement of the sample used for each test.

(3) A complete record of all data obtained in the course of each test, including the date and time the test was conducted, and all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or drug product for each lot tested.

(4) A statement of the results of tests and how the results compare with established acceptance criteria.

(5) The initials or signature of the person performing the test and the date on which the test was performed.

§ 212.61 What must I do to ensure the stability of my PET drug products through expiry?

(a) *Stability testing program.* You must establish, follow, and maintain a written testing program to assess the stability characteristics of your PET drug products. The test methods must be reliable, meaningful, and specific. The

samples tested for stability must be representative of the lot or batch from which they were obtained and must be stored under suitable conditions.

(b) *Storage conditions and expiration dates.* The results of such stability testing must be documented and used in determining appropriate storage conditions and expiration dates and times for each PET drug product you produce.

Subpart H—Finished Drug Product Controls and Acceptance

§ 212.70 What controls and acceptance criteria must I have for my finished PET drug products?

(a) *Specifications.* You must establish specifications for each PET drug product, including criteria for determining identity, strength, quality, purity, and, if appropriate, sterility and pyrogens.

(b) *Test procedures.* Before you implement a new test procedure in a specification, you must establish and document the accuracy, sensitivity, specificity, and reproducibility of the procedure. If you use an established compendial test procedure in a specification, you must first verify and document that the test works under the conditions of actual use.

(c) *Conformance to specifications.* Before final release, you must conduct an appropriate laboratory determination to ensure that each batch of a PET drug product conforms to specifications, except for sterility. For a PET drug product produced in sub-batches, before final release, you must conduct an appropriate laboratory determination to ensure that each sub-batch conforms to specifications, except for sterility.

(d) *Final release procedures.* Except as conditional final release is permitted in accordance with paragraph (f) of this section, you must establish and follow procedures to ensure that each batch of a PET drug product is not given final release until the following are done:

(1) An appropriate laboratory determination under paragraph (c) of this section is completed;

(2) Associated laboratory data and documentation are reviewed and they demonstrate that the PET drug product meets specifications, except for sterility; and

(3) A designated qualified individual authorizes final release by dated signature.

(e) *Sterility testing.* Sterility testing need not be completed before final release but must be started within 30 hours after completion of production. The 30-hour requirement may be exceeded due to a weekend or holiday. If the sample for sterility testing is held longer than 30 hours, you must demonstrate that the longer period does not adversely affect the sample and the test results obtained will be equivalent to test results that would have been obtained if the test had been started within the 30-hour time period. Tested samples must be from individual batches and not pooled. If the product fails to meet a criterion for sterility, you must immediately notify all facilities that received the product of the test results and provide any appropriate recommendations. The notification must be documented. Upon completion of an investigation into the failure to meet a criterion for sterility, you must notify all facilities that received the product of the findings from the investigation.

(f) *Conditional final release.* (1) If you cannot complete one of the required finished-product tests for a batch of a PET drug product because of a malfunction involving analytical equipment, you may approve the conditional final release of the product if you meet the following conditions:

(i) You have data documenting that preceding consecutive batches, produced using the same methods used for the conditionally released batch, demonstrate that the conditionally released batch will likely meet the established specifications;

(ii) You determine that all other acceptance criteria are met;

(iii) You retain a reserve sample of the conditionally released batch of drug product;

(iv) You promptly correct the malfunction of analytical equipment, complete the omitted test using the reserve sample after the malfunction is corrected, and document that reasonable efforts have been made to prevent recurrence of the malfunction;

(v) If you obtain an out-of-specification result when testing the reserve sample, you immediately notify the receiving facility; and

(vi) You document all actions regarding the conditional final release of the drug product, including the justification for the release, all followup actions, results of completed testing, all notifications, and corrective actions to prevent recurrence of the malfunction involving analytical equipment.

(2) Even if the criteria in paragraph (f)(1) of this section are met, you may not approve the conditional final release of the product if the malfunction involving analytical equipment prevents the performance of a radiochemical identity/purity test or prevents the determination of the product's specific activity.

(3) You may not release another batch of the PET drug product until you have corrected the problem concerning the malfunction of analytical equipment and completed the omitted finished-product test.

§ 212.71 What actions must I take if a batch of PET drug product does not conform to specifications?

(a) *Rejection of nonconforming product.* You must reject a batch of a PET drug product that does not conform to specifications. You must have and follow procedures to identify and segregate the product to avoid mix-ups. You must have and follow procedures to investigate the cause(s) of the nonconforming product. The investigation must include, but is not limited to, examination of processes, operations, records, complaints, and any other relevant sources of information concerning the nonconforming product.

(b) *Investigation.* You must document the investigation of a PET drug product that does not meet specifications, including the results of the investigation and what happened to the rejected PET drug product.

(c) *Correction of problems.* You must take action to correct any identified problems to prevent recurrence of a nonconforming product or other quality problem.

(d) *Reprocessing.* If appropriate, you may reprocess a batch of a PET drug product that does not conform to specifications. If material that does not meet acceptance criteria is reprocessed, you must follow procedures stated in the product's approved application and the finished product must conform to specifications, except for sterility, before final release.

Subpart I—Packaging and Labeling

§ 212.80 What are the requirements associated with labeling and packaging PET drug products?

(a) A PET drug product must be suitably labeled and packaged to protect the product from alteration, contamination, and damage during the established conditions of shipping, distribution, handling, and use.

(b) Labels must be legible and applied so as to remain legible and affixed during the established conditions of processing, storage, handling, distribution, and use.

(c) All information stated on each label must also be contained in each batch production record.

(d) Labeling and packaging operations must be controlled to prevent labeling and product mix-ups.

Subpart J—Distribution

§ 212.90 What actions must I take to control the distribution of PET drug products?

(a) *Written distribution procedures.* You must establish, maintain, and follow written procedures for the control of distribution of PET drug products shipped from the PET drug production facility to ensure that the method of shipping chosen will not adversely affect the identity, purity, or quality of the PET drug product.

(b) *Distribution records.* You must maintain distribution records for each PET drug product that include or refer to the following:

(1) The name, address, and telephone number of the receiving facility that received each batch of a PET drug product;

(2) The name and quantity of the PET drug product shipped;

(3) The lot number, control number, or batch number for the PET drug product shipped; and

(4) The date and time you shipped the PET drug product.

Subpart K—Complaint Handling

§ 212.100 What do I do if I receive a complaint about a PET drug product produced at my facility?

(a) *Written complaint procedures.* You must develop and follow written procedures for the receipt and handling of all complaints concerning the quality or purity of, or possible adverse reactions to, a PET drug product.

(b) *Complaint review.* The procedures must include review by a designated person of any complaint involving the possible failure of a PET drug product to meet any of its specifications and an investigation to determine the cause of the failure.

(c) *Complaint records.* A written record of each complaint must be maintained in a file designated for PET drug product complaints. The record must include the name and strength of the PET drug product, the batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It must also include the findings of any investigation and followup.

(d) *Returned products.* A PET drug product that is returned because of a complaint or for any other reason may not be reprocessed and must be destroyed in accordance with applicable Federal and State law.

Subpart L—Records

§ 212.110 How must I maintain records of my production of PET drugs?

(a) *Record availability.* Records must be maintained at the PET drug production facility or another location that is reasonably accessible to responsible officials of the production facility and to employees of FDA designated to perform inspections.

(b) *Record quality.* All records, including those not stored at the inspected establishment, must be legible, stored to prevent deterioration or loss, and readily available for review and copying by FDA employees.

(c) *Record retention period.* You must maintain all records and documentation referenced in this part for a period of at least 1 year from the date of final release, including conditional final release, of a PET drug product.

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.
216.23 [Reserved]
216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

AUTHORITY: 21 U.S.C. 351, 352, 353a, 355, and 371.

SOURCE: 64 FR 10944, Mar. 8, 1999, unless otherwise noted.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 [Reserved]

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium.

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.

Casein, iodinated: All drug products containing iodinated casein.
Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.
Chlormadinone acetate: All drug products containing chlormadinone acetate.
Chloroform: All drug products containing chloroform.
Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).
Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.
Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.
Dibromsalan: All drug products containing dibromsalan.
Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.
Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.
Dipyrone: All drug products containing dipyrone.
Encainide hydrochloride: All drug products containing encainide hydrochloride.
Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.
Flosequinan: All drug products containing flosequinan.
Gelatin: All intravenous drug products containing gelatin.
Glycerol, iodinated: All drug products containing iodinated glycerol.
Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.
Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.
Metabromsalan: All drug products containing metabromsalan.
Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.
Methapyrilene: All drug products containing methapyrilene.
Methopholine: All drug products containing methopholine.
Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.
Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatalogic application).
Nomifensine maleate: All drug products containing nomifensine maleate.
Oxyphenisatin: All drug products containing oxyphenisatin.
Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.
Phenacetin: All drug products containing phenacetin.
Phenformin hydrochloride: All drug products containing phenformin hydrochloride.
Pipamazine: All drug products containing pipamazine.
Potassium arsenite: All drug products containing potassium arsenite.
Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).
Povidone: All intravenous drug products containing povidone.
Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.
Sparteine sulfate: All drug products containing sparteine sulfate.
Sulfadimethoxine: All drug products containing sulfadimethoxine.
Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).
Suprofen: All drug products containing suprofen (except ophthalmic solutions).
Sweet spirits of nitre: All drug products containing sweet spirits of nitre.
Temafloxacin hydrochloride: All drug products containing temafloxacin.
Terfenadine: All drug products containing terfenadine.
3,3′,4′,5-tetrachlorosalicylanilide: All drug products containing 3,3′,4′,5-tetrachlorosalicylanilide.
Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.
Ticrynafen: All drug products containing ticrynafen.
Tribromsalan: All drug products containing tribromsalan.
Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.
Urethane: All drug products containing urethane.
Vinyl chloride: All aerosol drug products containing vinyl chloride.
Zirconium: All aerosol drug products containing zirconium.
Zomepirac sodium: All drug products containing zomepirac sodium.

PART 225—CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICATED FEEDS

Subpart A—General Provisions

Sec.
225.1 Current good manufacturing practice.
225.10 Personnel.

Subpart B—Construction and Maintenance of Facilities and Equipment

225.20 Buildings.
225.30 Equipment.
225.35 Use of work areas, equipment, and storage areas for other manufacturing and storage purpose.

Subpart C—Product Quality Control

225.42 Components.
225.58 Laboratory controls.
225.65 Equipment cleanout procedures.

Subpart D—Packaging and Labeling

225.80 Labeling.

Subpart E—Records and Reports

225.102 Master record file and production records.
225.110 Distribution records.
225.115 Complaint files.

Subpart F—Facilities and Equipment

225.120 Buildings and grounds.
225.130 Equipment.
225.135 Work and storage areas.

Subpart G—Product Quality Assurance

225.142 Components.
225.158 Laboratory assays.
225.165 Equipment cleanout procedures.

Subpart H—Labeling

225.180 Labeling.

Subpart I—Records

225.202 Formula, production, and distribution records.

AUTHORITY: 21 U.S.C. 351, 352, 360b, 371, 374.

SOURCE: 41 FR 52618, Nov. 30, 1976, unless otherwise noted.

Subpart A—General Provisions

§ 225.1 Current good manufacturing practice.

(a) Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act provides that a drug (including a drug contained in a medicated feed) shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirement of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

(b)(1) The provisions of this part set forth the criteria for determining whether the manufacture of a medicated feed is in compliance with current good manufacturing practice. These regulations shall apply to all types of facilities and equipment used in the production of medicated feeds, and they shall also govern those instances in which failure to adhere to the regulations has caused nonmedicated feeds that are manufactured, processed, packed, or held to be adulterated. In such cases, the medicated feed shall be deemed to be adulterated within the meaning of section 501(a)(2)(B) of the act, and the nonmedicated feed shall be deemed to be adulterated within the meaning of section 402(a)(2)(C)(ii) of the act.

(2) The regulations in §§ 225.10 through 225.115 apply to facilities manufacturing one or more medicated feeds for which an approved medicated feed mill license is required. The regulations in §§ 225.120 through 225.202 apply to facilities manufacturing solely medicated feeds for which an approved license is not required.

(c) In addition to the recordkeeping requirements in this part, Type B and Type C medicated feeds made from Type A articles or Type B feeds under approved NADAs or indexed listings and a medicated feed mill license are subject to the requirements of § 510.301 of this chapter.

[41 FR 52618, Nov. 30, 1976, as amended at 51 FR 7389, Mar. 3, 1986; 64 FR 63203, Nov. 19, 1999; 72 FR 69120, Dec. 6, 2007; 79 FR 3739, Jan. 23, 2014]

§ 225.10 Personnel.

(a) Qualified personnel and adequate personnel training and supervision are essential for the proper formulation, manufacture, and control of medicated feeds. Training and experience leads to proper use of equipment, maintenance of accurate records, and detection and prevention of possible deviations from current good manufacturing practices.

(b)(1) All employees involved in the manufacture of medicated feeds shall

have an understanding of the manufacturing or control operation(s) which they perform, including the location and proper use of equipment.

(2) The manufacturer shall provide an on-going program of evaluation and supervision of employees in the manufacture of medicated feeds.

[41 FR 52618, Nov. 30, 1976, as amended at 42 FR 12426, Mar. 4, 1977]

Subpart B—Construction and Maintenance of Facilities and Equipment

§ 225.20 Buildings.

(a) The location, design, construction, and physical size of the buildings and other production facilities are factors important to the manufacture of medicated feed. The features of facilities necessary for the proper manufacture of medicated feed include provision for ease of access to structures and equipment in need of routine maintenance; ease of cleaning of equipment and work areas; facilities to promote personnel hygiene; structural conditions for control and prevention of vermin and pest infestation; adequate space for the orderly receipt and storage of drugs and feed ingredients and the controlled flow of these materials through the processing and manufacturing operations; and the equipment for the accurate packaging and delivery of a medicated feed of specified labeling and composition.

(b) The construction and maintenance of buildings in which medicated feeds are manufactured, processed, packaged, labeled, or held shall conform to the following:

(1) The building grounds shall be adequately drained and routinely maintained so that they are reasonably free from litter, waste, refuse, uncut weeds or grass, standing water, and improperly stored equipment.

(2) The building(s) shall be maintained in a reasonably clean and orderly manner.

(3) The building(s) shall be of suitable construction to minimize access by rodents, birds, insects, and other pests.

(4) The buildings shall provide adequate space and lighting for the proper performance of the following medicated feed manufacturing operations:

(i) The receipt, control, and storage of components.

(ii) Component processing.

(iii) Medicated feed manufacturing.

(iv) Packaging and labeling.

(v) Storage of containers, packaging materials, labeling and finished products.

(vi) Routine maintenance of equipment.

§ 225.30 Equipment.

(a) Equipment which is designed to perform its intended function and is properly installed and used is essential to the manufacture of medicated feeds. Such equipment permits production of feeds of uniform quality, facilitates cleaning, and minimizes spillage of drug components and finished product.

(b)(1) All equipment shall possess the capability to produce a medicated feed of intended potency, safety, and purity.

(2) All equipment shall be maintained in a reasonably clean and orderly manner.

(3) All equipment, including scales and liquid metering devices, shall be of suitable size, design, construction, precision, and accuracy for its intended purpose.

(4) All scales and metering devices shall be tested for accuracy upon installation and at least once a year thereafter, or more frequently as may be necessary to insure their accuracy.

(5) All equipment shall be so constructed and maintained as to prevent lubricants and coolants from becoming unsafe additives in feed components or medicated feed.

(6) All equipment shall be designed, constructed, installed and maintained so as to facilitate inspection and use of cleanout procedure(s).

§ 225.35 Use of work areas, equipment, and storage areas for other manufacturing and storage purpose.

(a) Many manufacturers of medicated feeds are also involved in the manufacture, storage, or handling of products which are not intended for animal feed use, such as fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides. Manufacturing, storage, or handling of nonfeed and feed

products in the same facilities may cause adulteration of feed products with toxic or otherwise unapproved feed additives.

(b) Work areas and equipment used for the manufacture or storage of medicated feeds or components thereof shall not be used for, and shall be physically separated from, work areas and equipment used for the manufacture of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides unless such articles are approved drugs, indexed drugs, or approved food additives intended for use in the manufacture of medicated feed.

[41 FR 52618, Nov. 30, 1976, as amended at 72 FR 69120, Dec. 6, 2007]

Subpart C—Product Quality Control

§ 225.42 Components.

(a) A medicated feed, in addition to providing nutrients, is a vehicle for the administration of a drug, or drugs, to animals. To ensure proper safety and effectiveness, such medicated feeds must contain the labeled amounts of drugs. It is necessary that adequate procedures be established for the receipt, storage, and inventory control for all such drugs to aid in assuring their identity, strength, quality, and purity when incorporated into products.

(b) The receipt, storage, and inventory of drugs, including undiluted drug components, medicated premixes, and semiprocessed (i.e., intermediate premixes, inplant premixes and concentrates) intermediate mixes containing drugs, which are used in the manufacture and processing of medicated feeds shall conform to the following:

(1) Incoming shipments of drugs shall be visually examined for identity and damage. Drugs which have been subjected to conditions which may have adversely affected their identity, strength, quality, or purity shall not be accepted for use.

(2) Packaged drugs in the storage areas shall be stored in their original closed containers.

(3) Bulk drugs shall be identified and stored in a manner such that their identity, strength, quality, and purity will be maintained.

(4) Drugs in the mixing areas shall be properly identified, stored, handled, and controlled to maintain their integrity and identity. Sufficient space shall be provided for the location of each drug.

(5) A receipt record shall be prepared and maintained for each lot of drug received. The receipt record shall accurately indicate the identity and quantity of the drug, the name of the supplier, the supplier's lot number or an identifying number assigned by the feed manufacturer upon receipt which relates to the particular shipment, the date of receipt, the condition of the drug when received, and the return of any damaged drugs.

(6) A daily inventory record for each drug used shall be maintained and shall list by manufacturer's lot number or the feed manufacturer's shipment identification number at least the following information:

(i) The quantity of drug on hand at the beginning and end of the work day (the beginning amount being the same as the previous day's closing inventory if this amount has been established to be correct); the quantity shall be determined by weighing, counting, or measuring, as appropriate.

(ii) The amount of each drug used, sold, or otherwise disposed of.

(iii) The batches or production runs of medicated feed in which each drug was used.

(iv) When the drug is used in the preparation of a semiprocessed intermediate mix intended for use in the manufacture of medicated feed, any additional information which may be required for the purpose of paragraph (b)(7) of this section.

(v) Action taken to reconcile any discrepancies in the daily inventory record.

(7) Drug inventory shall be maintained of each lot or shipment of drug by means of a daily comparison of the actual amount of drug used with the theoretical drug usage in terms of the semiprocessed, intermediate and finished medicated feeds manufactured. Any significant discrepancy shall be investigated and corrective action taken. The medicated feed(s) remaining on the

premises which are affected by this discrepancy shall be detained until the discrepancy is reconciled.

(8) All records required by this section shall be maintained on the premises for at least one year after complete use of a drug component of a specific lot number or feed manufacturer's shipment identification number.

§ 225.58 Laboratory controls.

(a) The periodic assay of medicated feeds for drug components provides a measure of performance of the manufacturing process in manufacturing a uniform product of intended potency.

(b) The following assay requirements shall apply to medicated feeds:

(1) For feeds requiring a medicated feed mill license (Form FDA 3448) for their manufacture and marketing, at least three representative samples of medicated feed containing each drug or drug combination used in the establishment shall be collected and assayed by approved official methods, at periodic intervals during the calendar year, unless otherwise specified in this chapter. At least one of these assays shall be performed on the first batch using the drug. If a medicated feed contains a combination of drugs, only one of the drugs need be subject to analysis each time, provided the one tested is different from the one(s) previously tested.

(2) [Reserved]

(c) The originals or copies of all results of assays, including those from State feed control officials and any other governmental agency, shall be maintained on the premises for a period of not less than 1 year after distribution of the medicated feed. The results of assays performed by State feed control officials may be considered toward fulfillment of the periodic assay requirements of this section.

(d) Where the results of assays indicate that the medicated feed is not in accord with label specifications or is not within permissible assay limits as specified in this chapter, investigation and corrective action shall be implemented and an original or copy of the record of such action maintained on the premises.

(e) Corrective action shall include provisions for discontinuing distribution where the medicated feed fails to meet the labeled drug potency. Distribution of subsequent production of the particular feed shall not begin until it has been determined that proper control procedures have been established.

[41 FR 52618, Nov. 30, 1976, as amended at 51 FR 7390, Mar. 3, 1986; 55 FR 11577, Mar. 29, 1990; 64 FR 63203, Nov. 19, 1999]

§ 225.65 Equipment cleanout procedures.

(a) Adequate cleanout procedures for all equipment used in the manufacture and distribution of medicated feeds are essential to maintain proper drug potency and avoid unsafe contamination of feeds with drugs. Such procedures may consist of cleaning by physical means, e.g., vacuuming, sweeping, washing, etc. Alternatively, flushing or sequencing or other equally effective techniques may be used whereby the equipment is cleaned either through use of a feed containing the same drug(s) or through use of drug free feedstuffs.

(b) All equipment, including that used for storage, processing, mixing, conveying, and distribution that comes in contact with the active drug component, feeds in process, or finished medicated feed shall be subject to all reasonable and effective procedures to prevent unsafe contamination of manufactured feed. The steps used to prevent unsafe contamination of feeds shall include one or more of the following, or other equally effective procedures:

(1) Such procedures shall, where appropriate, consist of physical means (vacuuming, sweeping, or washing), flushing, and/or sequential production of feeds.

(2) If flushing is utilized, the flush material shall be properly identified, stored, and used in a manner to prevent unsafe contamination of other feeds.

(3) If sequential production of medicated feeds is utilized, it shall be on a predetermined basis designed to prevent unsafe contamination of feeds with residual drugs.

Subpart D—Packaging and Labeling

§ 225.80 Labeling.

(a) Appropriate labeling identifies the medicated feed, and provides the user with directions for use which, if adhered to, will assure that the article is safe and effective for its intended purposes.

(b)(1) Labels and labeling, including placards, shall be received, handled, and stored in a manner that prevents labeling mixups and assures that correct labeling is employed for the medicated feed.

(2) Labels and labeling, including placards, upon receipt from the printer shall be proofread against the Master Record File to verify their suitability and accuracy. The proofread label shall be dated, initialed by a responsible individual, and kept for 1 year after all the labels from that batch have been used.

(3) In those instances where medicated feeds are distributed in bulk, complete labeling shall accompany the shipment and be supplied to the consignee at the time of delivery. Such labeling may consist of a placard or other labels attached to the invoice or delivery ticket, or manufacturer's invoice that identifies the medicated feed and includes adequate information for the safe and effective use of the medicated feed.

(4) Label stock shall be reviewed periodically and discontinued labels shall be discarded.

Subpart E—Records and Reports

§ 225.102 Master record file and production records.

(a) The Master Record File provides the complete procedure for manufacturing a specific product, setting forth the formulation, theoretical yield, manufacturing procedures, assay requirements, and labeling of batches or production runs. The production record(s) includes the complete history of a batch or production run. This record includes the amounts of drugs used, the amount of medicated feed manufactured, and provides a check for the daily inventory record of drug components.

(b) The Master Record File and production records shall comply with the following provisions:

(1) A Master Record File shall be prepared, checked, dated, and signed or initialed by a qualified person and shall be retained for not less than 1 year after production of the last batch or production run of medicated feed to which it pertains. The Master Record File or card shall include at least the following:

(i) The name of the medicated feed.

(ii) The name and weight percentage or measure of each drug or drug combination and each nondrug ingredient to be used in manufacturing a stated weight of the medicated feed.

(iii) A copy or description of the label or labeling that will accompany the medicated feed.

(iv) Manufacturing instructions or reference thereto that have been determined to yield a properly mixed medicated feed of the specified formula for each medicated feed produced on a batch or continuous operation basis, including mixing steps, mixing times and, in the case of medicated feeds produced by continuous production run, any additional manufacturing directions including, when indicated, the settings of equipment.

(v) Appropriate control directions or reference thereto, including the manner and frequency of collecting the required number of samples for specified laboratory assay.

(2) The original production record or copy thereof shall be prepared by qualified personnel for each batch or run of medicated feed produced and shall be retained on the premises for not less than 1 year. The production record shall include at least the following:

(i) Product identification, date of production, and a written endorsement in the form of a signature or initials by a responsible individual.

(ii) The quantity and name of drug components used.

(iii) The theoretical quantity of medicated feed to be produced.

(iv) The actual quantity of medicated feed produced. In those instances where the finished feed is stored in bulk and actual yield cannot be accurately determined, the firm shall estimate the quantity produced and provide the

basis for such estimate in the Master Record File.

(3) In the case of a custom formula feed made to the specifications of a customer, the Master Record File and production records required by this section shall consist either of such records or of copies of the customer's purchase orders and the manufacturer's invoices bearing the information required by this section. When a custom order is received by telephone, the manufacturer shall prepare the required production records.

(4) Batch production records shall be checked by a responsible individual at the end of the working day in which the product was manufactured to determine whether all required production steps have been performed. If significant discrepancies are noted, an investigation shall be instituted immediately, and the production record shall describe the corrective action taken.

(5) Each batch or production run of medicated feed shall be identified with its own individual batch or production run number, code, date, or other suitable identification applied to the label, package, invoice or shipping document. This identification shall permit the tracing of the complete and accurate manufacturing history of the product by the manufacturer.

§ 225.110 Distribution records.

(a) Distribution records permit the manufacturer to relate complaints to specific batches and/or production runs of medicated feed. This information may be helpful in instituting a recall.

(b) Distribution records for each shipment of a medicated feed shall comply with the following provisions:

(1) Each distribution record shall include the date of shipment, the name and address of purchaser, the quantity shipped, and the name of the medicated feed. A lot or control number, or date of manufacture or other suitable identification shall appear on the distribution record or the label issued with each shipment.

(2) The originals or copies of the distribution records shall be retained on the premises for not less than one year after the date of shipment of the medicated feed.

§ 225.115 Complaint files.

(a) Complaints and reports of experiences of product defects relative to the drug's efficacy or safety may provide an indicator as to whether or not medicated feeds have been manufactured in conformity with current good manufacturing practices. These complaints and experiences may reveal the existence of manufacturing problems not otherwise detected through the normal quality control procedures. Timely and appropriate follow-up action can serve to correct a problem and minimize future problems.

(b) The medicated feed manufacturer shall maintain on the premises a file which contains the following information:

(1) The original or copy of a record of each oral and written complaint received relating to the safety and effectiveness of the product produced. The record shall include the date of the complaint, the complainant's name and address, name and lot or control number or date of manufacture of the medicated feed involved, and the specific details of the complaint. This record shall also include all correspondence from the complainant and/or memoranda of conversations with the complainant, and a description of all investigations made by the manufacturer and of the method of disposition of the complaint.

(2) For medicated feeds whose manufacture require a medicated feed mill license (Form FDA 3448), records and reports of clinical and other experience with the drug shall be maintained and reported, under § 510.301 of this chapter.

[41 FR 52618, Nov. 30, 1976, as amended at 51 FR 7390, Mar. 3, 1986; 57 FR 6475, Feb. 25, 1992; 64 FR 63203, Nov. 19, 1999]

Subpart F—Facilities and Equipment

SOURCE: 51 FR 7390, Mar. 3, 1986, unless otherwise noted.

§ 225.120 Buildings and grounds.

Buildings used for production of medicated feed shall provide adequate space for equipment, processing, and orderly receipt and storage of medicated feed. Areas shall include access

for routine maintenance and cleaning of equipment. Buildings and grounds shall be constructed and maintained in a manner to minimize vermin and pest infestation.

§ 225.130 Equipment.

Equipment shall be capable of producing a medicated feed of intended potency and purity, and shall be maintained in a reasonably clean and orderly manner. Scales and liquid metering devices shall be accurate and of suitable size, design, construction, precision, and accuracy for their intended purposes. All equipment shall be designed, constructed, installed, and maintained so as to facilitate inspection and use of cleanout procedure(s).

§ 225.135 Work and storage areas.

Work areas and equipment used for the production or storage of medicated feeds or components thereof shall not be used for, and shall be physically separated from, work areas and equipment used for the manufacture and storage of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides unless such articles are approved or index listed for use in the manufacture of animal feed.

[72 FR 69120, Dec. 6, 2007]

Subpart G—Product Quality Assurance

SOURCE: 51 FR 7390, Mar. 3, 1986, unless otherwise noted.

§ 225.142 Components.

Adequate procedures shall be established and maintained for the identification, storage, and inventory control (receipt and use) of all Type A medicated articles and Type B medicated feeds intended for use in the manufacture of medicated feeds to aid in assuring the identity, strength, quality, and purity of these drug sources. Packaged Type A medicated articles and Type B medicated feeds shall be stored in designated areas in their original closed containers. Bulk Type A medicated articles and bulk Type B medicated feeds shall be identified and stored in a manner such that their identity, strength, quality, and purity will be maintained. All Type A medicated articles and Type B medicated feeds shall be used in accordance with their labeled mixing directions.

§ 225.158 Laboratory assays.

Where the results of laboratory assays of drug components, including assays by State feed control officials, indicate that the medicated feed is not in accord with the permissible limits specified in this chapter, investigation and corrective action shall be implemented immediately by the firm and such records shall be maintained on the premises for a period of 1 year.

§ 225.165 Equipment cleanout procedures.

Adequate procedures shall be established and used for all equipment used in the production and distribution of medicated feeds to avoid unsafe contamination of medicated and nonmedicated feeds.

Subpart H—Labeling

§ 225.180 Labeling.

Labels shall be received, handled, and stored in a manner that prevents label mixups and assures that the correct labels are used for the medicated feed. All deliveries of medicated feeds, whether bagged or in bulk, shall be adequately labeled to assure that the feed can be properly used.

[51 FR 7390, Mar. 3, 1986]

Subpart I—Records

§ 225.202 Formula, production, and distribution records.

Records shall be maintained identifying the formulation, date of mixing, and if not for own use, date of shipment. The records shall be adequate to facilitate the recall of specific batches of medicated feed that have been distributed. Such records shall be retained on the premises for 1 year following the date of last distribution.

(Approved by the Office of Management and Budget under control number 0910–0152)

[51 FR 7390, Mar. 3, 1986]

PART 226—CURRENT GOOD MANUFACTURING PRACTICE FOR TYPE A MEDICATED ARTICLES

Subpart A—General Provisions

Sec.
226.1 Current good manufacturing practice.
226.10 Personnel.

Subpart B—Construction and Maintenance of Facilities and Equipment

226.20 Buildings.
226.30 Equipment.

Subpart C—Product Quality Control

226.40 Production and control procedures.
226.42 Components.
226.58 Laboratory controls.

Subpart D—Packaging and Labeling

226.80 Packaging and labeling.

Subpart E—Records and Reports

226.102 Master-formula and batch-production records.
226.110 Distribution records.
226.115 Complaint files.

AUTHORITY: 21 U.S.C. 351, 352, 360b, 371, 374.

SOURCE: 40 FR 14031, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 226.1 Current good manufacturing practice.

(a) The criteria in §§ 226.10 through 226.115, inclusive, shall apply in determining whether the methods used in, or the facilities and controls used for the manufacture, processing, packing, or holding of a Type A medicated article(s) conform to or are operated or administered in conformity with current good manufacturing practice to assure that a Type A medicated article(s) meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess, as required by section 501(a)(2)(B) of the act. The regulations in this part 226 permit the use of precision, automatic, mechanical, or electronic equipment in the production of a Type A medicated article(s) when adequate inspection and checking procedures or other quality control procedures are used to assure proper performance.

(b) In addition to maintaining records and reports required in this part, Type A medicated articles requiring approved NADAs are subject to the requirements of § 514.80 of this chapter. Similarly, Type A medicated articles listed in the index are subject to the requirements of § 516.165 of this chapter.

[40 FR 14031, Mar. 27, 1975, as amended at 68 FR 15364, Mar. 31, 2003; 72 FR 69120, Dec. 6, 2007]

§ 226.10 Personnel.

The key personnel and any consultants involved in the manufacture and control of the Type A medicated article(s) shall have a background of appropriate education or appropriate experience or combination thereof for assuming responsibility to assure that the Type A medicated article(s) has the proper labeling and the safety, identity, strength, quality, and purity that it purports to possess.

Subpart B—Construction and Maintenance of Facilities and Equipment

§ 226.20 Buildings.

Buildings in which Type A medicated article(s) are manufactured, processed, packaged, labeled, or held shall be maintained in a clear and orderly manner and shall be of suitable size, construction and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. The building shall:

(a) Provide adequate space for the orderly placement of equipment and materials used in any of the following operations for which they are employed to minimize risk of mixups between different Type A medicated article(s), their components, packaging, or labeling:

(1) The receipt, sampling, control, and storage of components.

(2) Manufacturing and processing operations performed on the Type A medicated article(s).

(3) Packaging and labeling operations.

(4) Storage of containers, packaging materials, labeling, and finished products.

(5) Control laboratory operations.

(b) Provide adequate lighting and ventilation, and when necessary for the intended production or control purposes, adequate screening, dust and temperature controls, to avoid contamination of Type A medicated article(s), and to avoid other conditions unfavorable to the safety, identity, strength, quality, and purity of the raw materials and Type A medicated article(s) before, during, and after production.

(c) Provide for adequate washing, cleaning, toilet, and locker facilities.

Work areas and equipment used for the production of Type A medicated article(s) or for the storage of the components of Type A medicated article(s) shall not be used for the production, mixing or storage of finished or unfinished insecticides, fungicides, rodenticides, or other pesticides or their components unless such materials are recognized as approved drugs intended for use in animal feeds.

§ 226.30 Equipment.

Equipment used for the manufacture, processing, packaging, bulk shipment, labeling, holding, or control of Type A medicated article(s) or their components shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction, and location to facilitate maintenance and operation for its intended purpose. The equipment shall:

(a) Be so constructed that any surfaces that come into contact with Type A medicated article(s) are suitable, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the Type A medicated article(s) or its components.

(b) Be so constructed that any substance required for the operation of the equipment, such as lubricants, coolants, etc., may be employed without hazard of becoming an unsafe additive to the Type A medicated article(s).

(c) Be constructed to facilitate adjustment, cleaning, and maintenance, and to assure uniformity of production and reliability of control procedures and to assure the exclusion from Type A medicated article(s) of contamination, including cross-contamination from manufacturing operations.

(d) Be suitably grounded electrically to prevent lack of uniform mixing due to electrically charged particles.

(e) Be of suitable size and accuracy for use in any intended measuring, mixing, or weighing operations.

Subpart C—Product Quality Control

§ 226.40 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the Type A medicated article(s) produced have the identity, strength, quality, and purity they purport to possess:

(a) Each critical step in the process, such as the selection, weighing, and measuring of components; the addition of drug components during the process; weighing and measuring during various stages of the processing; and the determination of the finished yield, shall be performed by one or more competent, responsible individuals. If such steps in the processing are controlled by precision, automatic, mechanical, or electronic equipment, their proper performance shall be adequately checked by one or more competent, responsible individuals.

(b) All containers to be used for undiluted drugs, drug components, intermediate mixtures thereof, and Type A medicated article(s) shall be received, adequately identified, and properly stored and handled in a manner adequate to avoid mixups and contamination.

(c) Equipment, including dust-control and other equipment, such as that used for holding and returning recovered or flush-out materials back into production, shall be maintained and operated in a manner to avoid contamination of the Type A medicated article(s) and to insure the integrity of the finished product.

(d) Competent and responsible personnel shall check actual against theoretical yield of a batch of Type A medicated article(s), and, in the event of

any significant discrepancies, key personnel shall prevent distribution of the batch in question and other associated batches of Type A medicated article(s) that may have been involved in a mixup with it.

(e) Adequate procedures for cleaning of those parts of storage, mixing conveying and other equipment coming in contact with the drug component of the Type A medicated article(s) shall be used to avoid contamination of Type A medicated article(s).

(f) If there is sequential production of batches of a Type A medicated article(s) containing the same drug component (or components) at the same or lower levels, there shall be sufficient safeguards to avoid any buildup above the specified levels of the drug components in any of the batches of the Type A medicated article(s).

(g) Production and control procedures shall include provision for discontinuing distribution of any Type A medicated article(s) found by the assay procedures, or other controls performed to fail to conform to appropriate specifications. Distribution of subsequent production of such Type A medicated article(s) shall not begin until it has been determined that proper control procedures have been established.

§ 226.42 Components.

(a) Drug components, including undiluted drugs and any intermediate mixes containing drugs used in the manufacture and processing of Type A medicated article(s), shall be received, examined or tested, stored, handled, and otherwise controlled in a manner to maintain the integrity and identification of such articles. Appropriate receipt and inventory records shall be maintained for 2 years, and such records shall show the origin of any drug components, the manufacturer's control number (if any), the dates and batches in which they were used, and the results of any testing of them.

(b) Nondrug components shall be stored and otherwise handled in a manner to avoid contamination, including cross-contamination from manufacturing operations.

§ 226.58 Laboratory controls.

Laboratory controls shall include the establishment of adequate specifications and test procedures to assure that the drug components and the Type A medicated article(s) conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications and a description of the test procedures used to check them for each kind of drug component used in the manufacture of Type A medicated article(s). This may consist of the manufacturer's or supplier's statement of specifications and methods of analyses.

(b) The establishment of specifications for Type A medicated article(s) and a description of necessary laboratory test procedures to check such specifications.

(c) Assays which shall be made of representative samples of finished Type A medicated article(s) in accordance with the following schedule:

(1) Each batch of a Type A medicated article(s) manufactured from an undiluted drug shall be assayed for its drug component(s).

(2) In the case of Type A medicated article(s) which are manufactured by dilution of Type A medicated article(s) assayed in accordance with paragraph (c)(1) of this section, each batch shall be assayed for its drug component(s) with the first five consecutive batches assaying within the limitations, followed thereafter by assay of representative samples of not less than 5 percent of all batches produced. When any batch does not assay within limitations, each batch should again be assayed until five consecutive batches are within limitations.

(d) A determination establishing that the drug components remain uniformly dispersed and stable in the Type A medicated article(s) under ordinary conditions of shipment, storage, and use. This may consist of a determination on a Type A medicated article(s) of substantially the same formula and characteristics. Suitable expiration dates shall appear on the labels of the Type A medicated article(s) to assure that the articles meet the appropriate

standards of identity, strength, quality, and purity at the time of use.

(e) Adequate provision to check the reliability, accuracy, and precision of any laboratory test procedure used. The official methods in ''Methods of Analysis of the Association of Official Analytical Chemists,''[1] methods described in an official compendium, and any method submitted as a part of a food additive petition or new-drug application that has been accepted by the Food and Drug Administration shall be regarded as meeting this provision.

(f) Provisions for the maintenance of the results of any assays, including dates and endorsement of analysts. Such records shall be retained in the possession of the manufacturer and shall be maintained for a period of at least 2 years after distribution by the manufacturer of the Type A medicated article(s) has been completed.

[40 FR 14031, Mar. 27, 1975, as amended at 55 FR 11577, Mar. 29, 1990; 55 FR 23703, June 12, 1990; 70 FR 40880, July 15, 2005; 70 FR 67651, Nov. 8, 2005]

Subpart D—Packaging and Labeling

§ 226.80 Packaging and labeling.

(a) Packaging and labeling operations shall be adequately controlled:

(1) To assure that only those Type A medicated article(s) that have met the specifications established in the master-formula records shall be distributed.

(2) To prevent mixups during the packaging and labeling operations.

(3) To assure that correct labeling is employed for each Type A medicated article(s).

(4) To identify Type A medicated article(s) with lot or control numbers that permit determination of the history of the manufacture and control of the batch of Type A medicated article(s).

(b) Packaging and labeling operations shall provide:

(1) For storage of labeling in a manner to avoid mixups.

(2) For careful checking of labeling for identity and conformity to the labeling specified in the batch-production records.

(3) For adequate control of the quantities of labeling issued for use with the Type A medicated article(s).

(c) Type A medicated article(s) shall be distributed in suitable containers to insure the safety, identity, strength, and quality of the finished product.

Subpart E—Records and Reports

§ 226.102 Master-formula and batch-production records.

(a) For each Type A medicated article(s) master-formula records shall be prepared, endorsed, and dated by a competent and responsible individual and shall be independently checked, reconciled, endorsed, and dated by a second competent and responsible individual. The record shall include:

(1) The name of the Type A medicated article(s) and a specimen copy of its label.

(2) The weight or measure of each ingredient, adequately identified, to be used in manufacturing a stated weight of the Type A medicated article(s).

(3) A complete formula for each batch size, or of appropriate size in the case of continuous systems to be produced from the master-formula record, including a complete list of ingredients designated by names or codes sufficiently specific to indicate any special quality characteristics; an accurate statement of the weight or measure of each ingredient, except that reasonable variations may be permitted in the amount of ingredients necessary in the preparation of the Type A medicated article(s), provided that the variations are stated in the master formula; an appropriate statement concerning any calculated excess of an ingredient; and a statement of the theoretical yield.

(4) Manufacturing instructions for each type of Type A medicated article(s) produced on a batch or continuous operation basis, including mixing steps and mixing times that have been determined to yield an adequately mixed Type A medicated article(s); and in the case of Type A medicated article(s) produced by continuous production run, any additional manufacturing

[1] Copies may be obtained from: AOAC INTERNATIONAL, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877.

directions including, when indicated, the settings of equipment that have been determined to yield an adequately mixed Type A medicated article(s) of the specified formula.

(5) Control instructions, procedures, specifications, special notations, and precautions to be followed.

(b) A separate batch-production and control record shall be prepared for each batch or run of Type A medicated article(s) produced and shall be retained for at least 2 years after distribution by the manufacturer has been completed. The batch-production and control record shall include:

(1) Product identification, date of production, and endorsement by a competent and responsible individual.

(2) Records of each step in the manufacturing, packaging, labeling, and controlling of the batch, including dates, specific identification of drug components used, weights or measures of all components, laboratory-control results, mixing times, and the endorsements of the individual actively performing or the individual actively supervising or checking each step in the operation.

(3) A batch number that permits determination of all laboratory-control procedures and results on the batch and all lot or control numbers appearing on the labels of the Type A medicated article(s).

§ 226.110 Distribution records.

Complete records shall be maintained for each shipment of Type A medicated article(s) in a manner that will facilitate the recall, diversion, or destruction of the Type A medicated article(s), if necessary. Such records shall be retained for at least 2 years after the date of the shipment by the manufacturer and shall include the name and address of the consignee, the date and quantity shipped, and the manufacturing dates, control numbers, or marks identifying the Type A medicated article(s) shipped.

§ 226.115 Complaint files.

Records shall be maintained for a period of 2 years of all written or verbal complaints concerning the safety or efficacy of each Type A medicated article(s). Complaints shall be evaluated by competent and responsible personnel and, where indicated, appropriate action shall be taken. The record shall indicate the evaluation and the action.

PART 250—SPECIAL REQUIREMENTS FOR SPECIFIC HUMAN DRUGS

Subpart A—Drugs Regarded as Misbranded

Sec.
250.11 Thyroid-containing drug preparations intended for treatment of obesity in humans.
250.12 Stramonium preparations labeled with directions for use in self-medication regarded as misbranded.

Subpart B—New Drug or Prescription Status of Specific Drugs

250.100 Amyl nitrite inhalant as a prescription drug for human use.
250.101 Amphetamine and methamphetamine inhalers regarded as prescription drugs.
250.102 Drug preparations intended for human use containing certain ''coronary vasodilators''.
250.103–250.104 [Reserved]
250.105 Gelsemium-containing preparations regarded as prescription drugs.
250.106–250.107 [Reserved]
250.108 Potassium permanganate preparations as prescription drugs.

Subpart C—Requirements for Drugs and Foods

250.201 Preparations for the treatment of pernicious anemia.

Subpart D—Requirements for Drugs and Cosmetics

250.250 Hexachlorophene, as a component of drug and cosmetic products.

AUTHORITY: 21 U.S.C. 321, 336, 342, 352, 353, 355, 361(a), 362(a) and (c), 371, 375(b).

SOURCE: 40 FR 14033, Mar. 27, 1975, unless otherwise noted.

Subpart A—Drugs Regarded as Misbranded

§ 250.11 Thyroid-containing drug preparations intended for treatment of obesity in humans.

(a) Investigation by the Food and Drug Administration has revealed that a large number of drug preparations

containing thyroid or thyrogenic substances in combination with central nervous system stimulants, with or without one or more additional drug substances such as barbiturates or laxatives, are being marketed for or as adjuncts to the treatment, control, or management of obesity in humans. The Commissioner of Food and Drugs finds that the administration of such combinations for said purposes is without medical rationale except possibly in those relatively uncommon instances where the condition is directly related to hypothyroidism and there exists a concurrent need for appetite control (in such instances the safety and effectiveness of such combinations are not generally recognized). In particular, the Commissioner of Food and Drugs finds that neither the consensus of informed medical opinion nor clinical experience justifies any representation that such combinations are safe and effective in connection with the treatment, control, or management of obesity in patients having normal thyroid function.

(b) Combinations of thyroid or other thyrogenic drugs with central nervous system stimulants with or without other drug substances when offered for or as adjuncts to the treatment, control, or management of obesity not related to hypothyroidism are regarded as misbranded. Such combinations when offered for obesity in humans directly attributable to established hypothyroidism are regarded as new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

§ 250.12 Stramonium preparations labeled with directions for use in self-medication regarded as misbranded.

(a) Stramonium products for inhalation have been offered for use in the therapy of the acute attacks of bronchial asthma for many years although their reliability and effectiveness are questionable. Recently, a significantly increased number of reports have come to the attention of the Food and Drug Administration showing that such products have been subject to abuse and misuse on a fairly large scale, mostly by young people, through oral ingestion for the purpose of producing hallucinations. Reports of such use have been received from physicians and police and other law enforcement authorities. Reports have also appeared in the public press and in medical journals.

(b) Labeling these products with a warning that they are not for oral ingestion has not been effective in protecting the public. Misuse of stramonium preparations can cause serious toxic effects including toxic delirium, visual disturbances, fever, and coma. A number of serious reactions have already occurred from the oral ingestion of such products.

(c) On the basis of this information, the Commissioner of Food and Drugs has concluded that such articles have a potentiality for harmful effect through misuse and are not safe for use except under the supervision of a physician. In the interest of public health protection, therefore, the Food and Drug Administration adopts the following policy:

(1) Preparations containing stramonium supplied from the leaves, seeds, or any other part of the plant in the form of a powder, pipe mixture, cigarette, or any other form, with or without admixture of other ingredients, will be regarded as misbranded if they are labeled with directions for use in self-medication.

(2) The Food and Drug Administration will, on request, furnish comment on proposed labeling limiting any such preparation to prescription sale.

(d) The labeling or dispensing of stramonium preparations contrary to this statement after 60 days following the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

Subpart B—New Drug or Prescription Status of Specific Drugs

§ 250.100 Amyl nitrite inhalant as a prescription drug for human use.

(a) Amyl nitrite inhalant has been available over-the-counter for emergency use by the patient in the management of angina pectoris for a number of years. As a result of a proposed policy statement published August 25, 1967 (32 FR 12404), the Commissioner of

Food and Drugs received reports of the abuse of this drug by those who do not require it for medical purposes. Additionally, comment included a great deal of concern expressed by individual physicians, medical associations, pharmaceutical associations, manufacturers, and State and local health authorities. Based on the information available, it is the opinion of the Commissioner of Food and Drugs, concurred in by the Food and Drug Administration Medical Advisory Board, that amyl nitrite inhalant is a drug with a potentiality for harmful effect and that it should be removed from over-the-counter status and restricted to sale on the prescription of a practitioner licensed by law to administer such drug.

(b) Therefore, amyl nitrite inhalant will be regarded as misbranded unless the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by physicians, in accordance with § 201.100(c) of this chapter, and its label bears the statement ''Rx only.''

(c) Regulatory proceedings may be initiated with regard to the interstate shipment of amyl nitrite inhalant that is labeled, advertised, or dispensed contrary to this statement of policy if such act occurs after July 1, 1969.

[40 FR 14033, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

§ 250.101 Amphetamine and methamphetamine inhalers regarded as prescription drugs.

(a) Recurring reports of abuse and misuse of methamphetamine (also known as desoxyephedrine) inhalers show that they have a potentiality for harmful effect and that they should not be freely available to the public through over-the-counter sale. From complaints by law-enforcement officials, health officials, individual physicians, parents, and others as well as from Food and Drug Administration investigations, it is evident that the wicks from these inhalers are being removed and the methamphetamine they contain is being used as a substitute for amphetamine tablets. Amphetamine tablets and amphetamine inhalers have been restricted to prescription sale because of their potentiality for harm to the user.

(b) It is the considered opinion of the Food and Drug Administration that, in order to adequately protect the public health, inhalers containing methamphetamine or methamphetamine salts (d-desoxyephedrine, or dl-desoxyephedrine, or their salts), as well as amphetamine inhalers should be restricted to prescription sale and should be labeled with the statement ''Rx only.''

[40 FR 14033, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

§ 250.102 Drug preparations intended for human use containing certain "coronary vasodilators".

(a)(1) The Food and Drug Administration finds that the following ''coronary vasodilators'' are extensively regarded by physicians as safe and useful as employed under medical supervision for the management of angina pectoris in some patients:

Amyl nitrite.
Erythrityl tetranitrate.
Mannitol hexanitrate.
Nitroglycerin.
Potassium nitrite.
Sodium nitrite.

(2) Additionally, new-drug applications have been approved for products containing:

Inositol hexanitrate.
Isosorbide dinitrate.
Octyl nitrite.
Pentaerythritol tetranitrate.
Triethanolamine trinitrate biphosphate (trolnitrate phosphate).

(b) The Food and Drug Administration also finds that there is neither substantial evidence of effectiveness nor a general recognition by qualified experts that such drugs are effective for any of the other purposes for which some such drugs are promoted to the medical profession in labeling and advertising. In particular, neither clinical investigations nor clinical experience justify any representations that such drugs are effective in the management of hypertension; in the management of coronary insufficiency or coronary artery disease, except for their

anginal manifestations; or in the management of the post coronary state, except angina pectoris present after coronary occlusion and myocardial infarction.

(c) Any preparation containing such drugs that is labeled or advertised for any use other than management of angina pectoris, or that is represented to be efficacious for any other purpose by reason of its containing such drug, will be regarded by the Food and Drug Administration as misbranded and subject to regulatory proceedings, unless such recommendations are covered by the approval of a new-drug application based on a showing of safety and effectiveness.

(d) Any such drug in long-acting dosage form is regarded as a new drug that requires an approved new-drug application before marketing.

(e) Any of the drugs listed in paragraph (a)(2) of this section is regarded as a new drug that requires an approved new-drug application. Articles for which new-drug approvals are now in effect should be covered by supplemental new-drug applications as necessary to provide for labeling revisions consistent with this policy statement.

§§ 250.103–250.104 [Reserved]

§ 250.105 Gelsemium-containing preparations regarded as prescription drugs.

It is the consensus of informed medical opinion that the margin of safety between the therapeutic and toxic concentration of gelsemium is narrow and it is difficult to predict the point at which the dose will be toxic. Very small doses may cause toxic symptoms. It is therefore the view of the Food and Drug Administration that gelsemium is not a proper ingredient in any product that is to be sold without prescription. Accordingly, any drug containing gelsemium will be regarded as misbranded under section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act if its label fails to bear in a prominent and conspicuous fashion the statement ''Rx only.''

[40 FR 14033, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

§§ 250.106–250.107 [Reserved]

§ 250.108 Potassium permanganate preparations as prescription drugs.

(a) There have been a number of reports in the medical literature of serious injuries to women resulting from the misuse of potassium permanganate in an effort to induce abortion. Reports from physicians who have treated such cases show that the injuries are commonly caused by introducing tablets or crystals of potassium permanganate into the vagina. Experience with these cases shows that such use of potassium permanganate is not effective in producing abortion, but that instead the drug produces serious and painful injury to the walls of the vagina, causing ulcers, massive hemorrhage, and infection. Such dangerous and useless employment of potassium permanganate is apparently encouraged among the misinformed by the mistaken idea that the vaginal bleeding caused by the corrosive action of the drug indicates a termination of pregnancy, which it does not.

(b) Potassium permanganate is a strong oxidizing agent, a highly caustic, tissue-destroying chemical, and a poison. There are no circumstances under which crystals and tablets of potassium permanganate constitute safe dosage forms for use in self-medication. It is the consensus of informed medical opinion that the only dosage forms of potassium permanganate known to be safe for use in self-medication are aqueous solutions containing not more than 0.04 percent potassium permanganate. Such solutions are safe for use in self-medication only by external application to the skin.

(c) In view of the very real potentiality for harmful effect, and the actual injuries caused by the misuse of potassium permanganate, the Food and Drug Administration believes that in order adequately to protect the public health:

(1) Potassium permanganate and potassium permanganate tablets intended for human use are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and should be restricted to prescription sale. Such drugs will be regarded as misbranded if at any time prior to dispensing the

label fails to bear the statement ''Rx only.''

(2) Potassium permanganate labeled for use as a prescription component in human drugs under the exemption provided in § 201.120 of this chapter or labeled for manufacturing use under the exemption provided in § 201.122 of this chapter will be regarded as misbranded unless the label bears the statement, ''Rx only.''

(3) These drugs will be regarded as misbranded when intended for veterinary use unless the label bears the legend, ''Caution: Federal law restricts this drug to sale by or on the order of a licensed veterinarian''; *Provided, however,* That this shall not apply to a drug labeled and marketed for veterinary use if such drug contains not more than 50 percent of potassium permanganate and includes other ingredients which make it unsuitable for human use and unlikely that the article would be used in an attempt to induce abortion.

(4) Any preparation of potassium permanganate intended for over-the-counter sale for human use internally or by application to any mucous membranes or for use in the vagina will be regarded as misbranded under the provisions of section 502(f) (1) and (2) and section 502(j) of the act.

(5) Any other preparation of potassium permanganate intended for over-the-counter sale for human use will be regarded as misbranded under section 502(f) (1) and (2) and section 502(j) of the act unless, among other things, all of the following conditions are met:

(i) It is an aqueous solution containing not more than 0.04 percent potassium permanganate.

(ii) The label and labeling bear, in juxtaposition with adequate directions for use, clear warning statements designated as ''Warning,'' and to the effect: ''Warning—For external use on the skin only. Severe injury may result from use internally or as a douche. Avoid contact with mucous membranes.''

(d) The labeling or dispensing of any potassium permanganate preparations intended for drug use within the jurisdiction of the Federal Food, Drug, and Cosmetic Act contrary to this statement after 60 days from the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

[40 FR 14033, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

Subpart C—Requirements for Drugs and Foods

§ 250.201 Preparations for the treatment of pernicious anemia.

(a) The ninth announcement of the Anti-anemia Preparations Advisory Board of the United States Pharmacopeia is concerned with the status of the treatment of pernicious anemia. It clearly presents the following facts:

(1) The Sixteenth Revision of the Pharmacopeia of the United States, which became official on October 1, 1960, does not include preparations intended for the treatment of pernicious anemia by oral administration.

(2) The U.S.P. unit for anti-anemia preparations no longer has any significance.

(3) The U.S.P. Anti-anemia Preparations Advisory Board was disbanded.

(b) On the basis of the scientific evidence and conclusions summarized in the statement of the U.S.P. Anti-anemia Preparations Advisory Board as well as pertinent information from other sources, the Commissioner of Food and Drugs finds it is the consensus of well informed medical opinion that:

(1) The parenteral administration of cyanocobalamin or vitamin B_{12} is generally recognized as a fully effective treatment of pernicious anemia. Parenteral cyanocobalamin preparations have not been and are not authorized for use except by or on the prescription of a duly licensed medical practitioner.

(2) Some patients afflicted with pernicious anemia do not respond to orally ingested products. There is no known way to predict which patients will fail to respond or will cease to respond to the treatment of pernicious anemia with orally ingested preparations.

(3) The substitution of a possibly inadequate treatment, such as the ingestion of oral preparations of vitamin B_{12} with intrinsic factor concentrate, in place of parenteral vitamin B_{12} products for a disease condition as serious

as pernicious anemia cannot be regarded as safe in all cases.

(4) The development of the classical symptoms of pernicious anemia that would cause a person to seek medical attention may in some cases be delayed by oral ingestion of intrinsic factor. Pernicious anemia is a disease that is associated, among other things, with a higher than normal incidence of cancer of the stomach and that for the safety of the patient, requires continuous expert medical supervision.

(5) With inadequate treatment there may be markedly deleterious effects on the nervous system. It is well established that whereas the development of anemia is completely reversible with adequate treatment, the involvement of the nervous system may not be completely reversible and thus may result in permanent damage.

(6) Some hematologists prescribe oral preparations of vitamin B_{12} in the treatment of pernicious-anemia patients.

(7) Intrinsic factor and intrinsic factor concentrate serve no known useful therapeutic or nutritive purpose except to the extent that they do increase the gastrointestinal absorption of vitamin B_{12} in patients with a deficiency or absence of intrinsic factor, which may eventually lead to pernicious anemia. This conclusion does not apply to diagnostic procedures using radioactive cyanocobalamin.

(8) Medical expertise is required for the diagnosis as well as the management of pernicious anemia.

(c) The Eleventh Edition of The National Formulary and its first Interim Revision include monographs for oral preparations of vitamin B_{12} with intrinsic factor concentrate, establish a unit of vitamin B_{12} with intrinsic factor concentrate, and provide for a National Formulary Anti-anemia Preparations Advisory Board to assign the potency of such preparations. This provides for the availability of such oral preparations, standardized within the meaning of the broad limits characteristic of the evaluation of such preparations.

(d) Any drug that is offered for or purports to contain intrinsic factor or intrinsic factor concentrate will be regarded as misbranded within the meaning of section 503(b) of the Federal Food, Drug, and Cosmetic Act unless it is labeled with the statement ''Rx only.''

(e) Any drug for oral ingestion intended, represented, or advertised for the prevention or treatment of pernicious anemia or which purports to contain any substance or mixture of substances described in paragraph (d) of this section (other than diagnostic drugs containing radioactive cyanocobalamin) will be regarded as misbranded under sections 502 (f)(2) and (j) of the act unless its labeling bears a statement to the effect that some patients afflicted with pernicious anemia may not respond to the orally ingested product and that there is no known way to predict which patients will respond or which patients may cease to respond to the orally ingested products. The labeling shall also bear a statement that periodic examinations and laboratory studies of pernicious anemia patients are essential and recommended.

(f) Under section 409 of the Federal Food, Drug, and Cosmetic Act, intrinsic factor and intrinsic factor concentrate are regarded as food additives. No food additive regulation nor existing extension of the effective date of section 409 of the act authorizes these additives in foods, including foods for special dietary uses. Any food containing added intrinsic factor or intrinsic factor concentrate will be regarded as adulterated within the meaning of section 402(a)(2)(C) of the act.

(g) Regulatory action may be initiated with respect to any article shipped within the jurisdiction of the act contrary to the provisions of this policy statement after the 180th day following publication of this statement in the FEDERAL REGISTER.

[40 FR 14033, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

Subpart D—Requirements for Drugs and Cosmetics

§ 250.250 Hexachlorophene, as a component of drug and cosmetic products.

(a) *Antibacterial component.* The use of hexachlorophene as an antibacterial

component in drug and cosmetic products has expanded widely in recent years. It is used in such products because of its bacteriostatic action against gram-positive organisms, especially against strains of staphylococcus; however, hexachlorophene offers no protection against gram-negative infections. In addition the antibacterial activity depends largely on repeated use. A notice published in the FEDERAL REGISTER of April 4, 1972 (37 FR 6775), invited data on OTC antimicrobial ingredients, including hexachlorophene, for review by an OTC Drug Advisory Review Panel to be convened under the procedures set forth in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464). This statement of policy will remain in effect unless and until replaced by a monograph resulting from the OTC Drug Advisory Review Panel.

(b) *Adverse effects*. Though considered safe for many years, recent information has become available associating hexachlorophene with toxic effects, including deaths. Studies have shown that toxic amounts of hexachlorophene can be absorbed through the skin of humans, especially the skin of premature babies or damaged skin. Human toxicity reports include data on symptomatology, blood and tissue levels of hexachlorophene, and descriptions of neuropathologic lesions. Recent infant deaths due to use of baby powder accidentally contaminated with 6 percent hexachlorophene have occurred. The accumulated evidence of toxicity is sufficient to require that continued marketing of hexachlorophene containing products be carefully defined in order to protect consumers.

(c) *Prescription drugs*. (1) Because of their potential for harmful effect, drugs containing hexachlorophene, other than as a preservative as described below, are not considered to have been shown to be safe and effective, are regarded as new drugs requiring approved new drug applications, and would be misbranded for over-the-counter distribution. In the interest of public health protection, hexachlorophene containing drugs will be regarded as misbranded and subject to regulatory proceedings unless the label bears the statement ''Rx only,'' and the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by practitioners, in accord with § 201.100(c) of this chapter.

(2) The Food and Drug Administration recognizes that hexachlorophene is useful as a bacteriostatic skin cleanser. It further concludes that the margin of safety is such that products containing hexachlorophene may appropriately be used within clearly delineated conditions of use.

(3) In order for such drugs to bear adequate information for safe and effective use the following statements are representative of the type of labeling for products shown to be effective bacteriostatic skin cleansers. Labeling for products other than bacteriostatic skin cleansers will be determined through the new drug procedures based on the available data.

(i) In the labeling other than on the immediate container label.

INDICATIONS

1. Bacteriostatic skin cleanser for surgical scrubbing or handwashing as part of patient care.

2. For topical application to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

CONTRAINDICATIONS

1. Not for use on burned or denuded skin or on mucous membranes.

2. Not for routine prophylactic total body bathing.

WARNINGS

Rinse thoroughly after use. Patients should be closely monitored and use should be immediately discontinued at the first sign of any of the symptoms described below.

Hexachlorophene is rapidly absorbed and may produce toxic blood levels when applied to skin lesions such as ichthyosis congenita or the dermatitis of Letterer-Siwe's syndrome or other generalized dermatologic conditions. Application to burns has also produced neurotoxicity and death.

Infants have developed dermatitis, irritability, generalized clonic muscular contractions and decerebrate rigidity following application of a 6 percent hexachlorophene powder. Examination of brainstems of those infants revealed vacuolization like that

which can be produced in newborn experimental animals following repeated topical application of 3 percent hexachlorophene. Moreover, a study of histologic sections of premature infants who died of unrelated causes has shown a positive correlation between hexachlorophene baths and lesions in white matter of brains.

(ii) On the immediate container label prominently displayed and in bold print:

''Special Warning: This compound may be toxic if used other than as directed. Rinse thoroughly after use. Monitor patients closely for toxicity symptoms.''

(4) Marketing of products for the indications listed in paragraph (c)(3) of this section may be continued without an approved new drug application (or required supplement thereto) either until a notice of opportunity for hearing is issued on a proposal by the Director of the Center for Drug Evaluation and Research to refuse to approve such new drug application (or required supplement) or until January 31, 1978, whichever comes first, if all the following conditions were met after September 27, 1972:

(i) The product is labeled with the statement ''Rx only'' and adequate information for safe and effective use as set forth in paragraph (c)(3) of this section.

(ii) Within 30 days, or by (10–27–72) the holder of an approved new drug application submits a supplement to provide for the revised label and full disclosure labeling. As the label and labeling will have been put into use, the supplement should be submitted under the provision of § 314.70(c)(6)(iii) of this chapter.

(iii) Within 30 days, or by (10–27–72) the holder of an approved new drug application submits a supplement to provide for a revised formulation where appropriate to comply with this order.

(iv) Within 90 days, or by (12–26–72) the holder of an approved new drug application submits a supplement containing blood level data obtained from use of the drug as recommended, unless such information is a part of the new drug application file.

(v) Within 90 days, or by (12–26–72), the manufacturer or distributor of such a drug for which a new drug approval is not in effect submits a new drug application in accord with § 314.50 of the new drug regulations (21 CFR 314.50), including blood level data obtained from use of the drug as recommended.

(5) Prescription drug products may contain hexachlorophene as part of an effective preservative system only under the conditions and limitations provided for under paragraph (d) of this section.

(d) *Over-the-counter (OTC) drugs.* Over-the-counter drug products, other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, may contain hexachlorophene only as part of an effective preservative system, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. This use of hexachlorophene will not, by itself, require an approved new drug application. Use of hexachlorophene as a preservative at a level higher than 0.1 percent is regarded as a new drug use requiring an approved new drug application, which must be submitted within the time set out in paragraph (c)(4) of this section.

(e) *Cosmetics.* Hexachlorophene may be used as a preservative in cosmetic products other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. The component of a preservative system whether hexachlorophene or other antimicrobial agent, should be selected on the basis of the effect on the total microbial ecology of the product, not merely on gram-positive bacteria.

(1) Adequate safety data do not presently exist to justify wider use of hexachlorophene in cosmetics.

(2) Antibacterial ingredients used as substitutes for hexachlorophene in cosmetic products, and finished cosmetic products containing such ingredients, shall be adequately tested for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing may be adulterated and will in any event be deemed misbranded unless it contains a conspicuous front panel statement that the product has not been adequately tested for safety and may be hazardous.

(f) *Content statement.* All reference to hexachlorophene limit in this order is on a weight-in-weight (w/w) basis. Quantitative declaration of hexachlorophene content on the labeling of the products, where required, shall be on a w/w basis.

(g) *Shipments of products.* Shipments of products falling within the scope of paragraphs (c), (d), or (e) of this section which are not in compliance with the guidelines stated herein shall be the subject of regulatory proceedings after the effective date of the final order.

(h) *Prior notices.* This order preempts any conditions for marketing products set forth in the following prior notices.

1. DESI No. 4749 (34 FR 15389, October 2, 1969), ''Certain OTC Drugs for Topical Use.''
2. DESI No. 2855 (35 FR 12423, August 4, 1970), ''Certain Mouthwash and Gargle Preparations.''
3. DESI No. 8940 (36 FR 14510, August 6, 1971), ''Topical Cream Containing Pyrilamine Maleate, Benzocaine, Hexachlorophene, and Cetrimonium Bromide.''
4. DESI No. 6615 (36 FR 18022, September 8, 1971), ''Deodorant/Antiperspirant.''
5. DESI No. 6270 (36 FR 23330, December 8, 1971), ''Certain Preparations Containing Hexachlorophene''.

[40 FR 14033, Mar. 27, 1975, as amended at 42 FR 63773, Dec. 20, 1977; 55 FR 11577, Mar. 29, 1990; 67 FR 4906, Feb. 1, 2002; 69 FR 18763, Apr. 8, 2004]

PART 290—CONTROLLED DRUGS

Subpart A—General Provisions

Sec.
290.1 Controlled substances.
290.2 Exemption from prescription requirements.
290.5 Drugs; statement of required warning.
290.6 Spanish-language version of required warning.
290.10 Definition of emergency situation.

Subpart B [Reserved]

Subpart C—Requirements for Specific Controlled Drugs [Reserved]

AUTHORITY: 21 U.S.C. 352, 353, 355, 371.

SOURCE: 40 FR 14040, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 290.1 Controlled substances.

Any drug that is a controlled substance listed in schedule II, III, IV, or V of the Federal Controlled Substances Act or implementing regulations must be dispensed by prescription only as required by section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act unless specifically exempted in § 290.2.

[67 FR 4906, Feb. 1, 2002]

§ 290.2 Exemption from prescription requirements.

The prescription-dispensing requirements of section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act are not necessary for the protection of the public health with respect to a compound, mixture, or preparation containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams that also includes one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the compound, mixture, or preparation valuable medicinal qualities other than those possessed by codeine alone.

[67 FR 4907, Feb. 1, 2002]

§ 290.5 Drugs; statement of required warning.

The label of any drug listed as a ''controlled substance'' in schedule II, III, or IV of the Federal Controlled Substances Act shall, when dispensed to or for a patient, contain the following warning: ''Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.'' This statement is not required to appear on the

label of a controlled substance dispensed for use in clinical investigations which are ''blind.''

§ 290.6 Spanish-language version of required warning.

By direction of section 305(c) of the Federal Controlled Substances Act, § 290.5, promulgated under section 503(b) of the Federal Food, Drug, and Cosmetic Act, requires the following warning on the label of certain drugs when dispensed to or for a patient: ''Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.'' The Spanish version of this is: ''Precaucion: La ley Federal prohibe el transferir de esta droga a otra persona que no sea el paciente para quien fue recetada.''

§ 290.10 Definition of emergency situation.

For the purposes of authorizing an oral prescription of a controlled substance listed in schedule II of the Federal Controlled Substances Act, the term *emergency situation* means those situations in which the prescribing practitioner determines:

(a) That immediate administration of the controlled substance is necessary, for proper treatment of the intended ultimate user; and

(b) That no appropriate alternative treatment is available, including administration of a drug which is not a controlled substance under schedule II of the Act, and

(c) That it is not reasonably possible for the prescribing practitioner to provide a written prescription to be presented to the person dispensing the substance, prior to the dispensing.

Subpart B [Reserved]

Subpart C—Requirements for Specific Controlled Drugs [Reserved]

PART 299—DRUGS; OFFICIAL NAMES AND ESTABLISHED NAMES

Subpart A—General Provisions

Sec.

299.3 Definitions and interpretations.
299.4 Established names for drugs.
299.5 Drugs; compendial name.

AUTHORITY: 21 U.S.C. 331, 351, 352, 355, 358, 360b, 371.

SOURCE: 40 FR 14041, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 299.3 Definitions and interpretations.

(a) As used in this part 299, *act* means the Federal Food, Drug, and Cosmetic Act, sections 201–902, 52 Stat. 1040 (21 U.S.C. 321–392), with all amendments thereto.

(b) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part 299.

(c) The term *official name* means, with respect to a drug or ingredient thereof, the name designated in this part 299 under section 508 of the act as the official name.

§ 299.4 Established names for drugs.

(a) Section 508 of the Federal Food, Drug, and Cosmetic Act (added by the Kefauver-Harris Drug Amendments of 1962; Pub. L. 87–781) authorizes the Commissioner of Food and Drugs to designate an official name for any drug if he determines that such action is necessary or desirable in the interest of usefulness and simplicity. Section 502(e) of the act (as amended by said Drug Amendments) prescribes that the labeling of a drug must bear its established name, if there is one, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula) and, if the drug is fabricated from two or more ingredients, the established name of each active ingredient.

(b) The term *established name* is defined in section 502(e)(3) of the act as (1) an official name designated pursuant to section 508 of the act; (2) if no such official name has been designated for the drug and the drug is an article recognized in an official compendium, then the official title thereof in such compendium; and (3) if neither paragraphs (b) (1) or (2) of this section applies, then the common or usual name of the drug.

(c) The Food and Drug Administration recognizes the skill and experience of the U.S. Adopted Names Council (USAN) in deriving names for drugs. The U.S. Adopted Names Council is a private organization sponsored by the American Medical Association, the United States Pharmacopeia, and the American Pharmaceutical Association, and has been engaged in the assignment of names to drugs since January 1964. The Council negotiates with manufacturing firms in the selection of nonproprietary names for drugs.

(d) The Food and Drug Administration cooperates with and is represented on the USAN Council. In addition, the Food and Drug Administration agrees with ''Guiding Principles for Coining U.S. Adopted Names for Drugs,'' published in *USAN and the USP Dictionary of Drug Names* (USAN 1985 ed., 1961–1984 cumulative list), which is incorporated by reference. Copies are available from: U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or are available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*. All applicants for new-drug applications and sponsors for ''Investigational New Drug Applications'' (IND's) are encouraged to contact the USAN Council for assistance in selection of a simple and useful name for a new chemical entity. Approval of a new-drug application providing for the use of a new drug substance may be delayed if a simple and useful nonproprietary name does not exist for the substance and if one is not proposed in the application that meets the above-cited guidelines. Prior use of a name in the medical literature or otherwise will not commit the Food and Drug Administration to adopting such terminology as official.

(e) The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common and usual name of the drug. Interested persons, in the absence of the designation by the food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names*. The Food and Drug Administration, however, will continue to publish official names under the provisions of section 508 of the act when the agency determines that:

(1) The USAN or other official or common or usual name is unduly complex or is not useful for any other reason;

(2) Two or more official names have been applied to a single drug, or to two or more drugs that are identical in chemical structure and pharmacological action and that are substantially identical in strength, quality, and purity; or

(3) No USAN or other official or common or usual name has been applied to a medically useful drug. Any official name published under section 508 of the act will be the established name of the drug.

(f) A cumulative list of U.S. adopted names selected and released since June 15, 1961, is published yearly by the U.S. Pharmacopeial Convention, Inc., in *USAN and the USP Dictionary of Drug Names*. Copies may be purchased from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

[40 FR 14041, Mar. 27, 1975, as amended at 49 FR 37575, Sept. 25, 1984; 53 FR 5369, Feb. 24, 1988; 55 FR 11577, Mar. 29, 1990; 64 FR 401, Jan. 5, 1999; 69 FR 18803, Apr. 9, 2004]

§ 299.5 Drugs; compendial name.

(a) The name by which a drug is designated shall be clearly distinguishing and differentiating from any name recognized in an official compendium unless such drug complies in identity with the identity prescribed in an official compendium under such recognized name.

(b) The term *drug defined in an official compendium* means a drug having the identity prescribed for a drug in an official compendium.

(c) A statement that a drug defined in an official compendium differs in strength, quality, or purity from the standard of strength, quality, or purity set forth for such drug in an official compendium shall show all the respects in which such drug so differs, and the extent of each such difference.