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men of weight reduction based on caloric restriction, for patients in whom obesity is refractory to other measures.

(3) Complete labeling guidelines are available from the Food and Drug Administration.

(h) Regulatory proceedings will be initiated with regard to any such drug within the jurisdiction of the act which is not in accord with this regulation.

[39 FR 11580, Mar. 29, 1974, as amended at 41 FR 10385, Mar. 15, 1976; 55 FR 11573, Mar. 29, 1990]

EFFECTIVE DATE NOTE: At 62 FR 12084, Mar. 14, 1997, §310.504 was removed, effective Apr. 14, 1997.

§310.506 Use of vinyl chloride as an ingredient, including propellant, of aerosol drug products.

(a) Vinyl chloride has been used as a propellant in aerosol drug preparations. Evidence indicates that vinyl chloride inhalation can result in acute toxicity manifested by dizziness, headache, disorientation, and unconsciousness where inhaled at high concentrations. Cardiac effects, bone changes, and degenerative changes in the brain, liver, and kidneys have been reported in animals. Studies also demonstrate carcinogenic effects in animals as a result of inhalation exposure to vinyl chloride. Recently, vinyl chloride has been linked to liver disease, including liver cancer, in workers engaged in the polymerization of vinyl chloride.

(b) The Commissioner finds that there is a lack of general recognition by qualified experts of the safety or effectiveness of aerosol drug preparations containing vinyl chloride as an ingredient, including propellant. Therefore, any such product containing vinyl chloride is a new drug and a new drug application approved under section 505 of the Federal Food, Drug, and Cosmetic Act is required for marketing.

(c) Clinical investigations designed to obtain evidence that any aerosol drug preparation containing vinyl chloride as an ingredient, including propellant, 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.

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(d) Any such drug within the jurisdiction of the act which is not in accord with this regulation is subject to regulatory action.

[39 FR 30830, Aug. 26, 1974, as amended at 55 FR 11578, Mar. 29, 1990]

EFFECTIVE DATE NOTE: At 52 FR 12084, Mar. 14, 1997, §310.506 was removed, effective Apr. 14, 1997.

§310.507 Aerosol drug products for human use containing 1,1,1-trichloroethane.

(a) Trichloroethane has been used in aerosol drug products as a solvent for the active ingredients and to reduce the vapor pressure of the propellants. It is potentially toxic to the cardiovascular system, i.e., can sensitize the heart to epinephrine. At a sufficiently large concentration, it is a potent anesthetic agent. Deaths associated with aerosol decongestant products intended to be inhaled and containing trichloroethane have been reported. Most of the deaths resulted from abuse or gross misuse of the preparations.

(b) The Food and Drug Administration finds that there is a lack of general recognition by qualified experts of the safety or effectiveness of trichloroethane in aerosol drug products intended for inhalation either directly or indirectly. Any aerosol drug product containing trichloroethane and labeled, represented, or advertised for use by inhalation is a new drug and subject to regulatory proceedings unless it is the subject of a new drug application approved pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act.

(c) Clinical investigations designed to obtain evidence that any aerosol drug product containing trichloroethane and labeled, represented, or advertised for use by inhalation either directly or indirectly is safe and effective for the purposes intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Regulatory proceedings will be initiated with regard to any such drug within the jurisdiction of the act which

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is not in accord with this regulation on January 16, 1978.

[42 FR 63387, Dec. 16, 1977, as amended at 55 FR 11573, Mar. 29, 1990]

EFFECTIVE DATE NOTE: At 52 FR 12084, Mar. 14, 1997, §310.507 was removed, effective Apr. 14, 1997.

§310.508 Use of certain halogenated salicylanilides as an inactive ingredient in drug products.

(a) Halogenated salicylanilides (tribromosalan (TBS), 3,4,5-tribromosalicylanilide), dibromosalan (DBS), 4, 5-dibromosalicylanilide), metabromosalan (MBS), 3, 5-dibromosalicylanilide), and 3,3', 4,4'-tetrachlorosalicylanilide (TC-SA)) have been used as active or inactive ingredients in a number of over-the-counter (OTC) drug products, largely antibacterial soaps, for antimicrobial, preservative, and other purposes. These halogenated salicylanilides are potent photosensitizers and can cause disabling skin disorders. In some instances the photosensitization may persist for prolonged periods as a severe reaction without further exposure to these chemicals. Safer alternative antimicrobial agents are available.

(b) These halogenated salicylanilides are not generally recognized as safe and effective for use as active or inactive ingredients in any drug products. Therefore, any drug product containing such a halogenated salicylanilide as an ingredient at any level for any purpose is 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 pursuant to 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 containing a halogenated salicylanilide as an ingredient at any level for any purpose 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 initially introduced into interstate commerce after December 1, 1975, that is not in

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compliance with this section is subject to regulatory action.

[40 FR 50530, Oct. 30, 1975, as amended at 55 FR 11578, Mar. 29, 1990]

EFFECTIVE DATE NOTE: At 62 FR 12084, Mar. 14, 1997, § 310.508 was removed, effective Apr. 14, 1997.

§ 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.

(4) This section does not apply to a biological product licensed under the Public Health Service Act of July 1, 1944 (21 U.S.C. 201).

[42 FR 12994, Mar. 14, 1997]

EFFECTIVE DATE NOTE: At 62 FR 12084, Mar. 14, 1997, § 310.509 was revised, effective Apr. 14, 1997. For the convenience of the user, the substance of the change is set forth as follows:

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§ 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 Federal Food, Drug, and Cosmetic Act, and requires an approved new drug application as a condition for marketing. A "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) It is common medical practice to add various drugs to containers of large volume parenteral drug products for single administration to the patient, although in many cases the safety and effectiveness of that practice has not been demonstrated. Accordingly the Commissioner of Food and Drugs concludes that reports of a full investigation of the compatibility of the immediate container of certain large volume parenteral drugs with certain other drugs that may be added regularly to the parenteral delivery system is necessary under section 505(k) of the act to determine whether there is ground for requiring revision of the labeling to provide for safer use of the large volume parenteral drug products or ground for withdrawing approval, under section 505(e) of the act, of any of the approved new drug applications for the products. 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) Each holder of an approved new drug application (NDA) for a large volume parenteral drug product for intravenous use in humans that is packaged in a plastic container shall submit the following to the Food and Drug Administration:

(1) The protocol that the NDA holder proposes to follow in conducting compatibility studies for its large volume parenteral drug product and each additive drug listed in paragraph (d) of this section, on or before April 16, 1979.

(2) A status report of the ongoing studies 9 months after the applicant has received written acceptance of the protocol from the Food and Drug Administration.

(3) The final report at the completion of the compatibility studies within 24 months following acceptance of the protocol by the Food and Drug Administration.

(d) Reports of compatibility studies with each of the following drugs shall be submitted under paragraph (c) of this section for each large volume parenteral drug product for intravenous use in humans that is packaged in a plastic immediate container.

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unless a waiver is granted under paragraph (e) of this section for a specific drug product:

- Aminophylline
- Amphotericin
- Ampicillin
- Calcium gluconate
- Carbencillin
- Cephalosporins
- Chloramphenicol
- Chloramphenicol sodium succinate
- Clindamycin phosphate
- Cyclophosphamide
- Cytarabine
- Diphenhydramine
- Erythromicins
- Fluorouracil
- Gentamicin
- Heparin
- Hydrocortisone sodium succinate
- Insulin
- Isoproterenol
- Kanamycin
- Levarterenol
- Lidocaine
- Lincomycin
- Magnesium sulfate
- Metaraminol
- Methicillin
- Methotrexate
- Methylodopa
- Oxacillin
- Oxytocin
- Penicillin G
- Potassium chloride
- Sodium bicarbonate
- Sodium chloride
- Tetracyclines
- Vitamins (single-entity and multiple vitamin products)

(e) The required submission of a report of a compatibility study of a large volume parenteral drug product packaged in plastic and any additive drug listed in paragraph (d) of this section may be waived upon a showing that the report is unnecessary or techniques are not available for conducting a compatibility study that would produce meaningful data. A request for a waiver shall be submitted to the Director of the Division of Surgical-Dental Drug Products (HFD-160), Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, 5600 Fishers Lane, Rockville, MD 20857.

(f) Until the results of the 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