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TITLE 21--FOOD AND DRUGS  
CHAPTER I--FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
SUBCHAPTER D--DRUGS FOR HUMAN USE

## **PART 310 NEW DRUGS**

### **Subpart A--General Provisions**

Sec. 310.3 Definitions and interpretations.

As used in this part:

(a) The term *act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 *et seq.*, as amended; 21 U.S.C. 321-392).

(b) *Department* means the Department of Health and Human Services.

(c) *Secretary* means the Secretary of Health and Human Services.

(d) *Commissioner* means the Commissioner of Food and Drugs.

(e) The term *person* includes individuals, partnerships, corporations, and associations.

(f) The definitions and interpretations of terms contained in section 201 of the act shall be applicable to such terms when used in the regulations in this part.

(g) *New drug substance* means any substance that when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance.

(h) The newness of a drug may arise by reason (among other reasons) of:

(1) The newness for drug use of any substance which composes such drug, in whole or in part, whether it be an active substance or a menstruum, excipient, carrier, coating, or other component.

(2) The newness for a drug use of a combination of two or more substances, none of which is a new drug.

(3) The newness for drug use of the proportion of a substance in a combination, even though such combination containing such substance in other proportion is not a new drug.

(4) The newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body.

(5) The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug.

(i) [Reserved]

(j) The term *sponsor* means the person or agency who assumes responsibility for an investigation of a new drug, including responsibility for compliance with applicable provisions of the act and regulations. The "sponsor" may be an individual, partnership, corporation, or Government agency and may be a

manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of new drugs.

(k) The phrase *related drug(s)* includes other brands, potencies, dosage forms, salts, and esters of the same drug moiety, including articles prepared or manufactured by other manufacturers: and any other drug containing a component so related by chemical structure or known pharmacological properties that, in the opinion of experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, it is prudent to assume or ascertain the liability of similar side effects and contraindications.

(l) *Special packaging* as defined in section 2(4) of the Poison Prevention Packaging Act of 1970 means packaging that is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and not difficult for normal adults to use properly, but does not mean packaging which all such children cannot open or obtain a toxic or harmful amount within a reasonable time.

(m) [Reserved]

(n) The term *radioactive drug* means any substance defined as a drug in section 201(g) (1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes a "radioactive biological product" as defined in 600.3(ee) of this chapter.

[39 FR 11680, Mar. 29, 1974, as amended at 39 FR 20484, June 11, 1974; 40 FR 31307, July 25, 1975; 46 FR 8952, Jan. 27, 1981; 50 FR 7492, Feb. 22, 1985]

#### Sec. 310.4 Biologics; products subject to license control.

(a) If a drug has an approved license under section 351 of the Public Health Service Act (42 U.S.C. 262 *et seq.* ) or under the animal virus, serum, and toxin law of March 4, 1913 (21 U.S.C. 151 *et seq.* ), it is not required to have an approved application under section 505 of the act.

(b) To obtain marketing approval for radioactive biological products for human use, as defined in 600.3(ee) of this chapter, manufacturers must comply with the provisions of 601.2(a) of this chapter.

[64 FR 56448, Oct. 20, 1999, as amended at 70 FR 14981, Mar. 24, 2005]

#### Sec. 310.6 Applicability of "new drug" or safety or effectiveness findings in drug efficacy study implementation notices and notices of opportunity for hearing to identical, related, and similar drug products.

(a) The Food and Drug Administration's conclusions on the effectiveness of drugs are currently being published in the Federal Register as Drug Efficacy Study Implementation (DESI) Notices and as Notices of Opportunity for Hearing. The specific products listed in these notices include only those that were introduced into the market through the new drug procedures from 1938-62 and were submitted for review by the National Academy of Sciences-National Research Council (NAS-NRC), Drug Efficacy Study Group. Many products which are identical to, related to, or similar to the products listed in these notices have been marketed under different names or by different firms during this same period or since 1962 without going through the new drug procedures or the Academy review. Even though these products are not listed in the notices, they are covered by the new drug applications reviewed and thus are subject to these notices. All persons with an interest in a product that is identical, related, or similar to a drug listed in a drug efficacy notice or a notice of opportunity for a hearing will be given the same opportunity as the applicant to submit data and information, to request a hearing, and to participate in any hearing. It is not feasible for the Food and Drug Administration to list all products which are covered by an NDA and thus subject to each notice. However, it is essential that the findings and conclusions that a drug product is a "new drug" or that there is a lack of evidence to show that a drug product is safe or effective be applied to all identical, related, and similar drug products to which they are reasonably applicable. Any product

not in compliance with an applicable drug efficacy notice is in violation of section 505 (new drugs) and/or section 502 (misbranding) of the act.

(b) (1) An identical, related, or similar drug includes other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties.

(2) Where experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs would conclude that the findings and conclusions, stated in a drug efficacy notice or notice of opportunity for hearing, that a drug product is a "new drug" or that there is a lack of evidence to show that a drug product is safe or effective are applicable to an identical, related, or similar drug product, such product is affected by the notice. A combination drug product containing a drug that is identical, related, or similar to a drug named in a notice may also be subject to the findings and conclusions in a notice that a drug product is a "new drug" or that there is a lack of evidence to show that a drug product is safe or effective.

(3) Any person may request an opinion on the applicability of such a notice to a specific product by writing to the Food and Drug Administration at the address shown in paragraph (e) of this section.

(c) Manufacturers and distributors of drugs should review their products as drug efficacy notices are published and assure that identical, related, or similar products comply with all applicable provisions of the notices.

(d) The published notices and summary lists of the conclusions are of particular interest to drug purchasing agents. These agents should take particular care to assure that the same purchasing policy applies to drug products that are identical, related, or similar to those named in the drug efficacy notices. The Food and Drug Administration applies the same regulatory policy to all such products. In many instances a determination can readily be made as to the applicability of a drug efficacy notice by an individual who is knowledgeable about drugs and their indications for use. Where the relationships are more subtle and not readily recognized, the purchasing agent may request an opinion by writing to the Food and Drug Administration at the address shown in paragraph (e) of this section.

(e) Interested parties may submit to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, the names of drug products, and of their manufacturers or distributors, that should be the subject of the same purchasing and regulatory policies as those reviewed by the Drug Efficacy Study Group. Appropriate action, including referral to purchasing officials of various government agencies, will be taken.

(f) This regulation does not apply to OTC drugs identical, similar, or related to a drug in the Drug Efficacy Study unless there has been or is notification in the Federal Register that a drug will not be subject to an OTC panel review pursuant to 330.10, 330.11, and 330.5 of this chapter.

[39 FR 11680, Mar. 29, 1974, as amended at 48 FR 2755, Jan. 21, 1983; 50 FR 8996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990; 74 FR 13113, Mar. 26, 2009]

#### **Subpart B--Specific Administrative Rulings and Decisions**

Sec. 310.100 New drug status opinions; statement of policy.

(a) Over the years since 1938 the Food and Drug Administration has given informal advice to inquirers as to the new drug status of preparations. These drugs have sometimes been identified only by general statements of composition. Generally, such informal opinions were incorporated in letters that did not explicitly relate all of the necessary conditions and qualifications such as the quantitative formula for the drug and the conditions under which it was prescribed, recommended, or suggested. This has contributed to misunderstanding and misinterpretation of such opinions.

(b) These informal opinions that an article is "not a new drug" or "no longer a new drug" require reexamination under the Kefauver-Harris Act (Public Law 87-781; 76 Stat. 788-89). In particular, when approval of a new drug application is withdrawn under provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act, a drug generally recognized as safe may become a "new drug" within the meaning of section 201(p) of said act as amended by the Kefauver-Harris Act on October 10, 1962. This is of special importance by reason of proposed actions to withdraw approval of new drug applications for lack of substantial evidence

of effectiveness as a result of reports of the National Academy of Sciences--National Research Council on its review of drug effectiveness; for example, see the notice published in the Federal Register of January 23, 1968 (33 FR 818), regarding rutin, quercetin, et al.

(c) Any marketed drug is a "new drug" if any labeling change made after October 9, 1962, recommends or suggests new conditions of use under which the drug is not generally recognized as safe and effective by qualified experts. Undisclosed or unreported side effects as well as the emergence of new knowledge presenting questions with respect to the safety or effectiveness of a drug may result in its becoming a "new drug" even though it was previously considered "not a new drug." Any previously given informal advice that an article is "not a new drug" does not apply to such an article if it has been changed in formulation, manufacture control, or labeling in a way that may significantly affect the safety of the drug.

(d) For these reasons, all opinions previously given by the Food and Drug Administration to the effect that an article is "not a new drug" or is "no longer a new drug" are hereby revoked. This does not mean that all articles that were the subjects of such prior opinions will be regarded as new drugs. The prior opinions will be replaced by opinions of the Food and Drug Administration that are qualified and current on when an article is "not a new drug," as set forth in this subchapter.

[39 FR 11680, Mar. 29, 1974]

#### Sec. 310.103 New drug substances intended for hypersensitivity testing.

(a) The Food and Drug Administration is aware of the need in the practice of medicine for the ingredients of a new drug to be available for tests of hypersensitivity to such ingredients and therefore will not object to the shipment of a new drug substance, as defined in 310.3(g), for such purpose if all of the following conditions are met:

(1) The shipment is made as a result of a specific request made to the manufacturer or distributor by a practitioner licensed by law to administer such drugs, and the use of such drugs for patch testing is not promoted by the manufacturer or distributor.

(2) The new drug substance requested is an ingredient in a marketed new drug and is not one that is an ingredient solely in a new drug that is legally available only under the investigational drug provisions of this part.

(3) The label bears the following prominently placed statements in lieu of adequate directions for use and in addition to complying with the other labeling provisions of the act:

(i) "Rx only"; and

(ii) "For use only in patch testing".

(4) The quantity shipped is limited to an amount reasonable for the purpose of patch testing in the normal course of the practice of medicine and is used solely for such patch testing.

(5) The new drug substance is manufactured by the same procedures and meets the same specifications as the component used in the finished dosage form.

(6) The manufacturer or distributor maintains records of all shipments for this purpose for a period of 2 years after shipment and will make them available to the Food and Drug Administration on request.

(b) When the requested new drug substance is intended for investigational use in humans or the substance is legally available only under the investigational drug provisions of part 312 of this chapter, the submission of an "Investigational New Drug Application" (IND) is required. The Food and Drug Administration will offer assistance to any practitioner wishing to submit an Investigational New Drug Application.

(c) This section does not apply to drugs or their components that are subject to the licensing requirements of the Public Health Service Act of 1944, as amended. (See subchapter F--Biologics, of this chapter.)

[39 FR 11680, Mar. 29, 1974, as amended at 55 FR 11578, Mar. 29, 1990; 67 FR 4907, Feb. 1, 2002]

## Subpart C--New Drugs Exempted From Prescription-Dispensing Requirements

Sec. 310.200 Prescription-exemption procedure.

(a) *Duration of prescription requirement.* Any drug limited to prescription use under section 503(b)(1)(B) of the act remains so limited until it is exempted as provided in paragraph (b) or (e) of this section.

(b) *Prescription-exemption procedure for drugs limited by a new drug application.* Any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling. A proposal to exempt a drug from the prescription-dispensing requirements of section 503(b)(1)(B) of the act may be initiated by the Commissioner or by any interested person. Any interested person may file a petition seeking such exemption, which petition may be pursuant to part 10 of this chapter, or in the form of a supplement to an approved new drug application.

(c) *New drug status of drugs exempted from the prescription requirement.* A drug exempted from the prescription requirement under the provisions of paragraph (b) of this section is a "new drug" within the meaning of section 201(p) of the act until it has been used to a material extent and for a material time under such conditions except as provided in paragraph (e) of this section.

(d) *Prescription legend not allowed on exempted drugs.* The use of the prescription caution statement quoted in section 503(b)(4) of the act, in the labeling of a drug exempted under the provisions of this section, constitutes misbranding. Any other statement or suggestion in the labeling of a drug exempted under this section, that such drug is limited to prescription use, may constitute misbranding.

(e) *Prescription-exemption procedure of OTC drug review.* A drug limited to prescription use under section 503(b)(1)(B) of the act may also be exempted from prescription-dispensing requirements by the procedure set forth in 330.13 of this chapter.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 32582, Aug. 4, 1976; 42 FR 4714, Jan. 25, 1977; 42 FR 15674, Mar. 22, 1977; 72 FR 15043, Mar. 30, 2007]

Sec. 310.201 Exemption for certain drugs limited by new-drug applications to prescription sale.

(a) The prescription-dispensing requirements of section 503(b)(1)(B) of the Federal Food, Drug, and Cosmetic Act are not necessary for the protection of the public health with respect to the following drugs subject to new drug applications:

(1) *N*-acetyl-*p*-aminophenol (acetaminophen, *p*-hydroxy-acetanilid) preparations meeting all the following conditions:

(i) The *N*-acetyl-*p*-aminophenol is prepared, with or without other drugs, in tablet or other dosage form suitable for oral use in self-medication, and containing no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The *N*-acetyl-*p*-aminophenol and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 0.325 gram (5 grains) of *N*-acetyl-*p*-aminophenol per dosage unit, or if it is in liquid form not more than 100 milligrams of *N*-acetyl-*p*-aminophenol per milliliter.

(v) The preparation is labeled with adequate directions for use in minor conditions as a simple analgesic.

(vi) The dosages of *N*-acetyl-*p*-aminophenol recommended or suggested in the labeling do not exceed: For adults, 0.65 gram (10 grains) per dose or 2.6 grams (40 grains) per 24-hour period; for children 6 to 12 years of age, one-half of the maximum adult dose or dosage; for children 3 to 6 years of age, one-fifth

of the maximum adult dose or dosage.

(vii) The labeling bears, in juxtaposition with the dosage recommendations, a clear warning statement against administration of the drug to children under 3 years of age and against use of the drug for more than 10 days, unless such uses are directed by a physician.

(viii) If the article is offered for use in arthritis or rheumatism, the labeling prominently bears a statement that the beneficial effects claimed are limited to the temporary relief of minor aches and pains of arthritis and rheumatism and, in juxtaposition with directions for use in such conditions, a conspicuous warning statement, such as "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".

(2) Sodium gentsiate (sodium-2, 5-dihydroxybenzoate) preparations meeting all the following conditions:

(i) The sodium gentsiate is prepared, with or without other drugs, in tablet or other dosage form suitable for oral use in self-medication, and containing no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The sodium gentsiate and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 0.5 gram (7.7 grains) of anhydrous sodium gentsiate per dosage unit.

(v) The preparation is labeled with adequate directions for use in minor conditions as a simple analgesic.

(vi) The dosages of sodium gentsiate recommended or suggested in the labeling do not exceed: For adults, 0.5 gram (7.7 grains) per dose of 2.0 grams (31 grains) per 24-hour period; for children 6 to 12 years of age, one-half of the maximum adult dose or dosage.

(vii) The labeling bears, in juxtaposition with the dosage recommendations, a clear warning statement against administration of the drug to children under 6 years of age and against use of the drug for a prolonged period, except as such uses may be directed by a physician.

(3) Isoamylhydrocupreine and zolamine hydrochloride (N, N-dimethyl-N'-2-thiazolyl-N'-p -methoxybenzyl-ethyl- enediamine hydrochloride) preparations meeting all the following conditions:

(i) The isoamylhydrocupreine and zolamine hydrochloride are prepared in dosage form suitable for self-medication as rectal suppositories or as an ointment and containing no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The isoamylhydrocupreine, zola-amine hydrochloride, and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 0.25 percent of isoamylhydrocupreine and 1.0 percent of zolamine hydrochloride.

(v) If the preparation is in suppository form, it contains not more than 5.0 milligrams of isoamylhydrocupreine and not more than 20.0 milligrams of zolamine hydrochloride per suppository.

(vi) The preparation is labeled with adequate directions for use in the temporary relief of local pain and itching associated with hemorrhoids.

(vii) The directions provide for the use of not more than two suppositories or two applications of ointment in a 24-hour period.

(viii) The labeling bears, in juxtaposition with the dosage recommendations, a clear warning statement against use of the preparation in case of rectal bleeding, as this may indicate serious disease.

(4) Phenyltoloxamine dihydrogen citrate (N,N -dimethyl-(a -phenyl-O -toloxy) ethylamine dihydrogen citrate), preparations meeting all the following conditions:

(i) The phenyltoloxamine dihydrogen citrate is prepared, with or without other drugs, in tablet or other dosage form suitable for oral use in self-medication,

and containing no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The phenyltoloxamine dihydrogen citrate and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 88 milligrams of phenyltoloxamine dihydrogen citrate (equivalent to 50 milligrams of phenyltoloxamine) per dosage unit.

(v) The preparation is labeled with adequate directions for use in the temporary relief of the symptoms of hay fever and/or the symptoms of other minor conditions in which it is indicated.

(vi) The dosages recommended or suggested in the labeling do not exceed: For adults, 88 milligrams of phenyltoloxamine dihydrogen citrate (equivalent to 50 milligrams of phenyltoloxamine) per dose or 264 milligrams of phenyltoloxamine dihydrogen citrate (equivalent to 150 milligrams of phenyltoloxamine) per 24-hour period; for children 6 to 12 years of age, one-half of the maximum adult dose or dosage.

(vii) The labeling bears, in juxtaposition with the dosage recommendations:

(a ) Clear warning statements against administration of the drug to children under 6 years of age, except as directed by a physician, and against driving a car or operating machinery while using the drug, since it may cause drowsiness.

(b ) If the article is offered for temporary relief of the symptoms of colds, a statement that continued administration for such use should not exceed 3 days, except as directed by a physician.

(5)-(7) [Reserved]

(8) Dicyclomine hydrochloride (1-cyclohexylhexahydrobenzoic acid. [beta]-diethylaminoethyl ester hydrochloride; diethylaminocarbethoxy-bicyclohexyl hydrochloride) preparations meeting all the following conditions:

(i) The dicyclomine hydrochloride is prepared with suitable antacid and other components, in tablet or other dosage form for oral use in self-medication, and containing no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The dicyclomine hydrochloride and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 5 milligrams of dicyclomine hydrochloride per dosage unit, or if it is in liquid form not more than 0.5 milligram of dicyclomine hydrochloride per milliliter.

(v) The preparation is labeled with adequate directions for use only by adults and children over 12 years of age, in the temporary relief of gastric hyperacidity.

(vi) The dosages recommended or suggested in the directions for use do not exceed 10 milligrams of dicyclomine hydrochloride per dose or 30 milligrams in a 24-hour period.

(vii) The labeling bears, in juxtaposition with the dosage recommendations, clear warning statements against:

(a ) Exceeding the recommended dosage.

(b ) Prolonged use, except as directed by a physician, since persistent or recurring symptoms may indicate a serious disease requiring medical attention.

(c ) Administration to children under 12 years of age except as directed by a physician.

(9)-(10) [Reserved]

(11) Hexadenol (a mixture of tetracosanes and their oxidation products) preparations meeting all the following conditions:

(i) The hexadenol is prepared and packaged, with or without other drugs, solvents, and propellants, in a form suitable for self-medication by external application to the skin as a spray, and containing no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The hexadenol and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 5 percent by weight of hexadenol.

(v) The preparation is labeled with adequate directions for use by external application in the treatment of minor burns and minor skin irritations.

(vi) The labeling bears, in juxtaposition with the directions for use, clear warning statements against:

(a ) Use on serious burns or skin conditions or prolonged use, except as directed by a physician.

(b ) Spraying the preparation in the vicinity of eyes, mouth, nose, or ears.

(12) Sulfur dioxide preparations meeting all the following conditions:

(i) The sulfur dioxide is prepared with or without other drugs, in an aqueous solution packaged in a hermetic container suitable for use in self-medication by external application to the skin, and containing no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The sulfur dioxide and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 5 grams of sulfur dioxide per 100 milliliters of solution.

(v) The preparation is labeled with adequate directions for use by external application to the smooth skin in the prevention or treatment of minor conditions in which it is indicated.

(vi) The directions for use recommend or suggest not more than two applications a day for not more than 1 week, except as directed by a physician.

(13)-(15) [Reserved]

(16) Tuaminoheptane sulfate (2-aminoheptane sulfate) preparations meeting all the following conditions:

(i) The tuaminoheptane sulfate is prepared, with or without other drugs, in an aqueous vehicle suitable for administration in self-medication as nose drops, and containing no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The preparation is packaged with a style of container or assembly suited to self-medication by the recommended route of administration, and delivering not more than 0.1 milliliter of the preparation per drop.

(iii) The tuaminoheptane sulfate and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iv) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(v) The tuaminoheptane sulfate content of the preparation does not exceed 10 milligrams per milliliter.

(vi) The preparation is labeled with adequate directions for use in the temporary relief of nasal congestion.

(vii) The dosages recommended or suggested in the directions for use do not exceed the equivalent: For adults, 5 drops of a 1 percent solution per nostril per dose, and 5 doses in a 24-hour period; for children 1 to 6 years of age, 3 drops of a 1 percent solution per nostril per dose, and 5 doses in a 24-hour period; for infants under 1 year of age, 2 drops of a 1 percent solution per nostril per dose, and 5 doses in a 24-hour period.

(viii) The labeling bears, in juxtaposition with the dosage recommendations:

(a ) Clear warning statements against use of more than 5 doses daily, and against use longer than 4 days unless directed by a physician.

(b ) A clear warning statement to the effect that frequent use may cause nervousness or sleeplessness, and that individuals with high blood pressure, heart disease, diabetes, or thyroid disease should not use the preparation unless directed by a physician.

(17) [Reserved]

(18) Vibesate (a mixture of copolymers of hydroxy-vinyl chlorideacetate, sebacic acid, and modified maleic rosin ester) preparations meeting all the following conditions.

(i) The vibesate is prepared and packaged, with or without other drugs, solvents, and propellants, in a form suitable for self-medication by external application to the skin as a spray, and containing no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The vibesate and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 13 percent by weight of vibesate.

(v) The preparation is labeled with adequate directions for use by external application as a dressing for minor burns, minor cuts, or other minor skin irritations.

(vi) The labeling bears in juxtaposition with the directions for use clear warning statements against:

(a ) Use on serious burns and on infected, deep, and puncture wounds unless directed by a physician.

(b ) Spraying the preparation near the eyes or other mucous membranes.

(c ) Inhaling the preparation.

(d ) Use near open flames.

(e ) Puncturing the container or throwing the container into fire.

(19) Pramoxine hydrochloride (4-N -butoxyphenyl [gamma]-morpholinopropyl ether hydrochloride) preparations meeting all the following conditions:

(i) The pramoxine hydrochloride is prepared, with or without other drugs, in a dosage form suitable for use in self-medication by external application to the skin, and containing no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The pramoxine hydrochloride and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 1.0 percent of pramoxine hydrochloride.

(v) The preparation is labeled with adequate directions for use by external application to the skin for the temporary relief of pain or itching due to minor burns and sunburn, nonpoisonous insect bites, and minor skin irritations.

(vi) The directions for use recommend or suggest not more than four applications of the preparation per day, unless directed by a physician.

(vii) The labeling bears, in juxtaposition with the directions for use, clear warning statements against:

(a ) Prolonged use.

(b ) Application to large areas of the body.

(c ) Continued use if redness, irritation, swelling, or pain persists or increases, unless directed by a physician.

(d ) Use in the eyes or nose.

(20) [Reserved]

(21) Pamabrom (2-amino-2-methylpropanol-1-8-bromotheophyllinate) preparations meeting all the following conditions:

(i) The pamabrom is prepared with appropriate amounts of a suitable analgesic and with or without other drugs, in tablet or other dosage form suitable for oral use in self-medication, and containing no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The pamabrom and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b)

of the act is approved for it.

(iv) The preparation contains not more than 50 milligrams of pamabrom per dosage unit.

(v) The preparation is labeled with adequate directions for use in the temporary relief of the minor pains and discomforts that may occur a few days before and during the menstrual period.

(vi) The dosages recommended or suggested in the labeling do not exceed 50 milligrams of pamabrom per dose or 200 milligrams per 24-hour period.

(22) Diphemanil methylsulfate (4-diphenylmethylene-1,1-dimethyl-piperidinium methylsulfate) preparations meeting all the following conditions:

(i) The diphemanil methylsulfate is prepared, with or without other drugs, in a dosage form suitable for use in self-medication by external application to the skin, and containing no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The diphemanil methylsulfate and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 2.0 percent of diphemanil methylsulfate.

(v) The preparation is labeled with adequate directions for use by external application to the skin for the relief of symptoms of mild poison ivy, oak, and sumac and other minor irritations and itching of the skin.

(vi) The directions for use recommend or suggest not more than four applications of the preparation per day, unless directed by a physician.

(vii) The labeling bears, in juxtaposition with the directions for use, a clear warning statement, such as: "Caution: If redness, irritation, swelling, or pain persists or increases, discontinue use and consult physician."

(23) Dyclonine hydrochloride (4-butoxy-3-piperidinopropiophenone hydrochloride; 4-*n*-butoxy-[beta]-piperidonopropiophenone hydrochloride) preparations meeting all the following conditions:

(i) The dyclonine hydrochloride is prepared, with or without other drugs, in a dosage form suitable for use as a cream or ointment in self-medication by external application to the skin, or rectally, and contains no drug limited to prescription sale under the provisions of section 503(b)(1) of the act.

(ii) The dyclonine hydrochloride and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 1.0 percent of dyclonine hydrochloride.

(v) The preparation is labeled with adequate directions for use:

(a ) By external application to the skin for the temporary relief of pain and itching in sunburn, nonpoisonous insect bites, minor burns, cuts, abrasions, and other minor skin irritations.

(b ) [Reserved]

(c ) In the prevention or treatment of other minor conditions in which it is indicated.

(vi) The labeling bears, in juxtaposition with the directions for use, clear warning statements against:

(a ) Continued use if redness, irritation, swelling, or pain persists or increases, unless directed by a physician.

(b ) Use in case of rectal bleeding, as this may indicate serious disease.

(c ) Use in the eyes.

(d ) Prolonged use.

(e ) Application to large areas of the body.

(f ) Use for deep or puncture wounds or serious burns.

(24) Chlorothen citrate (chloromethapyrilene citrate; *N,N*-dimethyl-*N*'-(2-pyridyl)-*N*'-(5-chloro-2-thenyl)

ethylenediamine citrate) preparations meeting all the following conditions:

(i) The chlorothen citrate is prepared, with or without other drugs, in tablet or other dosage form suitable for oral use in self-medication, and containing no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The chlorothen citrate and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 25 milligrams of chlorothen citrate per dosage unit.

(v) The preparation is labeled with adequate directions for use in the temporary relief of the symptoms of hay fever and/or the symptoms of other minor conditions in which it is indicated.

(vi) The dosages recommended or suggested in the labeling do not exceed: For adults, 25 milligrams of chlorothen citrate per dose or 150 milligrams of chlorothen citrate per 24-hour period; for children 6 to 12 years of age, one-half of the maximum adult dose or dosage.

(vii) The labeling bears, in juxtaposition with the dosage recommendations:

(a ) Clear warning statements against administration of the drug to children under 6 years of age or exceeding the recommended dosage, unless directed by a physician, and against driving a car or operating machinery while using the drug, since it may cause drowsiness.

(b ) If the article is offered for the temporary relief of symptoms of colds, a statement that continued administration for such use should not exceed 3 days, unless directed by a physician.

(25) [Reserved]

(26) Methoxyphenamine hydrochloride

([beta]-(o -methoxyphenyl)-isopropyl-methylamine hydrochloride; 1-(o -methoxyphenyl)- 2-methylamino-propane hydrochloride) preparations meeting all the following conditions:

(i) The methoxyphenamine hydrochloride is prepared with appropriate amounts of a suitable antitussive, with or without other drugs, in a dosage form suitable for oral use in self-medication, and containing no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The methoxyphenamine hydrochloride and all other components of the preparation meet their professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 3.5 milligrams of methoxyphenamine hydrochloride per milliliter.

(v) The preparation is labeled with adequate directions for use in the temporary relief of cough due to minor conditions in which it is indicated.

(vi) The dosages recommended or suggested in the labeling do not exceed: For adults, 35 milligrams of methoxyphenamine hydrochloride per dose or 140 milligrams of methoxyphenamine hydrochloride per 24-hour period; for children 6 to 12 years of age, one-half of the maximum adult dose or dosage.

(vii) The label bears a conspicuous warning to keep the drug out of the reach of children, and the labeling bears, in juxtaposition with the dosage recommendations:

(a ) A clear warning statement against administration of the drug to children under 6 years of age, unless directed by a physician.

(b ) A clear warning statement to the effect that frequent or prolonged use may cause nervousness, restlessness, or drowsiness, and that individuals with high blood pressure, heart disease, diabetes, or thyroid disease should not use the preparation unless directed by a physician.

(c ) A clear warning statement against use of the drug in the presence of high fever or if cough persists, since persistent cough as well as high fever may indicate the presence of a serious condition.

(27) Biphenamine hydrochloride

([beta]-diethylaminoethyl-3-phenyl-2-hydroxybenzoate hydrochloride)

preparations meeting all the following conditions:

(i) The biphenamine hydrochloride is prepared in a form suitable for use as a shampoo and contains no drug limited to prescription sale under the provisions of section 503(b) (1) of the act.

(ii) The biphenamine hydrochloride meets its professed standards of identity, strength, quality, and purity.

(iii) If the preparation is a new drug, an application pursuant to section 505(b) of the act is approved for it.

(iv) The preparation contains not more than 1 percent of biphenamine hydrochloride.

(v) The preparation is labeled with adequate directions for use for the temporary relief of itching and scaling due to dandruff.

(vi) The label bears a conspicuous warning to keep the drug out of the reach of children.

(28) Tyloxapol (an alkylaryl polyether alcohol) and benzalkonium chloride ophthalmic preparations meeting all the following conditions:

(i) The tyloxapol and benzalkonium chloride are prepared, with other appropriate ingredients which are not drugs limited to prescription sale under the provisions of section 503(b) (1) of the act, as a sterile, isotonic aqueous solution suitable for use in self-medication on eye prostheses.

(ii) The preparation is so packaged as to volume and type of container as to afford adequate protection and be suitable for self-medication with a minimum risk of contamination of the solution during use. Any dispensing unit is sterile and so packaged as to maintain sterility until the package is opened.

(iii) The tyloxapol, benzalkonium chloride, and other ingredients used to prepare the isotonic aqueous solution meet their professed standards of identity, strength, quality, and purity.

(iv) An application pursuant to section 505(b) of the act is approved for the drug.

(v) The preparation contains 0.25 percent of tyloxapol and 0.02 percent of benzalkonium chloride.

(vi) The label bears a conspicuous warning to keep the drug out of the reach of children and the labeling bears, in juxtaposition with the dosage recommendations, a clear warning that if irritation occurs, persists, or increases, use of the drug should be discontinued and a physician consulted. The labeling includes a statement that the dropper or other dispensing tip should not touch any surface, since this may contaminate the solution.

(29) [Reserved]

(b) [Reserved]

[39 FR 11680, Mar. 29, 1974, as amended at 42 FR 36994, July 19, 1977; 52 FR 15892, Apr. 30, 1987; 52 FR 30055, Aug. 12, 1987; 55 FR 31779, Aug. 3, 1990; 57 FR 58374, Dec. 9, 1992; 58 FR 49898, Sept. 23, 1993; 59 FR 4218, Jan. 28, 1994; 60 FR 52507, Oct. 6, 1995; 72 FR 15043, Mar. 30, 2007; 72 FR 67640, Nov. 30, 2007]

#### **Subpart D--Records and Reports**

Sec. 310.303 Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved.

(a) A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). After approval, the applicant is required to establish and maintain records and make reports related to clinical experience or other data or information necessary to make or facilitate a determination of whether there are or may be grounds under section 505(e) of the act for suspending or withdrawing approval of the application. Some drugs, because of the nature of the condition for which they are intended, must be used for long periods of time--even a lifetime. To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval. Nonetheless, the therapeutic or prophylactic usefulness of such drugs may make it inadvisable in the public interest to delay the availability of the drugs for widespread clinical use pending completion of such long-term studies. In such cases, the Food and

Drug Administration may approve the new drug application on condition that the necessary long-term studies will be conducted and the results recorded and reported in an organized fashion. The procedures required by paragraph (b) of this section will be followed in order to list such a drug in 310.304.

(b) A proposal to require additional or continued studies with a drug for which a new drug application has been approved may be made by the Commissioner on his own initiative or on the petition of any interested person, pursuant to part 10 of this chapter. Prior to issuance of such a proposal, the applicant will be provided an opportunity for a conference with representatives of the Food and Drug Administration. When appropriate, investigators or other individuals may be invited to participate in the conference. All requirements for special studies, records, and reports will be published in 310.304.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 4714, Jan. 25, 1976; 42 FR 15674, Mar. 22, 1977]

Sec. 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

(a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application to establish and maintain records and make reports to FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products. Any person subject to the reporting requirements of paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

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

*Adverse drug experience.* Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

*Disability.* A substantial disruption of a person's ability to conduct normal life functions.

*Individual case safety report (ICSR).* A description of an adverse drug experience related to an individual patient or subject.

*ICSR attachments.* Documents related to the adverse drug experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

*Life-threatening adverse drug experience.* Any adverse drug experience that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse drug experience as it occurred, *i.e.* , it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

*Serious adverse drug experience.* Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

*Unexpected adverse drug experience.* Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral

vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (*i.e.*, included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(c) *Reporting requirements.* Each person identified in paragraph (c)(1)(i) of this section must submit to FDA adverse drug experience information as described in this section. Except as provided in paragraph (e)(2) of this section, 15-day "Alert reports" and followup reports, including ICSRs and any ICSR attachments, must be submitted to the Agency in electronic format as described in paragraph (e)(1) of this section.

(1) *Postmarketing 15-day "Alert reports".* (i) Any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor must report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but no later than 15 calendar days from initial receipt of the information by the person whose name appears on the label. Each report must be accompanied by the current content of labeling in electronic format as an ICSR attachment unless it is already on file at FDA.

(ii) A person identified in paragraph (c)(1)(i) of this section is not required to submit a 15-day "Alert report" for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.

(2) *Postmarketing 15-day "Alert reports"--followup.* Each person identified in paragraph (c)(1)(i) of this section must promptly investigate all serious, unexpected adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and must submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information.

(3) *Submission of reports.* To avoid unnecessary duplication in the submission of, and followup to, reports required in this section, a packer's or distributor's obligations may be met by submission of all reports of serious adverse drug experiences to the manufacturer of the drug product. If a packer or distributor elects to submit these adverse drug experience reports to the manufacturer rather than to FDA, it must submit, by any appropriate means, each report to the manufacturer within 5 calendar days of its receipt by the packer or distributor, and the manufacturer must then comply with the requirements of this section even if its name does not appear on the label of the drug product. Under this circumstance, the packer or distributor must maintain a record of this action which must include:

- (i) A copy of each adverse drug experience report;
- (ii) The date the report was received by the packer or distributor;
- (iii) The date the report was submitted to the manufacturer; and
- (iv) The name and address of the manufacturer.

(4) [Reserved]

(5) A person identified in paragraph (c)(1)(i) of this section is not required to resubmit to FDA adverse drug experience reports forwarded to that person by FDA; however, the person must submit all *followup* information on such reports to FDA.

(d) *Information reported on ICSRs.* ICSRs include the following information:

(1) *Patient information.*

- (i) Patient identification code;
- (ii) Patient age at the time of adverse drug experience, or date of birth;
- (iii) Patient gender; and
- (iv) Patient weight.

(2) *Adverse drug experience.*

- (i) Outcome attributed to adverse drug experience;
- (ii) Date of adverse drug experience;
- (iii) Date of ICSR submission;

(iv) Description of adverse drug experience (including a concise medical narrative);

(v) Adverse drug experience term(s);

(vi) Description of relevant tests, including dates and laboratory data; and

(vii) Other relevant patient history, including preexisting medical conditions.

(3) *Suspect medical product(s)*.

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a combination product as defined in 3.2(e) of this chapter;

(vi) Whether the product is a prescription or nonprescription product;

(vii) Whether adverse drug experience abated after drug use stopped or dose reduced;

(viii) Whether adverse drug experience reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) *Initial reporter information*.

(i) Name, address, and telephone number;

(ii) Whether the initial reporter is a health care professional; and

(iii) Occupation, if a health care professional.

(5) *Manufacturer, packer, or distributor information*.

(i) Manufacturer, packer, or distributor name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by manufacturer, packer, or distributor;

(v) Whether the ICSR is a 15-day "Alert report";

(vi) Whether the ICSR is an initial report or followup report; and

(vii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(e) *Electronic format for submissions*. (1) Each report required to be submitted to FDA under this section, including the ICSR and any ICSR attachments, must be submitted in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) Each person identified in paragraph (c)(1)(i) of this section may request, in writing, a temporary waiver of the requirements in paragraph (e)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (e)(1) of this section.

(f) *Patient privacy*. Manufacturers, packers, and distributors should not include in reports under this section the names and addresses of individual patients; instead, the manufacturer, packer, and distributor should assign a unique code for identification of the patient. The manufacturer, packer, and distributor should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, individual reporters, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(g) *Recordkeeping*. (1) Each manufacturer, packer, and distributor must maintain for a period of 10 years records of all adverse drug experiences required under this section to be reported, including raw data and any correspondence relating to the adverse drug experiences, and the records required to be maintained under

paragraph (c) (3) of this section.

(2) Manufacturers and packers may retain the records required in paragraph (f) (1) of this section as part of its complaint files maintained under 211.198 of this chapter.

(3) Manufacturers, packers, and distributors must permit any authorized FDA employee, at all reasonable times, to have access to and copy and verify the records established and maintained under this section.

(h) *Disclaimer.* A report or information submitted by a manufacturer, packer, or distributor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer, packer, or distributor, or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. The manufacturer, packer, or distributor need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect.

[51 FR 24479, July 3, 1986, as amended at 52 FR 37936, Oct. 13, 1987; 55 FR 11578, Mar. 29, 1990; 57 FR 17980, Apr. 28, 1992; 62 FR 34167, June 25, 1997; 62 FR 52249, Oct. 7, 1997; 67 FR 9585, Mar. 4, 2002; 74 FR 13113, Mar. 26, 2009; 79 FR 33087, June 10, 2014]

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[Link to an amendment published at 80 FR 38938, July 8, 2015.](#)

#### **Subpart E--Requirements for Specific New Drugs or Devices**

Sec. 310.501 Patient package inserts for oral contraceptives.

(a) *Requirement for a patient package insert.* The safe and effective use of oral contraceptive drug products requires that patients be fully informed of the benefits and the risks involved in their use. An oral contraceptive drug product that does not comply with the requirements of this section is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. Each dispenser of an oral contraceptive drug product shall provide a patient package insert to each patient (or to an agent of the patient) to whom the product is dispensed, except that the dispenser may provide the insert to the parent or legal guardian of a legally incompetent patient (or to the agent of either). The patient package insert is required to be placed in or accompany each package dispensed to the patient.

(b) *Distribution requirements.* (1) For oral contraceptive drug products, the manufacturer and distributor shall provide a patient package insert in or with each package of the drug product that the manufacturer or distributor intends to be dispensed to a patient.

(2) Patient package inserts for oral contraceptives dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before administration of the first oral contraceptive and every 30 days thereafter, as long as the therapy continues.

(c) *Contents of patient package insert.* A patient package insert for an oral contraceptive drug product is required to contain the following:

(1) The name of the drug.

(2) A summary including a statement concerning the effectiveness of oral contraceptives in preventing pregnancy, the contraindications to the drug's use, and a statement of the risks and benefits associated with the drug's use.

(3) A statement comparing the effectiveness of oral contraceptives to other methods of contraception.

(4) A boxed warning concerning the increased risks associated with cigarette smoking and oral contraceptive use.

(5) A discussion of the contraindications to use, including information that the patient should provide to the prescriber before taking the drug.

(6) A statement of medical conditions that are not contraindications to use but deserve special consideration in connection with oral contraceptive use and about

which the patient should inform the prescriber.

(7) A warning regarding the most serious side effects of oral contraceptives.

(8) A statement of other serious adverse reactions and potential safety hazards that may result from the use of oral contraceptives.

(9) A statement concerning common, but less serious side effects which may help the patient evaluate the benefits and risks from the use of oral contraceptives.

(10) Information on precautions the patients should observe while taking oral contraceptives, including the following:

(i) A statement of risks to the mother and unborn child from the use of oral contraceptives before or during early pregnancy;

(ii) A statement concerning excretion of the drug in human milk and associated risks to the nursing infant;

(iii) A statement about laboratory tests which may be affected by oral contraceptives; and

(iv) A statement that identifies activities and drugs, foods, or other substances the patient should avoid because of their interactions with oral contraceptives.

(11) Information about how to take oral contraceptives properly, including information about what to do if the patient forgets to take the product, information about becoming pregnant after discontinuing use of the drug, a statement that the drug product has been prescribed for the use of the patient and should not be used for other conditions or given to others, and a statement that the patient's pharmacist or practitioner has a more technical leaflet about the drug product that the patient may ask to review.

(12) A statement of the possible benefits associated with oral contraceptive use.

(13) The following information about the drug product and the patient package insert:

(i) The name and place of business of the manufacturer, packer, or distributor, or the name and place of business of the dispenser of the product.

(ii) The date, identified as such, of the most recent revision of the patient package insert placed prominently immediately after the last section of the labeling.

(d) *Other indications.* The patient package insert may identify indications in addition to contraception that are identified in the professional labeling for the drug product.

(e) *Labeling guidance texts.* The Food and Drug Administration issues informal labeling guidance texts under 10.90(b) (9) of this chapter to provide assistance in meeting the requirements of this section. A request for a copy of the guidance texts should be directed to the Center for Drug Evaluation and Research, Division of Reproductive and Urologic Products, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

(f) *Requirement to supplement approved application.* Holders of approved applications for oral contraceptive drug products that are subject to the requirements of this section are required to submit supplements under 314.70(c) of this chapter to provide for the labeling required by this section. Such labeling may be put into use without advance approval by the Food and Drug Administration.

[54 FR 22587, May 25, 1989, as amended at 74 FR 13113, Mar. 26, 2009]

Sec. 310.502 Certain drugs accorded new drug status through rulemaking procedures.

(a) The drugs listed in this paragraph have been determined by rulemaking procedures to be new drugs within the meaning of section 201(p) of the act. An approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing the following drugs:

(1) Aerosol drug products for human use containing 1,1,1-trichloroethane.

(2) Aerosol drug products containing zirconium.

(3) Amphetamines (amphetamine, dextroamphetamine, and their salts, and levamfetamine and its salts) for human use.

(4) Camphorated oil drug products.

(5) Certain halogenated salicylanilides (tribromsalan (TBS,

3,4',5-tribromosalicylanilide), dibromsalan (DBS, 4', 5-dibromosalicylanilide), metabromsalan (MBS, 3, 5-dibromosalicylanilide), and 3,3', 4,5'-tetrachlorosalicylanilide (TC-SA)) as an ingredient in drug products.

(6) Chloroform used as an ingredient (active or inactive) in drug products.

(7) Cobalt preparations intended for use by man.

(8) Intrauterine devices for human use for the purpose of contraception that incorporate heavy metals, drugs, or other active substances.

(9) Oral prenatal drugs containing fluorides intended for human use.

(10) Parenteral drug products in plastic containers.

(11) Sterilization of drugs by irradiation.

(12) Sweet spirits of nitre drug products.

(13) Thorium dioxide for drug use.

(14) Timed release dosage forms.

(15) Vinyl chloride as an ingredient, including propellant, in aerosol drug products.

(b) [Reserved]

[62 FR 12084, Mar. 14, 1997, as amended at 64 FR 401, Jan. 5, 1999]

Sec. 310.503 Requirements regarding certain radioactive drugs.

(a) On January 8, 1963 (28 FR 183), the Commissioner of Food and Drugs exempted investigational radioactive new drugs from part 312 of this chapter provided they were shipped in complete conformity with the regulations issued by the Nuclear Regulatory Commission. This exemption also applied to investigational radioactive biologics.

(b) It is the opinion of the Nuclear Regulatory Commission, and the Food and Drug Administration that this exemption should not apply for certain specific drugs and that these drugs should be appropriately labeled for uses for which safety and effectiveness can be demonstrated by new drug applications or through licensing under the Public Health Service Act (42 U.S.C. 262 et seq. ) in the case of biologics. Continued distribution under the investigational exemption when the drugs are intended for established uses will not be permitted.

(c) Based on its experience in regulating investigational radioactive pharmaceuticals, the Nuclear Regulatory Commission has compiled a list of reactor-produced isotopes for which it considers that applicants may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling. Such use may include, among others, the uses in this tabulation:

Isotope	Chemical form	Use
Chromium 51	Chromate	Spleen scans.
Do	.....do	Placenta localization.
Do	.....do	Red blood cell labeling and survival studies.
Do	Labeled human serum albumin	Gastrointestinal protein loss studies.
Do	.....do	Placenta localization.
Do	Labeled red blood cells	Do.
Cobalt 58 or Cobalt 60	Labeled cyanocobalamin	Intestinal absorption studies.
Gold 198	Colloidal	Liver scans.
Do	.....do	Intracavitary treatment of pleural effusions and/or ascites.
Do	.....do	Interstitial treatment of cancer.
Iodine 131	Iodide	Diagnosis of thyroid functions.
Do	.....do	Thyroid scans.
Do	.....do	Treatment of hyperthyroidism and/or cardiac dysfunction.

Do	.....do	Treatment of thyroid carcinoma.
Do	Iodinated human serum albumin	Blood volume determinations.
Do	.....do	Cisternography.
Do	.....do	Brain tumor localization.
Do	.....do	Placenta localization.
Do	.....do	Cardiac scans for determination of pericardial effusions.
Do	Rose Bengal	Liver function studies.
Do	.....do	Liver scans.
Do	Iodopyracet, sodium iodohippurate, sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamate	Kidney function studies and kidney scans.
Do	Labeled fats and/or fatty acids	Fat absorption studies.
Do	Cholografin	Cardiac scans for determination of pericardial effusions.
Do	Macroaggregated iodinated human serum albumin	Lung scans.
Do	Colloidal microaggregated human serum albumin	Liver scans.
Iodine 125	Iodide	Diagnosis of thyroid function.
Do	Iodinated human serum albumin	Blood volume determinations.
Do	Rose Bengal	Liver function studies.
Do	Iodopyracet, sodium iodohippurate, sodium diatrizoate, diatrizoate methyl-glucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamate	Kidney function studies.
Do	Labeled fats and/or fatty acids	Fat absorption studies.
Iron 59	Chloride, citrate and/or sulfate	Iron turnover studies.
Krypton 85	Gas	Diagnosis of cardiac abnormalities.
Mercury 197	Chlormerodrin	Kidney scans.
Do	.....do	Brain scans.
Mercury 203	.....do	Kidney scans.
Do	.....do	Brain scans.
Phosphorus 32	Soluble phosphate	Treatment of polycythemia vera.
Do	.....do	Treatment of leukemia and bone metastasis.
Do	Colloidal chromic phosphate	Intracavitary treatment of pleural effusions and/or ascites.
Do	.....do	Interstitial treatment of cancer.
Potassium 42	Chloride	Potassium space studies.
Selenium 75	Labeled methionine	Pancreas scans.
Strontium 85	Nitrate or chloride	Bone scans on patients with diagnosed cancer.
Technetium 99m	Pertechnetate	Brain scans.
Do	.....do	Thyroid scans.
Do	Sulfur colloid	Liver and spleen scans.
Do	Pertechnetate	Placenta localization.
Do	.....do	Blood pool scans.
Do	.....do	Salivary gland scans.
Do	Diethylenetri-amine pentaacetic acid (DTPA)	Kidney scans.
Xenon 133	Gas	Diagnosis of cardia abnormalities. Cerebral bloodflow studies. Pulmonary function studies. Muscle bloodflow studies.

<sup>1</sup>This item has been removed from the AEC list for kidney scans but is included as the requirements of this order are applicable.

(d) (1) In view of the extent of experience with the isotopes listed in paragraph (c) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that such isotopes should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(2) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, is terminated on March 3, 1972, except as provided in paragraph (d) (3) of this section.

(3) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application or a "Investigational New Drug Application" was submitted prior to March 3, 1972, or for which biologic an application for product license or "Investigational New Drug Application" was submitted prior to March 3, 1972, is terminated on August 20, 1976, unless an approvable notice was issued on or before August 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on November 20, 1976, whichever occurs first.

(e) No exemption from section 505 of the act or from part 312 of this chapter is in effect or has been in effect for radioactive drugs prepared from accelerator-produced radioisotopes, naturally occurring isotopes, or nonradioactive substances used in conjunction with isotopes.

(f) (1) Based on its experience in regulating investigational radioactive pharmaceuticals, the Nuclear Regulatory Commission has compiled a list of reactor-produced isotopes for which it considers that applicants may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling; such use may include, among others, the uses in this tabulation:

Isotope	Chemical form	Use
Fluorine 18	Fluoride	Bone imaging.
Indium-113m	Diethylenetriamine pentaacetic acid (DTPA)	Brain imaging; kidney imaging.
Do	Chloride	Placenta imaging; blood pool imaging.
Technetium 99m	Human serum albumin microspheres	Lung imaging.
Do	Diethylenetriamine pentaacetic acid (Sn)	Kidney imaging; kidney function studies.
Do	.....do	Brain imaging.
Do	Polyphosphates	Bone imaging.
Do	Technetated aggregated albumin (human)	Lung imaging.
Do	Disodium etidronate	Bone imaging.

(2) In view of the extent of experience with the isotopes listed in paragraph (f) (1) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that they should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(3) Any manufacturer or distributor interested in continuing to ship in interstate commerce drugs containing the isotopes listed in paragraph (f) (1) of this section for any of the indications listed, shall submit, on or before August 25, 1975 to the Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, a new drug application or a "Investigational New Drug Application" for each such drug for which the manufacturer or distributor does not have an approved new drug application pursuant to section 505 (b) of the act. If the drug is a biologic, a "Investigational New Drug Application" or an application for a license under section 351 of the Public Health Service Act shall be submitted to the Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002, in lieu of any submission to the Center for Drug Evaluation and Research.

(4) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, is terminated on August 26, 1975 except as provided in paragraph (f)(5) of this section.

(5) (i) Except as provided in paragraph (f)(5)(ii) of this section, the exemption referred to in paragraph (a) of this section, as applied to any drug containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application or "Investigational New Drug Application" was submitted to the Center for Drug Evaluation and Research on or before August 25, 1975 is terminated on August 20, 1976, unless an approvable notice was issued on or before August 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on November 20, 1976, whichever occurs first.

(ii) The exemption referred to in paragraph (a) of this section, as applied to any biologic containing any of the isotopes listed in paragraph (f)(1) of this section in the "chemical form" and intended for the uses stated, for which biologic an application for product license or "Investigational New Drug Application" was submitted to the Center for Biologics Evaluation and Research on or before August 25, 1975 is terminated on October 20, 1976, unless an approvable notice was issued on or before October 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on January 20, 1977, whichever occurs first.

(g) The exemption referred to in paragraph (a) of this section, as applied to any drug intended solely for investigational use as part of a research project, which use had been approved on or before July 25, 1975 in accordance with 10 CFR 35.11 (or equivalent regulation of an Agreement State) is terminated on February 20, 1976 if the manufacturer of such drug or the sponsor of the investigation of such drug submits on or before August 25, 1975 to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20857, the following information:

- (1) The research project title;
- (2) A brief description of the purpose of the project;
- (3) The name of the investigator responsible;
- (4) The name and license number of the institution holding the specific license under 10 CFR 35.11 (or equivalent regulation of an Agreement State);
- (5) The name and maximum amount per subject of the radionuclide used;
- (6) The number of subjects involved; and
- (7) The date on which the administration of the radioactive drugs is expected to be completed.

(h) The exemption referred to in paragraph (a) of this section, as applied to any drug not referred to in paragraphs (d), (f), and (g) of this section, is terminated on August 26, 1975.

[39 FR 11680, Mar. 29, 1974, as amended at 40 FR 31307, July 25, 1975; 40 FR 44543, Sept. 29, 1975; 41 FR 35171, Aug. 20, 1976; 41 FR 42947, Sept. 29, 1976; 50 FR 8996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990; 64 FR 56449, Oct. 20, 1999; 80 FR 18091, Apr. 3, 2015]

#### Sec. 310.509 Parenteral drug products in plastic containers.

(a) Any parenteral drug product packaged in a plastic immediate container is not generally recognized as safe and effective, is a new drug within the meaning of section 201(p) of the act, and requires an approved new drug application as a condition for marketing. An "Investigational New Drug Application" set forth in part 312 of this chapter is required for clinical investigations designed to obtain evidence of safety and effectiveness.

(b) As used in this section, the term "large volume parenteral drug product" means a terminally sterilized aqueous drug product packaged in a single-dose container with a capacity of 100 milliliters or more and intended to be administered or used intravenously in a human.

(c) Until the results of compatibility studies are evaluated, a large volume parenteral drug product for intravenous use in humans that is packaged in a plastic immediate container on or after April 16, 1979, is misbranded unless its labeling

contains a warning that includes the following information:

- (1) A statement that additives may be incompatible.
- (2) A statement that, if additive drugs are introduced into the parenteral system, aseptic techniques should be used and the solution should be thoroughly mixed.
- (3) A statement that a solution containing an additive drug should not be stored.
- (d) This section does not apply to a biological product licensed under the Public Health Service Act of July 1, 1944 (42 U.S.C. 201).

[62 FR 12084, Mar. 14, 1997]

Sec. 310.515 Patient package inserts for estrogens.

(a) *Requirement for a patient package insert.* FDA concludes that the safe and effective use of drug products containing estrogens requires that patients be fully informed of the benefits and risks involved in the use of these drugs. Accordingly, except as provided in paragraph (e) of this section, each estrogen drug product restricted to prescription distribution, including products containing estrogens in fixed combinations with other drugs, shall be dispensed to patients with a patient package insert containing information concerning the drug's benefits and risks. An estrogen drug product that does not comply with the requirements of this section is misbranded under section 502(a) of the Federal Food, Drug, and Cosmetic Act.

(b) *Distribution requirements.* (1) For estrogen drug products, the manufacturer and distributor shall provide a patient package insert in or with each package of the drug product that the manufacturer or distributor intends to be dispensed to a patient.

(2) In the case of estrogen drug products in bulk packages intended for multiple dispensing, and in the case of injectables in multiple-dose vials, a sufficient number of patient labeling pieces shall be included in or with each package to assure that one piece can be included with each package or dose dispensed or administered to every patient. Each bulk package shall be labeled with instructions to the dispenser to include one patient labeling piece with each package dispensed or, in the case of injectables, with each dose administered to the patient. This section does not preclude the manufacturer or labeler from distributing additional patient labeling pieces to the dispenser.

(3) Patient package inserts for estrogens dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before administration of the first estrogen and every 30 days thereafter, as long as the therapy continues.

(c) *Patient package insert contents.* A patient package insert for an estrogen drug product is required to contain the following information:

- (1) The name of the drug.
- (2) The name and place of business of the manufacturer, packer, or distributor.
- (3) A statement regarding the benefits and proper uses of estrogens.
- (4) The contraindications to use, *i.e.*, when estrogens should not be used.
- (5) A description of the most serious risks associated with the use of estrogens.
- (6) A brief summary of other side effects of estrogens.
- (7) Instructions on how a patient may reduce the risks of estrogen use.
- (8) The date, identified as such, of the most recent revision of the patient package insert.

(d) *Guidance language.* The Food and Drug Administration issues informal labeling guidance texts under 10.90(b)(9) of this chapter to provide assistance in meeting the requirements of paragraph (c) of this section. Requests for a copy of the guidance text should be directed to the Center for Drug Evaluation and Research, Division of Reproductive and Urologic Products, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

(e) *Exemptions.* This section does not apply to estrogen-progestogen oral contraceptives. Labeling requirements for these products are set forth in 310.501.

(f) *Requirement to supplement approved application.* Holders of approved applications for estrogen drug products that are subject to the requirements of this section must submit supplements under 314.70(c) of this chapter to provide

for the labeling required by paragraph (a) of this section. Such labeling may be put into use without advance approval by the Food and Drug Administration.

[55 FR 18723, May 4, 1990, as amended at 74 FR 13113, Mar. 26, 2009]

Sec. 310.517 Labeling for oral hypoglycemic drugs of the sulfonylurea class.

(a) The University Group Diabetes Program clinical trial has reported an association between the administration of tolbutamide and increased cardiovascular mortality. The Food and Drug Administration has concluded that this reported association provides adequate basis for a warning in the labeling. In view of the similarities in chemical structure and mode of action, the Food and Drug Administration also believes it is prudent from a safety standpoint to consider that the possible increased risk of cardiovascular mortality from tolbutamide applies to all other sulfonylurea drugs as well. Therefore, the labeling for oral hypoglycemic drugs of the sulfonylurea class shall include a warning concerning the possible increased risk of cardiovascular mortality associated with such use, as set forth in paragraph (b) of this section.

(b) Labeling for oral hypoglycemic drugs of the sulfonylurea class shall include in boldface type at the beginning of the "Warnings" section of the labeling the following statement:

**Special Warning on Increased Risk of Cardiovascular Mortality**

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19 (supp. 2): 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of (name of drug) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

[49 FR 14331, Apr. 11, 1984]

Sec. 310.518 Drug products containing iron or iron salts.

Drug products containing elemental iron or iron salts as an active ingredient in solid oral dosage form, e.g., tablets or capsules shall meet the following requirements:

(a) *Labeling*. (1) The label of any drug in solid oral dosage form (e.g., tablets or capsules) that contains iron or iron salts for use as an iron source shall bear the following statement:

**WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.**

(2) (i) The warning statement required by paragraph (a) (1) of this section shall appear prominently and conspicuously on the information panel of the immediate container label.

(ii) If a drug product is packaged in unit-dose packaging, and if the immediate container bears labeling but not a label, the warning statement required by

paragraph (a) (1) of this section shall appear prominently and conspicuously on the immediate container labeling in a way that maximizes the likelihood that the warning is intact until all of the dosage units to which it applies are used.

(3) Where the immediate container is not the retail package, the warning statement required by paragraph (a) (1) of this section shall also appear prominently and conspicuously on the information panel of the retail package label.

(4) The warning statement shall appear on any labeling that contains warnings.

(5) The warning statement required by paragraph (a) (1) of this section shall be set off in a box by use of hairlines.

(b) The iron-containing inert tablets supplied in monthly packages of oral contraceptives are categorically exempt from the requirements of paragraph (a) of this section.

[68 FR 59715, Oct. 17, 2003]

#### Sec. 310.519 Drug products marketed as over-the-counter (OTC) daytime sedatives.

(a) Antihistamines, bromides, and scopolamine compounds, either singly or in combinations, have been marketed as ingredients in over-the-counter (OTC) drug products for use as daytime sedatives. The following claims have been made for daytime sedative products: "occasional simple nervous tension," "nervous irritability," "nervous tension headache," "simple nervousness due to common every day overwork and fatigue," "a relaxed feeling," "calming down and relaxing," "gently soothe away the tension," "calmative," "resolving that irritability that ruins your day," "helps you relax," "restlessness," "when you're under occasional stress . . . helps you work relaxed." Based on evidence presently available, there are no ingredients that can be generally recognized as safe and effective for use as OTC daytime sedatives.

(b) Any OTC drug product that is labeled, represented, or promoted as an OTC daytime sedative (or any similar or related indication) is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted as an OTC daytime sedative (or any similar or related indication) is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any OTC daytime sedative drug product introduced into interstate commerce after December 24, 1979, that is not in compliance with this section is subject to regulatory action.

[44 FR 36380, June 22, 1979; 45 FR 47422, July 15, 1980, as amended at 55 FR 11579, Mar. 29, 1990]

#### Sec. 310.527 Drug products containing active ingredients offered over-the-counter (OTC) for external use as hair growers or for hair loss prevention.

(a) Amino acids, aminobenzoic acid, ascorbic acid, benzoic acid, biotin and all other B-vitamins, dexpanthenol, estradiol and other topical hormones, jojoba oil, lanolin, nucleic acids, polysorbate 20, polysorbate 60, sulfanilamide, sulfur 1 percent on carbon in a fraction of paraffinic hydrocarbons, tetracaine hydrochloride, urea, and wheat germ oil have been marketed as ingredients in OTC drug products for external use as hair growers or for hair loss prevention. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients intended for OTC external use as a hair grower or for hair loss prevention. Based on evidence currently available, all labeling claims for OTC hair grower and hair loss prevention drug products for external use are either false, misleading, or unsupported by scientific data. Therefore, any OTC drug product for external use containing an ingredient offered for use as a hair grower or for hair loss prevention cannot be considered generally recognized as safe and effective for its intended use.

(b) Any OTC drug product that is labeled, represented, or promoted for external use as a hair grower or for hair loss prevention is regarded as a new drug within

the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC external use as a hair grower or for hair loss prevention is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After January 8, 1990, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[54 FR 28777, July 7, 1989]

Sec. 310.528 Drug products containing active ingredients offered over-the-counter (OTC) for use as an aphrodisiac.

(a) Any product that bears labeling claims that it will arouse or increase sexual desire, or that it will improve sexual performance, is an aphrodisiac drug product. Anise, cantharides, don qual, estrogens, fennel, ginseng, golden seal, gotu kola, Korean ginseng, licorice, mandrake, methyltestosterone, minerals, nux vomica, Pega Palo, sarsaparilla, strychnine, testosterone, vitamins, yohimbine, yohimbine hydrochloride, and yohimbinum have been present as ingredients in such drug products. Androgens (e.g., testosterone and methyltestosterone) and estrogens are powerful hormones when administered internally and are not safe for use except under the supervision of a physician. There is a lack of adequate data to establish general recognition of the safety and effectiveness of any of these ingredients, or any other ingredient, for OTC use as an aphrodisiac. Labeling claims for aphrodisiacs for OTC use are either false, misleading, or unsupported by scientific data. The following claims are examples of some that have been made for aphrodisiac drug products for OTC use: "acts as an aphrodisiac;" "arouses or increases sexual desire and improves sexual performance;" "helps restore sexual vigor, potency, and performance;" "improves performance, staying power, and sexual potency;" and "builds virility and sexual potency." Based on evidence currently available, any OTC drug product containing ingredients for use as an aphrodisiac cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or prompted for use as an aphrodisiac is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, (the act), for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as an aphrodisiac is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After January 8, 1990, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[54 FR 28786, July 7, 1989]

Sec. 310.529 Drug products containing active ingredients offered over-the-counter (OTC) for oral use as insect repellents.

(a) Thiamine hydrochloride (vitamin B-1) has been marketed as an ingredient in over-the-counter (OTC) drug products for oral use as an insect repellent (an orally administered drug product intended to keep insects away). There is a lack of adequate data to establish the effectiveness of this, or any other ingredient for OTC oral use as an insect repellent. Labeling claims for OTC orally administered insect repellent drug products are either false, misleading, or unsupported by scientific data. The following claims are examples of some that have been made for orally administered OTC insect repellent drug products: "Oral mosquito repellent," "mosquitos avoid you," "bugs stay away," "keep mosquitos

away for 12 to 24 hours," and "the newest way to fight mosquitos." Therefore, any drug product containing ingredients offered for oral use as an insect repellent cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for oral use as an insect repellent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug and Cosmetic Act for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted OTC for oral use as an insect repellent is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any such drug product in interstate commerce after December 17, 1985, that is not in compliance with this section is subject to regulatory action.

[40 FR 25171, June 17, 1985, as amended at 55 FR 11579, Mar. 29, 1990]

Sec. 310.530 Topically applied hormone-containing drug products for over-the-counter (OTC) human use.

(a) The term "hormone" is used broadly to describe a chemical substance formed in some organ of the body, such as the adrenal glands or the pituitary, and carried to another organ or tissue, where it has a specific effect. Hormones include, for example, estrogens, progestins, androgens, anabolic steroids, and adrenal corticosteroids, and synthetic analogs. Estrogens, progesterone, pregnenolone, and pregnenolone acetate have been present as ingredients in OTC drug products marketed for topical use as hormone creams. However, there is a lack of adequate data to establish effectiveness for any OTC drug use of these ingredients. Therefore, with the exception of those hormones identified in paragraph (e) of this section, any OTC drug product containing an ingredient offered for use as a topically applied hormone cannot be considered generally recognized as safe and effective for its intended use. The intended use of the product may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor. The use of the word "hormone" in the text of the labeling or in the ingredient statement is an implied drug claim. The claim implied by the use of this term is that the product will have a therapeutic or some other physiological effect on the body. Therefore, reference to a product as a "hormone cream" or any statement in the labeling indicating that "hormones" are present in the product, or any statement that features or emphasizes the presence of a hormone ingredient in the product, will be considered to be a therapeutic claim for the product, or a claim that the product will affect the structure or function of the body, and will consequently cause the product to be a drug.

(b) Any OTC drug product that is labeled, represented, or promoted as a topically applied hormone-containing product for drug use, with the exception of those hormones identified in paragraph (e) of this section, is regarded as a new drug within the meaning of section 201(p) of the act, for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as a topically applied hormone-containing drug product is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After March 9, 1994, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(e) This section does not apply to hydrocortisone and hydrocortisone acetate labeled, represented, or promoted for OTC topical use in accordance with part 348 of this chapter.

[58 FR 47610, Sept. 9, 1993]

Sec. 310.531 Drug products containing active ingredients offered

over-the-counter (OTC) for the treatment of boils.

(a) Aminacrine hydrochloride, benzocaine, bismuth subnitrate, calomel, camphor, cholesterol, ergot fluid extract, hexachlorophene, ichthammol, isobutamben, juniper tar (oil of cade), lanolin, magnesium sulfate, menthol, methyl salicylate, oxyguinoline sulfate, petrolatum, phenol, pine tar, rosin, rosin cerate, sassafras oil, sulfur, thymol, triclosan, and zinc oxide have been present in OTC boil treatment drug products. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredient for OTC use for the treatment of boils. Treatment is defined as reducing the size of a boil or reducing an infection related to a boil. Treatment has involved the use of "drawing salves" for these purposes. These "drawing salves" contained various ingredients. Based on evidence currently available, any OTC drug product offered for the treatment of boils cannot be considered generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for the treatment of boils is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any OTC boil treatment drug product is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After May 7, 1991, any such OTC drug product that contains aminacrine hydrochloride, bismuth subnitrate, calomel, camphor, cholesterol, ergot fluid extract, hexachlorophene, isobutamben, juniper tar (oil of cade), lanolin, magnesium sulfate, menthol, methyl salicylate, oxyguinoline sulfate, petrolatum, phenol, pine tar, rosin, rosin cerate, sassafras oil, thymol, or zinc oxide initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(e) After May 16, 1994, any such OTC drug product that contains benzocaine, ichthammol, sulfur, or triclosan initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(f) This section does not apply to drug products that contain benzocaine labeled, represented, or promoted for OTC topical use in accordance with part 348 of this chapter.

[58 FR 60336, Nov. 15, 1993]

Sec. 310.532 Drug products containing active ingredients offered over-the-counter (OTC) to relieve the symptoms of benign prostatic hypertrophy.

(a) The amino acids glycine, alanine, and glutamic acid (alone or in combination) and the ingredient sabal have been present in over-the-counter (OTC) drug products to relieve the symptoms of benign prostatic hypertrophy, e.g., urinary urgency and frequency, excessive urinating at night, and delayed urination. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients for OTC use in relieving the symptoms of benign prostatic hypertrophy. In addition, there is no definitive evidence that any drug product offered for the relief of the symptoms of benign prostatic hypertrophy would alter the obstructive or inflammatory signs and symptoms of this condition. Therefore, self-medication with OTC drug products might unnecessarily delay diagnosis and treatment of progressive obstruction and secondary infections. Based on evidence currently available, any OTC drug product containing ingredients offered for use in relieving the symptoms of benign prostatic hypertrophy cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted to relieve the symptoms of benign prostatic hypertrophy is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use to relieve the symptoms of benign prostatic hypertrophy is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After August 27, 1990, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[55 FR 6930, Feb. 27, 1990]

Sec. 310.533 Drug products containing active ingredients offered over-the-counter (OTC) for human use as an anticholinergic in cough-cold drug products.

(a) Atropine sulfate, belladonna alkaloids, and belladonna alkaloids as contained in *Atropa belladonna* and *Datura stramonium* have been present as ingredients in cough-cold drug products for use as an anticholinergic. Anticholinergic drugs have been marketed OTC in cough-cold drug products to relieve excessive secretions of the nose and eyes, symptoms that are commonly associated with hay fever, allergy, rhinitis, and the common cold. Atropine sulfate for oral use as an anticholinergic is probably safe at dosages that have been used in marketed cough-cold products (0.2 to 0.3 milligram); however, there are inadequate data to establish general recognition of the effectiveness of this ingredient. The belladonna alkaloids, which contain atropine (*d, dl* hyoscyamine) and scopolamine (*l-* hyoscyne), are probably safe for oral use at dosages that have been used in marketed cough-cold products (0.2 milligram) but there are inadequate data to establish general recognition of the effectiveness of these ingredients as an anticholinergic for cough-cold use. Belladonna alkaloids for inhalation use, as contained in *Atropa belladonna* and *Datura stramonium*, are neither safe nor effective as an OTC anticholinergic. There are inadequate safety and effectiveness data to establish general recognition of the safety and/or effectiveness or any of these ingredients, or any other ingredient, for OTC use as an anticholinergic in cough-cold drug products.

(b) Any OTC cough-cold drug product that is labeled, represented, or promoted for use as an anticholinergic is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any cough-cold drug product labeled, represented, or promoted for OTC use as an anticholinergic is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After the effective date of the final regulation, any such OTC cough-cold drug product that is labeled, represented, or promoted for use as an anticholinergic may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application.

[50 FR 46587, Nov. 8, 1985, as amended at 55 FR 11579, Mar. 29, 1990]

Sec. 310.534 Drug products containing active ingredients offered over-the-counter (OTC) for human use as oral wound healing agents.

(a) Allantoin, carbamide peroxide in anhydrous glycerin, water soluble chlorophyllins, and hydrogen peroxide in aqueous solution have been present in oral mucosal injury drug products for use as oral wound healing agents. Oral wound healing agents have been marketed as aids in the healing of minor oral wounds by means other than cleansing and irrigating, or by serving as a protectant. Allantoin, carbamide peroxide in anhydrous glycerin, water soluble chlorophyllins, and hydrogen peroxide in aqueous solution are safe for use as oral wound healing agents, but there are inadequate data to establish general recognition of the effectiveness of these ingredients as oral wound healing agents.

(b) Any OTC drug product that is labeled, represented, or promoted for use as

an oral wound healing agent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as an oral wound healing agent is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After the effective date of the final regulation, any OTC drug product that is labeled, represented, or promoted for use as an oral wound healing agent may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application.

[51 FR 26114, July 18, 1986, as amended at 55 FR 11579, Mar. 29, 1990]

Sec. 310.536 Drug products containing active ingredients offered over-the-counter (OTC) for use as a nailbiting or thumbsucking deterrent.

(a) Denatonium benzoate and sucrose octaacetate have been present in OTC nailbiting and thumbsucking deterrent drug products. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these and any other ingredients (e.g., cayenne pepper) for OTC use as a nailbiting or thumbsucking deterrent. Based on evidence currently available, any OTC drug product containing ingredients offered for use as a nailbiting or thumbsucking deterrent cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, and promoted as a nailbiting or thumbsucking deterrent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as a nailbiting or thumbsucking deterrent is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After March 2, 1994, any such OTC drug product 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 46754, Sept. 2, 1993]

Sec. 310.537 Drug products containing active ingredients offered over-the-counter (OTC) for oral administration for the treatment of fever blisters and cold sores.

(a) l-lysine (lysine, lysine hydrochloride), *Lactobacillus acidophilus*, and *Lactobacillus bulgaricus* have been present in orally administered OTC drug products to treat fever blisters and cold sores. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other orally administered ingredients for OTC use to treat or relieve the symptoms or discomfort of fever blisters and cold sores. Based on evidence currently available, any OTC drug product for oral administration containing ingredients offered for use in treating or relieving the symptoms or discomfort of fever blisters and cold sores cannot be generally recognized as safe and effective.

(b) Any OTC drug product for oral administration that is labeled, represented, or promoted to treat or relieve the symptoms or discomfort of fever blisters and cold sores is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product for oral administration labeled, represented, or promoted for OTC use to treat or relieve the symptoms or discomfort of fever blisters and cold sores is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After December 30, 1992, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[57 FR 29173, June 30, 1992]

Sec. 310.538 Drug products containing active ingredients offered over-the-counter (OTC) for use for ingrown toenail relief.

(a) Any product that bears labeling claims such as for "temporary relief of discomfort from ingrown toenails," or "ingrown toenail relief product," or "ingrown toenail reliever," or similar claims is considered an ingrown toenail relief drug product. Benzocaine, chlorobutanol, chloroxylenol, dibucaine, tannic acid, and urea have been present as ingredients in such products. There is lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients for OTC use for ingrown toenail relief. Based on evidence currently available, any OTC drug product containing ingredients offered for use for ingrown toenail relief cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for ingrown toenail relief is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use for ingrown toenail relief is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After March 9, 1994, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(e) This section does not apply to sodium sulfide labeled, represented, or promoted for OTC topical use for ingrown toenail relief in accordance with part 358, subpart D of this chapter, after June 6, 2003.

[58 FR 47605, Sept. 9, 1993, as amended at 68 FR 24348, May 7, 2003]

Sec. 310.540 Drug products containing active ingredients offered over-the-counter (OTC) for use as stomach acidifiers.

(a) Betaine hydrochloride, glutamic acid hydrochloride, diluted hydrochloric acid, and pepsin have been present as ingredients in over-the-counter (OTC) drug products for use as stomach acidifiers. Because of the lack of adequate data to establish the effectiveness of these or any other ingredients for use in treating achlorhydria and hypochlorhydria, and because such conditions are asymptomatic, any OTC drug product containing ingredients offered for use as a stomach acidifier cannot be considered generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for use as a stomach acidifier is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted as a stomach acidifier for OTC use is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312

of this chapter.

(d) After the effective date of the final regulation, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[53 FR 31271, Aug. 17, 1988]

Sec. 310.541 Over-the-counter (OTC) drug products containing active ingredients offered for use in the treatment of hypophosphatemia.

(a) Hypophosphatemia is a condition in which an abnormally low plasma level of phosphate occurs in the blood. This condition is not amenable to self-diagnosis or self-treatment. Treatment of this condition should be restricted to the supervision of a physician. For this reason, any drug product containing ingredients offered for OTC use in the treatment of hypophosphatemia cannot be considered generally recognized as safe and effective.

(b) Any drug product that is labeled, represented, or promoted for OTC use in the treatment of hypophosphatemia is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use in the treatment of hypophosphatemia is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After November 12, 1990, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[55 FR 19858, May 11, 1990]

Sec. 310.542 Over-the-counter (OTC) drug products containing active ingredients offered for use in the treatment of hyperphosphatemia.

(a) Hyperphosphatemia is a condition in which an abnormally high plasma level of phosphate occurs in the blood. This condition is not amenable to self-diagnosis or self-treatment. Treatment of this condition should be restricted to the supervision of a physician. For this reason, any drug product containing ingredients offered for OTC use in the treatment of hyperphosphatemia cannot be considered generally recognized as safe and effective.

(b) Any drug product that is labeled, represented, or promoted for OTC use in the treatment of hyperphosphatemia is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for use in the treatment of hyperphosphatemia is safe and effective for the purpose intended must comply with the requirements and procedures governing use of investigational new drugs set forth in part 312 of this chapter.

(d) After November 12, 1990, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[55 FR 19858, May 11, 1990]

Sec. 310.543 Drug products containing active ingredients offered over-the-counter (OTC) for human use in exocrine pancreatic insufficiency.

(a) Hemicellulase, pancreatin, and pancrelipase have been present as ingredients in exocrine pancreatic insufficiency drug products. Pancreatin and pancrelipase are composed of enzymes: amylase, trypsin (protease), and lipase. Significant differences have been shown in the bioavailability of marketed exocrine pancreatic insufficiency drug products produced by different manufacturers. These differences raise a potential for serious risk to patients using these drug products. The bioavailability of pancreatic enzymes is dependent on the process used to manufacture the drug products. Information on this process is not included in an OTC drug monograph. Therefore, the safe and effective use of these enzymes for treating exocrine pancreatic insufficiency cannot be regulated adequately by an OTC drug monograph. Information on the product's formulation, manufacture, quality control procedures, and final formulation effectiveness testing are necessary in an approved application to ensure that a company has the ability to manufacture a proper bioactive formulation. In addition, continuous physician monitoring of patients who take these drug products is a collateral measure necessary to the safe and effective use of these enzymes, causing such products to be available by prescription only.

(b) Any drug product that is labeled, represented, or promoted for OTC use in the treatment of exocrine pancreatic insufficiency is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use in the treatment of exocrine pancreatic insufficiency is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After May 7, 1991, any such OTC drug product that contains hemicellulase initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(e) After October 24, 1995, any such OTC drug product that contains pancreatin or pancrelipase initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[60 FR 20165, Apr. 24, 1995]

Sec. 310.544 Drug products containing active ingredients offered over-the-counter (OTC) for use as a smoking deterrent.

(a) Any product that bears labeling claims that it "helps stop or reduce the cigarette urge," "helps break the cigarette habit," "helps stop or reduce smoking," or similar claims is a smoking deterrent drug product. Cloves, coriander, eucalyptus oil, ginger (Jamaica), lemon oil (terpeneless), licorice root extract, lobeline (in the form of lobeline sulfate or natural lobelia alkaloids or *Lobelia inflata* herb), menthol, methyl salicylate, povidone-silver nitrate, quinine ascorbate, silver acetate, silver nitrate, and thymol have been present as ingredients in such drug products. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients for OTC use as a smoking deterrent. Based on evidence currently available, any OTC drug product containing ingredients offered for use as a smoking deterrent cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted as a smoking deterrent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as a smoking deterrent is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After May 7, 1991, any such OTC drug product containing cloves, coriander,

eucalyptus oil, ginger (Jamaica), lemon oil (terpeneless), licorice root extract, menthol, methyl salicylate, quinine ascorbate, silver nitrate, and/or thymol initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action. After December 1, 1993, any such OTC drug product containing lobeline (in the form of lobeline sulfate or natural lobelia alkaloids or *Lobelia inflata* herb), povidone-silver nitrate, silver acetate, or any other ingredients 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 31241, June 1, 1993]

Sec. 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses:

(1) *Topical acne drug products.*

Alcloxa

Alkyl isoquinolinium bromide

Aluminum chlorohydrate

Aluminum hydroxide

Benzocaine

Benzoic acid

Boric acid

Calcium polysulfide

Calcium thiosulfate

Camphor

Chloroxylenol

Cloxyquin

Coal tar

Dibenzothiophene

Estrone

Magnesium aluminum silicate

Magnesium sulfate

Phenol

Phenolate sodium

Phenyl salicylate

Povidone-iodine

Pyridamine maleate

Resorcinol (as single ingredient)

Resorcinol monoacetate (as single ingredient)

Salicylic acid (over 2 up to 5 percent)

Sodium borate

Sodium thiosulfate

Tetracaine hydrochloride

Thymol

Vitamin E

Zinc oxide

Zinc stearate

Zinc sulfide

(2) *Anticaries drug products --(i) Approved as of May 7, 1991.*

Hydrogen fluoride

Sodium carbonate

Sodium monofluorophosphate (6 percent rinse)

Sodium phosphate

(ii) *Approved as of October 7, 1996.*

Calcium sucrose phosphate

Dicalcium phosphate dihydrate

Disodium hydrogen phosphate <sup>1</sup>

Phosphoric acid <sup>1</sup>

Sodium dihydrogen phosphate

Sodium dihydrogen phosphate monohydrate

Sodium phosphate, dibasic anhydrous reagent <sup>1</sup>

(3) *Antidiarrheal drug products --(i) Approved as of May 7, 1991.*

Aluminum hydroxide

Atropine sulfate

Calcium carbonate

Carboxymethylcellulose sodium

Glycine

Homatropine methylbromide

Hyoscyamine sulfate

Lactobacillus acidophilus

Lactobacillus bulgaricus

Opium, powdered

Opium tincture

Paregoric

Phenyl salicylate

Scopolamine hydrobromide

Zinc phenolsulfonate

(ii) *Approved as of April 19, 2004; April 18, 2005, for products with annual sales less than \$25,000.*

Attapulgate, activated

Bismuth subnitrate

Calcium hydroxide

Calcium polycarbophil

Charcoal (activated)

Pectin

Polycarbophil

Potassium carbonate

Rhubarb fluidextract

(4) *Antiperspirant drug products --(i) Ingredients --Approved as of May 7, 1991.*

Alum, potassium

Aluminum bromohydrate

Aluminum chloride (alcoholic solutions)

Aluminum chloride (aqueous solution) (aerosol only)

Aluminum sulfate

Aluminum sulfate, buffered (aerosol only)

Sodium aluminum chlorohydroxy lactate

(ii) *Approved as of December 9, 2004; June 9, 2005, for products with annual sales less than \$25,000.*

Aluminum sulfate buffered with sodium aluminum lactate

(5) [Reserved]

(6) *Cold, cough, allergy, bronchodilator, and antiasthmatic drug products --(i) Antihistamine drug products --(A) Ingredients.*

Methapyrilene hydrochloride

Methapyrilene fumarate

Thenyldiamine hydrochloride

(B) *Ingredients.*

Phenyltoloxamine dihydrogen citrate

Methapyrilene hydrochloride

Methapyrilene fumarate

Thenyldiamine hydrochloride

(ii) *Nasal decongestant drug products --(A) Approved as of May 7, 1991.*

Allyl isothiocyanate

Camphor (lozenge)

Creosote, beechwood (oral)

Eucalyptol (lozenge)

Eucalyptol (mouthwash)

Eucalyptus oil (lozenge)

Eucalyptus oil (mouthwash)

Menthol (mouthwash)

Peppermint oil (mouthwash)

Thenyldiamine hydrochloride

Thymol

Thymol (lozenge)

Thymol (mouthwash)

Turpentine oil

(B) *Approved as of August 23, 1995.*

Bornyl acetate (topical)

Cedar leaf oil (topical)

Creosote, beechwood (topical)

Ephedrine (oral)

Ephedrine hydrochloride (oral)

Ephedrine sulfate (oral)

Racephedrine hydrochloride (oral/topical)

(C) *Approved as of April 11, 2007; October 11, 2007, for products with annual sales less than \$25,000. Any ingredient(s) labeled with claims or directions for use for sinusitis or for relief of nasal congestion associated with sinusitis.*

(iii) *Expectorant drug products.*

Ammonium chloride

Antimony potassium tartrate

Beechwood creosote

Benzoin preparations (compound tincture of benzoin, tincture of benzoin)

Camphor

Chloroform

Eucalyptol/eucalyptus oil

Horehound

Iodides (calcium iodide anhydrous, hydroiodic acid syrup, iodized lime, potassium iodide)

Ipecac

Ipecac fluidextract

Ipecac syrup

Menthol/peppermint oil

Pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine)

Potassium guaiacolsulfonate

Sodium citrate

Squill preparations (squill, squill extract)

Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir)

Tolu preparations (tolu, tolu balsam, tolu balsam tincture)

Turpentine oil (spirits of turpentine)

(iv) *Bronchodilator drug products -- (A) Approved as of October 2, 1987.*

Aminophylline

Belladonna alkaloids

Euphorbia pilulifera

Metaproterenol sulfate

Methoxyphenamine hydrochloride

Pseudoephedrine hydrochloride

Pseudoephedrine sulfate

Theophylline, anhydrous

Theophylline calcium salicylate

Theophylline sodium glycinate

(B) Approved as of January 29, 1996. Any combination drug product containing theophylline (e.g., theophylline and ephedrine, or theophylline and ephedrine and phenobarbital).

(C) Approved as of June 19, 1996. Any ingredient(s) in a pressurized metered-dose inhaler container.

(D) Approved as of October 29, 2001. Any oral bronchodilator active ingredient (e.g., ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, or any other ephedrine salt) in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient.

(7) *Dandruff/seborrheic dermatitis/psoriasis drug products.*

Alkyl isoquinolinium bromide

Allantoin

Benzalkonium chloride

Benzethonium chloride

Boric acid

Calcium undecylenate

Captan

Chloroxylenol

Colloidal oatmeal

Cresol, saponated

Ethohexadiol

Eucalyptol

Juniper tar

Lauryl isoquinolinium bromide

Menthol  
Mercury oleate  
Methylbenzethonium chloride  
Methyl salicylate  
Phenol  
Phenolate sodium  
Pine tar  
Povidone-iodine  
Resorcinol  
Sodium borate  
Sodium salicylate  
Thymol

Undecylenic acid

(8) *Digestive aid drug products --(i) Approved as of May 7, 1991.*

Bismuth sodium tartrate  
Calcium carbonate  
Cellulase  
Dehydrocholic acid  
Dihydroxyaluminum sodium carbonate  
Duodenal substance  
Garlic, dehydrated  
Glutamic acid hydrochloride  
Hemicellulase  
Homatropine methylbromide  
Magnesium hydroxide  
Magnesium trisilicate  
Ox bile extract  
Pancreatin  
Pancrelipase  
Papain  
Peppermint oil  
Pepsin  
Sodium bicarbonate  
Sodium citrate

Sorbitol

(ii) *Approved as of November 10, 1993.*

Alcohol  
Aluminum hydroxide  
Amylase  
Anise seed  
Aromatic powder  
Asafetida  
Aspergillus oryza enzymes (except lactase enzyme derived from *Aspergillus oryzae* )  
Bacillus acidophilus  
Bean  
Belladonna alkaloids  
Belladonna leaves, powdered extract

Betaine hydrochloride  
Bismuth subcarbonate  
Bismuth subgallate  
Black radish powder  
Blessed thistle (*Cnicus benedictus*)  
Buckthorn  
Calcium gluconate  
Capsicum  
Capsicum, fluid extract of  
Carbon  
Cascara sagrada extract  
Catechu, tincture  
Catnip  
Chamomile flowers  
Charcoal, wood  
Chloroform  
Cinnamon oil  
Cinnamon tincture  
Citrus pectin  
Diastase  
Diastase malt  
Dog grass  
Elecampane  
Ether  
Fennel acid  
Galega  
Ginger  
Glycine  
Hydrastis canadensis (golden seal)  
Hectorite  
Horsetail  
Huckleberry  
Hydrastis fluid extract  
Hydrochloric acid  
Iodine  
Iron ox bile  
Johnswort  
Juniper  
Kaolin, colloidal  
Knotgrass  
Lactic acid  
Lactose  
Lavender compound, tincture of  
Linden  
Lipase  
Lysine hydrochloride  
Mannitol  
Mycozyme

Myrrh, fluid extract of  
Nettle  
Nickel-pectin  
Nux vomica extract  
Orthophosphoric acid  
Papaya, natural  
Pectin  
Peppermint  
Peppermint spirit  
Phenacetin  
Potassium bicarbonate  
Potassium carbonate  
Protease  
Prolase  
Rhubarb fluid extract  
Senna  
Sodium chloride  
Sodium salicylate  
Stem bromelain  
Strawberry  
Strychnine  
Tannic acid  
Trillium  
Woodruff  
(iii) Charcoal, activated  
(9) [Reserved]  
(10) *External analgesic drug products --(i) Analgesic and anesthetic drug products.*  
Aspirin  
Chloral hydrate  
Chlorobutanol  
Cyclomethycaine sulfate  
Eugenol  
Hexylresorcinol  
Methapyrilene hydrochloride  
Salicylamide  
Thymol  
(ii) *Counterirritant drug products.*  
Chloral hydrate  
Eucalyptus oil  
(iii) *Male genital desensitizer drug products.*  
Benzyl alcohol  
Camphorated metacresol  
Ephedrine hydrochloride  
(iv) *Diaper rash drug products.* Any ingredient(s) labeled with claims or directions for use in the treatment and/or prevention of diaper rash.  
(v) *Fever blister and cold sore treatment drug products.*  
Allyl isothiocyanate

Aspirin  
Bismuth sodium tartrate  
Camphor (exceeding 3 percent)  
Capsaicin  
Capsicum  
Capsicum oleoresin  
Chloral hydrate  
Chlorobutanol  
Cyclomethycaine sulfate  
Eucalyptus oil  
Eugenol  
Glycol salicylate  
Hexylresorcinol  
Histamine dihydrochloride  
Menthol (exceeding 1 percent)  
Methapyrilene hydrochloride  
Methyl nicotinate  
Methyl salicylate  
Pectin  
Salicylamide  
Strong ammonia solution  
Tannic acid  
Thymol  
Tripelennamine hydrochloride  
Trolamine salicylate  
Turpentine oil  
Zinc sulfate  
(vi) *Insect bite and sting drug products.*

Alcohol  
Alcohol, ethoxylated alkyl  
Benzalkonium chloride  
Calamine  
Ergot fluidextract  
Ferric chloride  
Panthenol  
Peppermint oil  
Pyrilamine maleate  
Sodium borate  
Trolamine salicylate  
Turpentine oil  
Zinc oxide  
Zirconium oxide  
(vii) *Poison ivy, poison oak, and poison sumac drug products.*

Alcohol  
Aspirin  
Benzethonium chloride  
Benzocaine (0.5 to 1.25 percent)  
Bithionol

Calamine  
Cetalkonium chloride  
Chloral hydrate  
Chlorobutanol  
Chlorpheniramine maleate  
Creosote, beechwood  
Cyclomethycaine sulfate  
Dexpanthenol  
Diperodon hydrochloride  
Eucalyptus oil  
Eugenol  
Glycerin  
Glycol salicylate  
Hectorite  
Hexylresorcinol  
Hydrogen peroxide  
Impatiens biflora tincture  
Iron oxide  
Isopropyl alcohol  
Lanolin  
Lead acetate  
Merbromin  
Mercuric chloride  
Methapyrilene hydrochloride  
Panthenol  
Parethoxycaine hydrochloride  
Phenyltoloxamine dihydrogen citrate  
Povidone-vinylacetate copolymers  
Pyrilamine maleate  
Salicylamide  
Salicylic acid  
Simethicone  
Sulfur  
Tannic acid  
Thymol  
Trolamine salicylate  
Turpentine oil  
Zirconium oxide  
Zyloxin  
(11) [Reserved]  
(12) *Laxative drug products --(i) (A) Bulk laxatives.*

Agar

Carrageenan (degraded)

Carrageenan (native)

Guar gum

(i) (B) *Bulk laxatives --Approved as of March 29, 2007.*

Granular dosage forms containing psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), psyllium seed husks, plantago

husks, or plantago seed including, but not limited to, any granules that are:

- (1 ) Swallowed dry prior to drinking liquid,
- (2 ) Dispersed, suspended, or partially dissolved in liquid prior to swallowing,
- (3 ) Chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid, or
- (4 ) Sprinkled over food.

(ii) *Saline laxative.*

Tartaric acid

(iii) *Stool softener.*

Poloxamer 188

(iv) (A) *Stimulant laxatives--Approved as of May 7, 1991.*

Aloin

Bile salts/acids

Calcium pantothenate

Calomel

Colocynth

Elaterin resin

Frangula

Gamboge

Ipomea

Jalap

Ox bile

Podophyllum resin

Prune concentrate dehydrate

Prune powder

Rhubarb, Chinese

Sodium Oleate

(iv) (B) *Stimulant laxatives--Approved as of January 29, 1999.*

Danthron

Phenolphthalein

(C) *Stimulant laxatives --Approved as of November 5, 2002.*

Aloe ingredients (aloe, aloe extract, aloe flower extract)

Cascara sagrada ingredients (casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluidextract).

(13) [Reserved]

(14) *Oral health care drug products (nonantimicrobial).*

Antipyrine

Camphor

Cresol

Dibucaine

Dibucaine hydrochloride

Eucalyptol

Lidocaine

Lidocaine hydrochloride

Methly salicylate

Myrrh tincture

Pyrilamine maleate

Sorbitol

Sugars

Tetracaine

Tetracaine hydrochloride

Thymol

(15) *Topical otic drug products --(i) For the prevention of swimmer's ear and for the drying of water-clogged ears, approved as of May 7, 1991.*

Acetic acid

(ii) *For the prevention of swimmer's ear, approved as of August 15, 1995.*

Glycerin and anhydrous glycerin

Isopropyl alcohol

(16) *Poison treatment drug products.*

Ipecac fluidextract

Ipecac tincture

Zinc sulfate

(17) *Skin bleaching drug products.*

Mercury, ammoniated

(18) *Skin protectant drug products --(i) (A) Ingredients--Approved as of May 7, 1991.*

Allantoin (wound healing claims only)

Sulfur

Tannic acid

Zinc acetate (wound healing claims only)

(B) *Ingredients--Approved as of June 4, 2004; June 6, 2005, for products with annual sales less than \$25,000.*

Beeswax

Bismuth subnitrate

Boric acid

Cetyl alcohol

Glyceryl stearate

Isopropyl palmitate

Live yeast cell derivative

Shark liver oil

Stearyl alcohol

(ii) *Astringent drug products.*

Acetone

Alcohol

Alum, ammonium

Alum, potassium

Aluminum chlorhydroxy complex

Aromatics

Benzalkonium chloride

Benzethonium chloride

Benzocaine

Benzoic acid

Boric acid

Calcium acetate (except calcium acetate monohydrate when combined with aluminum sulfate tetradecahydrate to provide an aluminum acetate solution as described in 347.20(b) of this chapter)

Camphor gum

Clove oil

Colloidal oatmeal  
Cresol  
Cupric sulfate  
Eucalyptus oil  
Eugenol  
Ferric subsulfate (Monsel's Solution)  
Honey  
Isopropyl alcohol  
Menthol  
Methyl salicylate  
Oxyquinoline sulfate  
P-t-butyl-m-cresol  
Peppermint oil  
Phenol  
Polyoxyethylene laurate  
Potassium ferrocyanide  
Sage oil  
Silver nitrate  
Sodium borate  
Sodium diacetate  
Talc  
Tannic acid glycerite  
Thymol  
Topical starch  
Zinc chloride  
Zinc oxide  
Zinc phenolsulfonate  
Zinc stearate  
Zinc sulfate  
(iii) *Diaper rash drug products.*  
Aluminum hydroxide  
Cocoa butter  
Cysteine hydrochloride  
Glycerin  
Protein hydrolysate  
Racemethionine  
Sulfur  
Tannic acid  
Zinc acetate  
Zinc carbonate  
(iv) *Fever blister and cold sore treatment drug products.*  
Bismuth subnitrate  
Boric acid  
Pyridoxine hydrochloride  
Sulfur  
Tannic acid  
Topical starch  
Trolamine

Zinc sulfate

(v) *Insect bite and sting drug products --(A) Ingredients--Approved as of November 10, 1993.*

Alcohol

Alcohol, ethoxylated alkyl

Ammonia solution, strong

Ammonium hydroxide

Benzalkonium chloride

Camphor

Ergot fluid extract

Ferric chloride

Menthol

Peppermint oil

Phenol

Pyrilamine maleate

Sodium borate

Trolamine

Turpentine oil

Zirconium oxide

(B) *Ingredients--Approved as of June 4, 2004; June 6, 2005, for products with annual sales less than \$25,000.*

Beeswax

Bismuth subnitrate

Boric acid

Cetyl alcohol

Glyceryl stearate

Isopropyl palmitate

Live yeast cell derivative

Shark liver oil

Stearyl alcohol

(vi) *Poison ivy, poison oak, and poison sumac drug products --(A) Ingredients--Approved as of November 10, 1993.*

Alcohol

Anion and cation exchange resins buffered

Benzethonium chloride

Benzocaine

Benzyl alcohol

Bismuth subnitrate

Bithionol

Boric acid

Camphor

Cetalkonium chloride

Chloral hydrate

Chlorpheniramine maleate

Creosote

Diperodon hydrochloride

Diphenhydramine hydrochloride

Eucalyptus oil

Ferric chloride

Glycerin  
Hectorite  
Hydrogen peroxide  
Impatiens biflora tincture  
Iron oxide  
Isopropyl alcohol  
Lanolin  
Lead acetate  
Lidocaine  
Menthol  
Merbromin  
Mercuric chloride  
Panthenol  
Parethoxycaine hydrochloride  
Phenol  
Phenyltoloxamine dihydrogen citrate  
Povidone-vinylacetate copolymers  
Salicylic acid  
Simethicone  
Tannic acid  
Topical starch  
Trolamine  
Turpentine oil  
Zirconium oxide  
Zyloxin

(B) *Ingredients--Approved as of June 4, 2004; June 6, 2005, for products with annual sales less than \$25,000.*

Beeswax  
Bismuth subnitrate  
Boric acid  
Cetyl alcohol  
Glyceryl stearate  
Isopropyl palmitate  
Live yeast cell derivative  
Shark liver oil  
Stearyl alcohol  
(19) [Reserved]  
(20) *Weight control drug products.*  
Alcohol  
Alfalfa  
Alginic acid  
Anise oil  
Arginine  
Ascorbic acid  
Bearberry  
Biotin  
Bone marrow, red  
Buchu

Buchu, potassium extract  
Caffeine  
Caffeine citrate  
Calcium  
Calcium carbonate  
Calcium caseinate  
Calcium lactate  
Calcium pantothenate  
Carboxymethylcellulose sodium  
Carrageenan  
Cholecalciferol  
Choline  
Chondrus  
Citric acid  
Cnicus benedictus  
Copper  
Copper gluconate  
Corn oil  
Corn syrup  
Corn silk, potassium extract  
Cupric sulfate  
Cyanocobalamin (vitamin B12)  
Cystine  
Dextrose  
Docusate sodium  
Ergocalciferol  
Ferric ammonium citrate  
Ferric pyrophosphate  
Ferrous fumarate  
Ferrous gluconate  
Ferrous sulfate (iron)  
Flax seed  
Folic acid  
Fructose  
Guar gum  
Histidine  
Hydrastis canadensis  
Inositol  
Iodine  
Isoleucine  
Juniper, potassium extract  
Karaya gum  
Kelp  
Lactose  
Lecithin  
Leucine  
Liver concentrate  
Lysine

Lysine hydrochloride  
Magnesium  
Magnesium oxide  
Malt  
Maltodextrin  
Manganese citrate  
Mannitol  
Methionine  
Methylcellulose  
Mono- and di-glycerides  
Niacinamide  
Organic vegetables  
Pancreatin  
Pantothenic acid  
Papain  
Papaya enzymes  
Pepsin  
Phenacetin  
Phenylalanine  
Phosphorus  
Phytolacca  
Pineapple enzymes  
Plantago seed  
Potassium citrate  
Pyridoxine hydrochloride (vitamin B6)  
Riboflavin  
Rice polishings  
Saccharin  
Sea minerals  
Sesame seed  
Sodium  
Sodium bicarbonate  
Sodium caseinate  
Sodium chloride (salt)  
Soybean protein  
Soy meal  
Sucrose  
Thiamine hydrochloride (vitamin B1)  
Thiamine mononitrate (vitamin B1 mononitrate)  
Threonine  
Tricalcium phosphate  
Tryptophan  
Tyrosine  
Uva ursi, potassium extract  
Valine  
Vegetable  
Vitamin A  
Vitamin A acetate

Vitamin A palmitate

Vitamin E

Wheat germ

Xanthan gum

Yeast

(21) *Ophthalmic drug products.* (i) *Ophthalmic anesthetic drug products.*

Antipyrine

Piperocaine hydrochloride

(ii) *Ophthalmic anti-infective drug products.*

Boric acid

Mild silver protein

Yellow mercuric oxide

(iii) *Ophthalmic astringent drug products.*

Infusion of rose petals

(iv) *Ophthalmic demulcent drug products.*

Polyethylene glycol 6000

(v) *Ophthalmic vasoconstrictor drug products.*

Phenylephrine hydrochloride (less than 0.08 percent)

(22) *Topical antifungal drug products.* (i) *Diaper rash drug products.* Any ingredient(s) labeled with claims or directions for use in the treatment and/or prevention of diaper rash.

(ii) *Ingredients.*

Alcloxa

Alum, potassium

Aluminum sulfate

Amyltricresols, secondary

Basic fuchsin

Benzethonium chloride

Benzoic acid

Benzoxiquine

Boric acid

Camphor

Candicidin

Chlorothymol

Coal tar

Dichlorophen

Menthol

Methylparaben

Oxyquinoline

Oxyquinoline sulfate

Phenol

Phenolate sodium

Phenyl salicylate

Propionic acid

Propylparaben

Resorcinol

Salicylic acid

Sodium borate

Sodium caprylate

Sodium propionate

Sulfur

Tannic acid

Thymol

Tolindate

Triacetin

Zinc caprylate

Zinc propionate

(iii) Any ingredient(s) labeled with claims or directions for use on the scalp or on the nails.

(iv) *Ingredients.*

Camphorated metacresol

Chloroxylenol

*m* -cresol

Nystatin

(23) *Internal analgesic drug products --(i) Approved as of November 10, 1993.*

Aminobenzoic acid

Antipyrine

Aspirin, aluminum

Calcium salicylate

Codeine

Codeine phosphate

Codeine sulfate

Iodoantipyrine

Lysine aspirin

Methapyrilene fumarate

Phenacetin

Pheniramine maleate

Pyrilamine maleate

Quinine

Salsalate

Sodium aminobenzoate

(ii) *Approved as of February 22, 1999.*

Any atropine ingredient

Any ephedrine ingredient

(24) *Orally administered menstrual drug products --(i) Approved as of November 10, 1993.*

Alcohol

Alfalfa leaves

Aloes

Asclepias tuberosa

Asparagus

Barosma

Bearberry (extract of uva ursi)

Bearberry fluidextract (extract of bearberry)

Blessed thistle (cnicus benedictus)

Buchu powdered extract (extract of buchu)

Calcium lactate  
Calcium pantothenate  
Capsicum oleoresin  
Cascara fluidextract, aromatic (extract of cascara)  
Chlorprophenpyridamine maleate  
Cimicifuga racemosa  
Codeine  
Collinsonia (extract stone root)  
Corn silk  
Couch grass  
Dog grass extract  
Ethyl nitrite  
Ferric chloride  
Ferrous sulfate  
Gentiana lutea (gentian)  
Glycyrrhiza (licorice)  
Homatropine methylbromide  
Hydrangea, powdered extract (extract of hydrangea)  
Hydrastis canadensis (golden seal)  
Hyoscyamine sulfate  
Juniper oil (oil of juniper)  
Magnesium sulfate  
Methapyrilene hydrochloride  
Methenamine  
Methylene blue  
Natural estrogenic hormone  
Niacinamide  
Nutmeg oil (oil of nutmeg)  
Oil of erigeron  
Parsley  
Peppermint spirit  
Pepsin, essence  
Phenacetin  
Phenindamine tartrate  
Phenyl salicylate  
Piscidia erythrina  
Pipsissewa  
Potassium acetate  
Potassium nitrate  
Riboflavin  
Saw palmetto  
Senecio aureus  
Sodium benzoate  
Sodium nitrate  
Sucrose  
Sulferated oils of turpentine  
Taraxacum officinale  
Theobromine sodium salicylate

Theophylline  
Thiamine hydrochloride  
Triticum  
Turpentine, venice (venice turpentine)  
Urea  
(ii) *Approved as of February 22, 1999.*  
Any atropine ingredient  
Any ephedrine ingredient  
(25) *Pediculicide drug products --(i) Approved as of November 10, 1993.*  
Benzocaine  
Benzyl alcohol  
Benzyl benzoate  
Chlorophenothane (dichlorodiphenyl trichloroethane)  
Coconut oil soap, aqueous  
Copper oleate  
Docusate sodium  
Formic acid  
Isobornyl thiocynoacetate  
Picrotoxin  
Propylene glycol  
Sabadilla alkaloids  
Sulfur, sublimed  
Thiocynoacetate  
(ii) *Approved as of June 14, 1994.* The combination of pyrethrum extract (formerly named pyrethrins) and piperonyl butoxide in an aerosol dosage formulation.  
(26) *Anorectal drug products --(i) Anticholinergic drug products.*  
Atropine  
Belladonna extract  
(ii) *Antiseptic drug products.*  
Boric acid  
Boroglycerin  
Hydrastis  
Phenol  
Resorcinol  
Sodium salicylic acid phenolate  
(iii) *Astringent drug products.*  
Tannic acid  
(iv) *Counterirritant drug products.*  
Camphor (greater than 3 to 11 percent)  
Hydrastis  
Menthol (1.25 to 16 percent)  
Turpentine oil (rectified) (6 to 50 percent)  
(v) *Keratolytic drug products.*  
Precipitated sulfur  
Sublimed sulfur  
(vi) *Local anesthetic drug products.*  
Diperodon  
Phenacaine hydrochloride

(vii) *Other drug products.*

Collinsonia extract

Escherichia coli vaccines

Lappa extract

Leptandra extract

Live yeast cell derivative

Mullein

(viii) *Protectant drug products.*

Bismuth oxide

Bismuth subcarbonate

Bismuth subgallate

Bismuth subnitrate

Lanolin alcohols

(ix) *Vasoconstrictor drug products.*

Epinephrine undecylenate

(x) *Wound healing drug products.*

Cholecalciferol

Cod liver oil

Live yeast cell derivative

Peruvian balsam

Shark liver oil

Vitamin A

(xi) *Combination drug products.* Any combination drug product containing hydrocortisone and pramoxine hydrochloride.

(27) *Topical antimicrobial drug products --(i) First aid antiseptic drug products.*

Ammoniated mercury

Calomel (mercurous chloride)

Merbromin (mercurochrome)

Mercurfenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride)

Mercuric chloride (bichloride of mercury, mercury chloride)

Mercuric oxide, yellow

Mercuric salicylate

Mercuric sulfide, red

Mercury

Mercury oleate

Mercury sulfide

Nitromersol

Para-chloromercuriphenol

Phenylmercuric nitrate

Thimerosal

Vitromersol

Zyloxin

(ii) *Diaper rash drug products.*

Para-chloromercuriphenol

Any other ingredient containing mercury

(28) *Vaginal contraceptive drug products --(i) Approved as of October 22, 1998.*

Dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate)

Laureth 10S

Methoxypolyoxyethyleneglycol 550 laurate

Phenylmercuric acetate

Phenylmercuric nitrate

Any other ingredient containing mercury

(ii) *Approved as of November 5, 2002.*

Octoxynol 9

(29) *Sunscreen drug products. (i) Ingredients.*

Diethanolamine methoxycinnamate

Digalloyl trioleate

Ethyl 4-[bis(hydroxypropyl)] aminobenzoate

Glyceryl aminobenzoate

Lawsone with dihydroxyacetone

Red petrolatum

(ii) Any ingredients labeled with any of the following or similar claims. Instant protection or protection immediately upon application.

Claims for "all-day" protection or extended wear claims citing a specific number of hours of protection that is inconsistent with the directions for application in 21 CFR 201.327.

(30) [Reserved]

(b) Any OTC drug product that is labeled, represented, or promoted for the uses specified and containing any active ingredient(s) as specified in paragraph (a) of this section is regarded as a new drug within the meaning of section 210(p) of the Federal Food, Drug, and Cosmetic Act (the Act), for which an approved new drug application under section 505 of the Act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the Act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for the OTC uses and containing any active ingredient(s) as specified in paragraph (a) of this section is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d) (1) through (d) (39) of this section.

(1) May 7, 1991, for products subject to paragraphs (a) (1) through (a) (2) (i), (a) (3) (i), (a) (4) (i), (a) (6) (i) (A), (a) (6) (ii) (A), (a) (7) (except as covered by paragraph (d) (3) of this section), (a) (8) (i), (a) (10) (i) through (a) (10) (iii), (a) (12) (i) (A), (a) (12) (ii) through (a) (12) (iv) (A), (a) (14) through (a) (15) (i), (a) (16) through (a) (18) (i) (A), (a) (18) (ii) (except as covered by paragraph (d) (22) of this section), (a) (18) (iii), (a) (18) (iv), (a) (18) (v) (A), and (a) (18) (vi) (A) of this section.

(2) February 10, 1992, for products subject to paragraph (a) (20) of this section.

(3) December 4, 1992, for products subject to paragraph (a) (7) of this section that contain menthol as an antipruritic in combination with the antidandruff ingredient coal tar identified in 358.710(a) (1) of this chapter. This section does not apply to products allowed by 358.720(b) of this chapter after April 5, 2007.

(4) February 28, 1990, for products subject to paragraph (a) (6) (iii) of this section, except those that contain ipecac.

(5) September 14, 1993, for products subject to paragraph (a) (6) (iii) of this section that contain ipecac.

(6) December 9, 1993, for products subject to paragraph (a) (6) (i) (B) of this section.

(7) March 6, 1989, for products subject to paragraph (a) (21) of this section, except those that contain ophthalmic anti-infective ingredients listed in paragraph (a) (21) (ii).

- (8) June 18, 1993, for products subject to paragraph (a) (21) of this section that contain ophthalmic anti-infective ingredients.
- (9) June 18, 1993, for products subject to paragraph (a) (10) (iv) of this section.
- (10) June 18, 1993, for products subject to paragraph (a) (22) (i) of this section.
- (11) November 10, 1993, for products subject to paragraphs (a) (8) (ii), (a) (10) (v) through (a) (10) (vii), (a) (18) (ii) (except products that contain ferric subsulfate as covered by paragraph (d) (22) of this section and except products that contain calcium acetate monohydrate as covered by paragraph (d) (39) of this section) through (a) (18) (v) (A), (a) (18) (vi) (A), (a) (22) (ii), (a) (23) (i), (a) (24) (i), and (a) (25) of this section.
- (12) March 2, 1994, for products subject to paragraph (a) (22) (iii) of this section.
- (13) August 5, 1991, for products subject to paragraph (a) (26) of this section, except for those that contain live yeast cell derivative and a combination of hydrocortisone and pramoxine hydrochloride.
- (14) September 2, 1994, for products subject to paragraph (a) (26) (vii) and (a) (26) (x) of this section that contain live yeast cell derivative.
- (15) September 23, 1994, for products subject to paragraph (a) (22) (iv) of this section.
- (16) June 14, 1994, for products subject to paragraph (a) (25) (ii) of this section.
- (17) April 19, 2004, for products subject to paragraph (a) (3) (ii) of this section. April 18, 2005, for products with annual sales less than \$25,000.
- (18) August 15, 1995, for products subject to paragraph (a) (15) (ii) of this section.
- (19) October 2, 1987, for products subject to paragraph (a) (6) (iv) (A) of this section.
- (20) January 29, 1996, for products subject to paragraph (a) (6) (iv) (B) of this section.
- (21) April 21, 1994, for products subject to paragraph (a) (8) (iii) of this section.
- (22) April 21, 1993, for products subject to paragraph (a) (18) (ii) of this section that contain ferric subsulfate.
- (23) August 23, 1995, for products subject to paragraph (a) (6) (ii) (B) of this section.
- (24) October 7, 1996, for products subject to paragraph (a) (2) (ii) of this section.
- (25) June 19, 1996, for products subject to paragraph (a) (6) (iv) (C) of this section.
- (26) February 22, 1999, for products subject to paragraphs (a) (23) (ii) and (a) (24) (ii) of this section.
- (27) [Reserved]
- (28) October 22, 1998, for products subject to paragraphs (a) (27) and (a) (28) (i) of this section.
- (29) January 29, 1999, for products subject to paragraph (a) (12) (iv) (B) of this section.
- (30) November 5, 2002, for products subject to paragraph (a) (12) (iv) (C) of this section.
- (31) December 31, 2002, for products subject to paragraph (a) (29) (i) of this section.
- (32) June 4, 2004, for products subject to paragraphs (a) (18) (i) (B), (a) (18) (v) (B), and (a) (18) (vi) (B) of this section. June 6, 2005, for products with annual sales less than \$25,000.
- (33) October 29, 2001, for products subject to paragraph (a) (6) (iv) (D) of this section.
- (34) December 9, 2004, for products subject to paragraph (a) (4) (ii) of this section. June 9, 2005, for products with annual sales less than \$25,000.
- (35) [Reserved]
- (36) November 5, 2002, for products subject to paragraph (a) (28) (ii) of this section.
- (37) September 25, 2003, for products subject to paragraph (a) (26) (xi) of this section.

(38) October 1, 2007, for products subject to paragraph (a) (12) (i) (B) of this section.

(39) September 6, 2010, for products subject to paragraph (a) (18) (ii) of this section that contain calcium acetate monohydrate, except as provided in 347.20 (b) of this chapter.

(40) December 17, 2012, for products subject to paragraph (a) (29) (ii) of this section. December 17, 2013, for products with annual sales less than \$25,000.

<sup>1</sup>These ingredients are nonmonograph except when used to prepare acidulated phosphate fluoride treatment rinses identified in 355.10 (a) (3) of this chapter.

[55 FR 46919, Nov. 7, 1990]

Editorial Note:

For Federal Register citations affecting 310.545, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and at [www.fdsys.gov](http://www.fdsys.gov).

Effective Date Note:

At 61 FR 9571, Mar. 8, 1996, in 310.545 in paragraph (a) (6) (ii) (B), the entry for "l-desoxyephedrine (topical)" was stayed until further notice.

Sec. 310.546 Drug products containing active ingredients offered over-the-counter (OTC) for the treatment and/or prevention of nocturnal leg muscle cramps.

(a) Quinine sulfate alone or in combination with vitamin E has been present in over-the-counter (OTC) drug products for the treatment and/or prevention of nocturnal leg muscle cramps, *i.e.*, a condition of localized pain in the lower extremities usually occurring in middle life and beyond with no regular pattern concerning time or severity. There is a lack of adequate data to establish general recognition of the safety and effectiveness of quinine sulfate, vitamin E, or any other ingredients for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps. In the doses used to treat or prevent this condition, quinine sulfate has caused adverse events such as transient visual and auditory disturbances, dizziness, fever, nausea, vomiting, and diarrhea. Quinine sulfate may cause unpredictable serious and life-threatening hypersensitivity reactions requiring medical intervention and hospitalization; fatalities have been reported. The risk associated with use of quinine sulfate, in the absence of evidence of its effectiveness, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition. Based upon the adverse benefit-to-risk ratio, any drug product containing quinine or quinine sulfate cannot be considered generally recognized as safe for the treatment and/or prevention of nocturnal leg muscle cramps.

(b) Any OTC drug product that is labeled, represented, or promoted for the treatment and/or prevention of nocturnal leg muscle cramps is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use for the treatment and/or prevention of nocturnal leg muscle cramps is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After February 22, 1995, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[59 FR 43252, Aug. 22, 1994]

Sec. 310.547 Drug products containing quinine offered over-the-counter (OTC) for the treatment and/or prevention of malaria.

(a) Quinine and quinine salts have been used OTC for the treatment and/or prevention of malaria, a serious and potentially life-threatening disease.

Quinine is no longer the drug of choice for the treatment and/or prevention of most types of malaria. In addition, there are serious and complicating aspects of the disease itself and some potentially serious and life-threatening risks associated with the use of quinine at doses employed for the treatment of malaria. There is a lack of adequate data to establish general recognition of the safety of quinine drug products for OTC use in the treatment and/or prevention of malaria. Therefore, quinine or quinine salts cannot be safely and effectively used for the treatment and/or prevention of malaria except under the care and supervision of a doctor.

(b) Any OTC drug product containing quinine or quinine salts that is labeled, represented, or promoted for the treatment and/or prevention of malaria is regarded as a new drug within the meaning of section 201(p) of the act, for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use for the treatment and/or prevention of malaria is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After April 20, 1998, any such OTC drug product 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 13528, Mar. 20, 1998]

Sec. 310.548 Drug products containing colloidal silver ingredients or silver salts offered over-the-counter (OTC) for the treatment and/or prevention of disease.

(a) Colloidal silver ingredients and silver salts have been marketed in over-the-counter (OTC) drug products for the treatment and prevention of numerous disease conditions. There are serious and complicating aspects to many of the diseases these silver ingredients purport to treat or prevent. Further, there is a lack of adequate data to establish general recognition of the safety and effectiveness of colloidal silver ingredients or silver salts for OTC use in the treatment or prevention of any disease. These ingredients and salts include, but are not limited to, silver proteins, mild silver protein, strong silver protein, silver, silver ion, silver chloride, silver cyanide, silver iodide, silver oxide, and silver phosphate.

(b) Any OTC drug product containing colloidal silver ingredients or silver salts that is labeled, represented, or promoted for the treatment and/or prevention of any disease is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product containing colloidal silver or silver salts labeled, represented, or promoted for any OTC drug use is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs as set forth in part 312 of this chapter.

(d) After September 16, 1999, any such OTC drug product containing colloidal silver or silver salts initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[64 FR 44658, Aug. 17, 1999]

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e, 379k-1; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.