§ 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 6 months after the applicant has received written acceptance of the protocol from the Food and Drug Administration.

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

(d) Reports of compatibility studies of 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, unless a waiver is granted under paragraph (e) of this section for a specific drug product:

Aminophylline
Amphotericin
Ampicillin
Calcium gluconate
Carbenicillin
Cephalosporins
Chloramphenicol
Chloramphenicol sodium succinate
Clindamycin phosphate
Cyclophosphamide
Cytarabine
Diphenhydramine
Erythromycins
Fluorouracil
Gentamicin
Heparin
Hydrocortisone sodium succinate
Insulin
Isoproterenol
Kanamycin
Levarterenol
Lidocaine
Lincomycin
Magnesium sulfate
Metaraminol
Methicillin
Methotrexate
Methyldopa
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 results. A request for a waiver shall be submitted to the Director of the Division of Surgical and 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) If 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 statement that includes the following information:

(1) A statement that additives may be introduced into the parenteral system.

(2) A statement that, if additive drugs are added to 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.

(g) After February 13, 1979, the Food and Drug Administration shall approve a new drug application for a large volume parenteral drug product for intravenous use in humans that is packaged in a plastic immediate container if all of the following conditions are met:

(1) The application is otherwise approvable.

(2) The application contains the results of studies to determine the compatibility of the large volume parenteral drug product's plastic container with drugs that may be added regularly to the parenteral delivery system.

(h) After February 13, 1979, the Food and Drug Administration shall approve a new drug application for a drug product intended to be added to a parenteral delivery system that includes a large volume parenteral drug product for intravenous use in humans that is packaged in a plastic immediate container if all of the following conditions are met:

(1) The application is otherwise approvable.

(2) The application contains the results of studies to determine the compatibility of the additive drug product with the plastic immediate container of marketed large volume parenteral drug products for intravenous use in humans.

(i) Holders of new drug applications for large volume parenteral drug products that are subject to this section and who must submit supplements under § 314.70(c)(2) of this chapter to provide for the labeling required under paragraph (f) of this section may put the labeling into use without advance approval by the Food and Drug Administration.

(j) 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).

[43 FR 58562, Dec. 15, 1978, as amended at 50 FR 3996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990]

§ 310.510 Use of aerosol drug products containing zirconium.

(a) Aerosol products containing zirconium have been used in over-the-counter drug products as antiperspirants. Based upon the lack of toxicological data adequate to establish a safe level for use and the adverse benefit-to-risk ratio, such aerosol products containing zirconium cannot be considered generally recognized as safe for use in drug products. The benefit from using aerosol drug products containing zirconium is insignificant when

At 62 FR 12084, Mar. 14, 1997, effective Apr. 14, 1997, this section was revised. effective Apr. 14, 1997, this section was revised. At the request of the user, the section is set forth as follows:

compared to the risk. Safer alternative antiperspirant products are available.

(b) Any aerosol drug product containing zirconium 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 aerosol drug product containing zirconium is safe 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 introduced in interstate commerce after September 15, 1977 that is not in compliance with this section is subject to regulatory action.

[42 FR 41376, Aug. 16, 1977, as amended at 55 FR 11579, Mar. 29, 1990]

EFFECTIVE DATE NOTE: At 62 FR 12085, Mar. 14, 1997, §310.510 was removed, effective Apr. 14, 1997.

§ 310.513 Chloroform, use as an ingredient (active or inactive) in drug products.

(a) Chloroform has been used as an ingredient in drug products, such as cough preparations, liniments, and toothpastes. Although considered safe for many years, recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats.

(b) Any drug product containing chloroform as an ingredient is a new drug within the meaning of section 201(p) of the act and misbranded and is subject to regulatory action under sections 301, 502, and 505 of the act. Any drug product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

(c) Any holder of an approved new drug application for a drug product containing chloroform as an ingredient shall submit to the Food and Drug Administration on or before July 29, 1976 a supplemental application providing for a revised formulation removing chloroform as an ingredient.

(1) The supplemental application shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) The date that the composition of the drug product will be changed.

(iii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iv) Data available to establish the stability of the revised formulation and, if the data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, a commitment from the applicant:

(*a*) To test the stability of marketed batches at reasonable intervals;

(*b*) To submit the data as they become available; and

(*c*) To recall from the market any batch found to fall outside the approved specifications for the drug.

(v) Copies of the label and all other labeling to be used for the drug product (a total of 12 copies if in final printed form, 4 copies if in draft form).

(2) If such drug product now contains more than one percent chloroform, the revised formulation containing no chloroform shall not be marketed before the receipt of written notice of approval of the supplemental application by the Food and Drug Administration.

(3) If such drug product now contains one percent or less chloroform, the revised formulation containing no chloroform may be marketed, subject to the conditions of §314.70(c) of this chapter, after submission of the supplemental application but prior to the receipt of written notice of its approval by the Food and Drug Administration.

(d) Any sponsor of a "Investigational New Drug Application" (IND) for a drug product containing chloroform as

an ingredient shall amend the IND on or before July 29, 1976 to revise the formulation removing chloroform as an ingredient.

(e) The Commissioner will initiate action to withdraw approval of an application or terminate an IND in accordance with the applicable provisions of section 505 of the act and parts 312 and 314 of this chapter upon failure of a holder of an approved new drug application or sponsor of an IND to comply with the provisions of paragraph (c) or (d) of this section.

[41 FR 26845, June 29, 1976, as amended at 55 FR 11579, Mar. 29, 1990]

EFFECTIVE DATE NOTE: At 62 FR 12085, Mar. 14, 1997, §310.513 was removed, effective Apr. 14, 1997.

§ 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 la-