

as pernicious anemia cannot be regarded as safe in all cases.

(4) The development of the classical symptoms of pernicious anemia that would cause a person to seek medical attention may in some cases be delayed by oral ingestion of intrinsic factor. Pernicious anemia is a disease that is associated, among other things, with a higher than normal incidence of cancer of the stomach and that for the safety of the patient, requires continuous expert medical supervision.

(5) With inadequate treatment there may be markedly deleterious effects on the nervous system. It is well established that whereas the development of anemia is completely reversible with adequate treatment, the involvement of the nervous system may not be completely reversible and thus may result in permanent damage.

(6) Some hematologists prescribe oral preparations of vitamin B<sub>12</sub> in the treatment of pernicious-anemia patients.

(7) Intrinsic factor and intrinsic factor concentrate serve no known useful therapeutic or nutritive purpose except to the extent that they do increase the gastrointestinal absorption of vitamin B<sub>12</sub> in patients with a deficiency or absence of intrinsic factor, which may eventually lead to pernicious anemia. This conclusion does not apply to diagnostic procedures using radioactive cyanocobalamin.

(8) Medical expertise is required for the diagnosis as well as the management of pernicious anemia.

(c) The Eleventh Edition of The National Formulary and its first Interim Revision include monographs for oral preparations of vitamin B<sub>12</sub> with intrinsic factor concentrate, establish a unit of vitamin B<sub>12</sub> with intrinsic factor concentrate, and provide for a National Formulary Anti-anemia Preparations Advisory Board to assign the potency of such preparations. This provides for the availability of such oral preparations, standardized within the meaning of the broad limits characteristic of the evaluation of such preparations.

(d) Any drug that is offered for or purports to contain intrinsic factor or intrinsic factor concentrate will be regarded as misbranded within the mean-

ing of section 503(b) of the Federal Food, Drug, and Cosmetic Act unless it is labeled with the statement "Rx only."

(e) Any drug for oral ingestion intended, represented, or advertised for the prevention or treatment of pernicious anemia or which purports to contain any substance or mixture of substances described in paragraph (d) of this section (other than diagnostic drugs containing radioactive cyanocobalamin) will be regarded as misbranded under sections 502 (f)(2) and (j) of the act unless its labeling bears a statement to the effect that some patients afflicted with pernicious anemia may not respond to the orally ingested product and that there is no known way to predict which patients will respond or which patients may cease to respond to the orally ingested products. The labeling shall also bear a statement that periodic examinations and laboratory studies of pernicious anemia patients are essential and recommended.

(f) Under section 409 of the Federal Food, Drug, and Cosmetic Act, intrinsic factor and intrinsic factor concentrate are regarded as food additives. No food additive regulation nor existing extension of the effective date of section 409 of the act authorizes these additives in foods, including foods for special dietary uses. Any food containing added intrinsic factor or intrinsic factor concentrate will be regarded as adulterated within the meaning of section 402(a)(2)(C) of the act.

(g) Regulatory action may be initiated with respect to any article shipped within the jurisdiction of the act contrary to the provisions of this policy statement after the 180th day following publication of this statement in the FEDERAL REGISTER.

[40 FR 14033, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

#### Subpart D—Requirements for Drugs and Cosmetics

##### § 250.250 Hexachlorophene, as a component of drug and cosmetic products.

(a) *Antibacterial component.* The use of hexachlorophene as an antibacterial

component in drug and cosmetic products has expanded widely in recent years. It is used in such products because of its bacteriostatic action against gram-positive organisms, especially against strains of staphylococcus; however, hexachlorophene offers no protection against gram-negative infections. In addition the antibacterial activity depends largely on repeated use. A notice published in the FEDERAL REGISTER of April 4, 1972 (37 FR 6775), invited data on OTC antimicrobial ingredients, including hexachlorophene, for review by an OTC Drug Advisory Review Panel to be convened under the procedures set forth in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464). This statement of policy will remain in effect unless and until replaced by a monograph resulting from the OTC Drug Advisory Review Panel.

(b) *Adverse effects.* Though considered safe for many years, recent information has become available associating hexachlorophene with toxic effects, including deaths. Studies have shown that toxic amounts of hexachlorophene can be absorbed through the skin of humans, especially the skin of premature babies or damaged skin. Human toxicity reports include data on symptomatology, blood and tissue levels of hexachlorophene, and descriptions of neuropathologic lesions. Recent infant deaths due to use of baby powder accidentally contaminated with 6 percent hexachlorophene have occurred. The accumulated evidence of toxicity is sufficient to require that continued marketing of hexachlorophene containing products be carefully defined in order to protect consumers.

(c) *Prescription drugs.* (1) Because of their potential for harmful effect, drugs containing hexachlorophene, other than as a preservative as described below, are not considered to have been shown to be safe and effective, are regarded as new drugs requiring approved new drug applications, and would be misbranded for over-the-counter distribution. In the interest of public health protection, hexachlorophene containing drugs will be regarded as misbranded and subject to regulatory proceedings unless the label bears the statement "Rx only,"

and the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by practitioners, in accord with §201.100(c) of this chapter.

(2) The Food and Drug Administration recognizes that hexachlorophene is useful as a bacteriostatic skin cleanser. It further concludes that the margin of safety is such that products containing hexachlorophene may appropriately be used within clearly delineated conditions of use.

(3) In order for such drugs to bear adequate information for safe and effective use the following statements are representative of the type of labeling for products shown to be effective bacteriostatic skin cleansers. Labeling for products other than bacteriostatic skin cleansers will be determined through the new drug procedures based on the available data.

(i) In the labeling other than on the immediate container label.

#### INDICATIONS

1. Bacteriostatic skin cleanser for surgical scrubbing or handwashing as part of patient care.
2. For topical application to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

#### CONTRAINDICATIONS

1. Not for use on burned or denuded skin or on mucous membranes.
2. Not for routine prophylactic total body bathing.

#### WARNINGS

Rinse thoroughly after use. Patients should be closely monitored and use should be immediately discontinued at the first sign of any of the symptoms described below.

Hexachlorophene is rapidly absorbed and may produce toxic blood levels when applied to skin lesions such as ichthyosis congenita or the dermatitis of Letterer-Siwe's syndrome or other generalized dermatologic conditions. Application to burns has also produced neurotoxicity and death.

Infants have developed dermatitis, irritability, generalized clonic muscular contractions and decerebrate rigidity following application of a 6 percent hexachlorophene powder. Examination of brainstems of those infants revealed vacuolization like that

which can be produced in newborn experimental animals following repeated topical application of 3 percent hexachlorophene. Moreover, a study of histologic sections of premature infants who died of unrelated causes has shown a positive correlation between hexachlorophene baths and lesions in white matter of brains.

(ii) On the immediate container label prominently displayed and in bold print:

“Special Warning: This compound may be toxic if used other than as directed. Rinse thoroughly after use. Monitor patients closely for toxicity symptoms.”

(4) Marketing of products for the indications listed in paragraph (c)(3) of this section may be continued without an approved new drug application (or required supplement thereto) either until a notice of opportunity for hearing is issued on a proposal by the Director of the Center for Drug Evaluation and Research to refuse to approve such new drug application (or required supplement) or until January 31, 1978, whichever comes first, if all the following conditions were met after September 27, 1972:

(i) The product is labeled with the statement “Rx only” and adequate information for safe and effective use as set forth in paragraph (c)(3) of this section.

(ii) Within 30 days, or by (10-27-72) the holder of an approved new drug application submits a supplement to provide for the revised label and full disclosure labeling. As the label and labeling will have been put into use, the supplement should be submitted under the provision of §314.70(c)(6)(iii) of this chapter.

(iii) Within 30 days, or by (10-27-72) the holder of an approved new drug application submits a supplement to provide for a revised formulation where appropriate to comply with this order.

(iv) Within 90 days, or by (12-26-72) the holder of an approved new drug application submits a supplement containing blood level data obtained from use of the drug as recommended, unless such information is a part of the new drug application file.

(v) Within 90 days, or by (12-26-72), the manufacturer or distributor of such a drug for which a new drug approval is not in effect submits a new drug appli-

cation in accord with §314.50 of the new drug regulations (21 CFR 314.50), including blood level data obtained from use of the drug as recommended.

(5) Prescription drug products may contain hexachlorophene as part of an effective preservative system only under the conditions and limitations provided for under paragraph (d) of this section.

(d) *Over-the-counter (OTC) drugs.* Over-the-counter drug products, other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, may contain hexachlorophene only as part of an effective preservative system, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. This use of hexachlorophene will not, by itself, require an approved new drug application. Use of hexachlorophene as a preservative at a level higher than 0.1 percent is regarded as a new drug use requiring an approved new drug application, which must be submitted within the time set out in paragraph (c)(4) of this section.

(e) *Cosmetics.* Hexachlorophene may be used as a preservative in cosmetic products other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. The component of a preservative system whether hexachlorophene or other antimicrobial agent, should be selected on the basis of the effect on the total microbial ecology of the product, not merely on gram-positive bacteria.

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(1) Adequate safety data do not presently exist to justify wider use of hexachlorophene in cosmetics.

(2) Antibacterial ingredients used as substitutes for hexachlorophene in cosmetic products, and finished cosmetic products containing such ingredients, shall be adequately tested for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing may be adulterated and will in any event be deemed misbranded unless it contains a conspicuous front panel statement that the product has not been adequately tested for safety and may be hazardous.

(f) *Content statement.* All reference to hexachlorophene limit in this order is on a weight-in-weight (w/w) basis. Quantitative declaration of hexachlorophene content on the labeling of the products, where required, shall be on a w/w basis.

(g) *Shipments of products.* Shipments of products falling within the scope of paragraphs (c), (d), or (e) of this section which are not in compliance with the guidelines stated herein shall be the subject of regulatory proceedings after the effective date of the final order.

(h) *Prior notices.* This order preempts any conditions for marketing products set forth in the following prior notices.

1. DESI No. 4749 (34 FR 15389, October 2, 1969), "Certain OTC Drugs for Topical Use."
2. DESI No. 2855 (35 FR 12423, August 4, 1970), "Certain Mouthwash and Gargle Preparations."
3. DESI No. 8940 (36 FR 14510, August 6, 1971), "Topical Cream Containing Pyrillamine Maleate, Benzocaine, Hexachlorophene, and Cetrimonium Bromide."
4. DESI No. 6615 (36 FR 18022, September 8, 1971), "Deodorant/Antiperspirant."
5. DESI No. 6270 (36 FR 23330, December 8, 1971), "Certain Preparations Containing Hexachlorophene".

[40 FR 14033, Mar. 27, 1975, as amended at 42 FR 63773, Dec. 20, 1977; 55 FR 11577, Mar. 29, 1990; 67 FR 4906, Feb. 1, 2002; 69 FR 18763, Apr. 8, 2004]

**PART 290—CONTROLLED DRUGS**

**Subpart A—General Provisions**

Sec.

290.1 Controlled substances.

290.2 Exemption from prescription requirements.

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290.6 Spanish-language version of required warning.

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**Subpart B [Reserved]**

**Subpart C—Requirements for Specific Controlled Drugs [Reserved]**

AUTHORITY: 21 U.S.C. 352, 353, 355, 371.

SOURCE: 40 FR 14040, Mar. 27, 1975, unless otherwise noted.

**Subpart A—General Provisions**

**§ 290.1 Controlled substances.**

Any drug that is a controlled substance listed in schedule II, III, IV, or V of the Federal Controlled Substances Act or implementing regulations must be dispensed by prescription only as required by section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act unless specifically exempted in § 290.2.

[67 FR 4906, Feb. 1, 2002]

**§ 290.2 Exemption from prescription requirements.**

The prescription-dispensing requirements of section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act are not necessary for the protection of the public health with respect to a compound, mixture, or preparation containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams that also includes one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the compound, mixture, or preparation valuable medicinal qualities other than those possessed by codeine alone.

[67 FR 4907, Feb. 1, 2002]

**§ 290.5 Drugs; statement of required warning.**

The label of any drug listed as a "controlled substance" in schedule II, III, or IV of the Federal Controlled Substances Act shall, when dispensed to or for a patient, contain the following warning: "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed." This statement is not required to appear on the