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D. Category II Labeling.

The Panel concludes that since there are no Category I or Category III ingredients, any labeling which claims insect repellency for an orally administered drug product is considered to be Category II and may not be used.

PART 310—NEW DRUGS

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended in Part 310 by adding to Subpart E new § 310.529, to read as follows:

§ 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 internal 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 internal 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 internal 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 internal use as an insect repellent is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is regarded as a new drug within the meaning of section 201(p) of 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.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571) as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted OTC as an insect repellent for internal use is safe and effective for the purpose intended.

(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.

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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Tuesday
January 5, 1982

Part V

Department of Health and Human Services

Food and Drug Administration

Topically Applied Hormone-Containing Drug Products for Over-the-Counter Human Use

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 310

[Docket No. 81N-0144]

Topically Applied Hormone-Containing Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would classify hormone-containing drug products for over-the-counter (OTC) oral human use as not generally recognized as safe and effective and as being misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305) Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on December 15, 1980 a report on OTC topically applied hormone-containing drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products. FDA regulations (21 CFR 330.10(a)(6) provide that the agency issue in the **Federal Register** a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC topically applied hormone-containing drug products are generally recognized as safe and effective and not misbranded: (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The Panel's recommendations on topically applied hormone-containing drug products for OTC use contain no Category I or Category III conditions, and FDA is issuing the Panel's recommendations proposing Category II classification of topically applied hormone-containing drug products for OTC use.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations that the ingredients in topically applied hormone-containing drug products for OTC use be classified as Category II. If the agency proposes to adopt the Panel's recommendations, a regulation declaring these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) will be proposed for inclusion in Part 310, Subpart E (21 CFR 310, Subpart E). The agency is including, in this advance notice of proposed rulemaking, a regulation based upon the Panel's recommendations in order to obtain full public comment at this time.

After reviewing all comments submitted in response to this document, FDA will publish in the **Federal Register** a notice of proposed rulemaking on topically applied hormone-containing drug products for OTC use. The agency's position on OTC topically applied hormone-containing drug products will be stated initially when that notice of proposed rulemaking is published in the **Federal Register**. In the notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC topically applied hormone-containing drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC topically applied hormone-containing drug products should be accompanied by appropriate documentation.

If FDA proposes to adopt the Panel's recommendations, the agency will propose that topically applied hormone-containing drug products be eliminated from the OTC market, effective 6 months after the date of publication of a final rule in the **Federal Register**, regardless of whether further testing is undertaken to justify their future use.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning topically applied hormone-containing drug products for OTC use submitted for consideration by the Panel. All this information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous external drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31697). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and

understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or preventation of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of active ingredients in miscellaneous external drug products to be considered in the OTC drug review. The list, which included hormone cream active ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of the opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC review to all OTC drug products.

Under § 330.10(a)(1) and (5), the Commissioner appointed the following Panel to review the information submitted and to prepare a report on the safety, effectivenss, and labeling of the active ingredients in these miscellaneous external drug products:

William E. Lotterhos, M.D., Chairman
Rose Dagirmanjian, Ph. D.
Vincent J. Derbes, M.D. (resigned July 1976)
George C. Cypress, M.D. (resigned November 1978)
Yelva L. Lynfield, M.D. (appointed October 1977)
Harry E. Morton, Sc. D.
Marianne N. O'Donohue, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D. (appointed September 1978)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union, served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominated by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph. D., and Jon J. Tanja, R.Ph., M.S., have provided assistance to the Panel since February 1977.

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by John T. McElroy, J.D. Thomas D. DeCillis, R.Ph., served as Panel Administrator until April 1976, followed by Michael D. Kennedy until January 1978, followed by John T. McElroy, J.D. Joseph Hussion, R.Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for topically applied hormone-containing drug products for OTC use in this document. The Panel's findings on other categories of miscellaneous external drug products are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on: January 28 and 29, 1978; November 7 and 8, and December 14 and 15, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

No individuals requested to appear before the Panel to discuss topically applied hormone-containing drug products for OTC use, nor was any individual requested to appear by the Panel.

The Panel has thoroughly reviewed the literature and data submissions, and has considered all pertinent information submitted through December 15, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed topically applied hormone-containing drug products for OTC use with respect to the following three categories:

Category I. Conditions under which topically applied hormone-containing drug products for OTC use are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which topically applied hormone-containing drug products for OTC use are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed three active ingredients in topically applied hormone-containing drug products and classified no ingredients in Category I, three ingredients in Category II, and no ingredients in Category III.

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients, recognized either through historical use or use in marketed products, of hormone active ingredients contained in topically applied products (hormone creams). Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC hormone cream drug products.

A. Submissions of Data and Information

Pursuant to the above notices, the following submissions were received:

Firms and Products

Helena Rubinstein, New York, NY 10022—Ultra Feminine Cream with Natural Estrogen and Progesterone, Ultra Feminine Beauty Oil with Natural Estrogen and Progesterone.

Sterling Drug, Inc., New York, NY 10016—Satura Moisture Cream with Hormones, Satura Moisture Lotion with Hormones, Moisturing Hormone Hand Cream, Cellogen Moisturizing Hormone Cream with Protein Hydrolysate.

USV Pharmaceutical Corporation, Tuckahoe, NY 10707—Hormonex Beauty Serum, Hormonex in Cream, Hormonex Hair and Scalp Serum.

In addition, FDA's Bureau of Drugs' Office of Compliance provided information to the Panel regarding potential hazards of topical skin and hair preparations containing various hormones (OTC Volune 160195). (See paragraph D. below—Referenced OTC Volumes.)

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Estrone

Lanolin
Natural estrogenic hormones
Natural estrogens
Progesterone
Sesame oil
Vitamin A

2. *Other ingredients reviewed by the Panel.*

Estradiol
Estrogenic hormones
Estrogen
Pregnenolone acetate

C. Classification of Ingredients

1. *Active ingredients.*

Estrogens (estrogen, natural estrogens, estrogenic hormones, natural estrogenic hormones, estradiol, estrone)
Progesterone

2. *Inactive ingredients.*

Lanolin
Sesame oil
Vitamin A

3. *Other ingredient.* The Panel was not able to locate nor is it aware of any data demonstrating the safety and effectiveness of pregnenolone acetate, or any other ingredient, when used in topically applied hormone-containing drug products for OTC use. The Panel, therefore, classifies all such ingredients as Category II for this use, and they will not be discussed further in this document.

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

E. General Discussion

The Panel has discussed topically applied hormone-containing drug products as a therapeutic class, as well as the two groups of active ingredients, the estrogens and progesterone, that are generally used in these products. The medical literature indicates that the topical application of hormone-containing drug products may affect the cellular structure of the skin but that these changes are observable only through a microscope.

Estrogenic hormones are responsible for the development of secondary sex characteristics in women at puberty. These hormones cause maturation of the internal and external genitals, enlargement of the breasts, and growth of pubic and axillary hair. Estrogens alone can produce proliferation of the uterine lining sufficient to cause menstrual bleeding; the normal ovulatory menstrual cycle results from the synergistic action of estrogens and progesterone. Pregnancy is associated with a large increase in levels of estrogens and progesterone. At the menopause, with declining levels of these hormones, menstrual cycles become irregular and then cease. Estrogen deficiency causes vasomotor disturbances (hot flashes) and atrophic vaginitis (Ref. *1*).

The ovary is the principal site of estrogen production in the nonpregnant premenopausal woman, and it secretes chiefly estradiol-17B (estradiol) and estrone. During pregnancy, the placenta produces more estrogens, primarily estradiol, than does the ovary. Estradiol is readily oxidized in the body to estrone, which in turn can be hydrated to estriol. These transformations take place mainly in the liver, where estrogens are also conjugated with sulfate of glucuronic acid. The conjugated estrogens are excreted by the kidney.

Natural estrogens for medicinal use are extracted from the urine of horses. A pregnant mare excrets over 100 milligrams (mg) of conjugated estrogens daily, more than any other mammal except a stallion.

Synthetic estrogens are often used therapeutically instead of natural estrogens. Alkylation of estradiol at the C17 position produces the orally potent estrogenic substances ethinyl estradiol and mestranol. Diethylstilbestrol and similar compounds have potent estrogenic activity although they do not have the steroidal configuration that estrogens have.

Progesterone is the ovarian hormone which changes the estrogen-primed lining of the womb into the secretory state necessary for pregnancy. In the mature menstrual cycle, a mature ovum is released; if it is not fertilized, a decline in the level of progesterone causes the lining of the womb to be shed—a change visible as menstrual bleeding. The activity of progesterone is determined by studying the cytology of vaginal smears and by measuring urinary pregnanediol, a metabolite of progesterone. Daily secretion of progesterone in a young woman ranges from a few milligrams during the early phase of the menstrual cycle to 10 to 20 mg in the latter half of the cycle to several hundred milligrams during the latter part of pregnancy, when progesterone is produced by the placenta as well as the ovary (Ref. *1*).

1. *Safety.* Estrogens are readily absorbed through the skin and mucous membranes, and systemic effects may result from topical application. In factory workers, gynecomastia (male breast development) followed the handling of diethylstilbestrol.

Masters (Ref. *2*) demonstrated an increased estrogen level in the urine and an estrogen-induced vaginal keratinization when two healthy postmenopausal women applied various estrogen creams topically. Five cream formulations were tested on each of the two women: Cream alone, cream plus 1 milligram per ounce (mg/oz) estrogen, cream plus 2 mg/oz estrogen, cream plus 4 mg/oz estrogen, and cream plus 1 mg/oz estrogen and 5 mg/oz progesterone. Haznam, Mahesh, and Greenblatt (Ref. *3*) reported similar vaginal keratinization effects in a 67-year-old woman from cutaneous application of estrogen creams containing 10,000 International Units per ounce (I.U./oz) and 50,000 I.U./oz estrogen. Greenblatt (Ref. *4*) treated an 18-year-old girl with Turner's Syndrome with an estrogen cream containing 10,000 I.U./oz estrone and 5 mg/oz progesterone. She developed vaginal keratinization, breast enlargement, and an increase in pubic hair. After applying radioactive estrogen under plastic or aluminum foil to women's backs, radioactive metabolites were promptly detected in their urine (Refs. *5* and *6*).

The Panel received three submissions for creams and oils claiming to improve the appearance of skin and hair (Refs. *7*, *8*, and *9*). These creams and oils contained 5,000 to 33,000 I.U./oz natural estrogen; in addition, one product contained progesterone 5 mg/oz.

Using 10,000 I.U./oz as an example for making calculations, and assuming for the calculation that the estrogen is estrone, the Panel calculated the concentration of estrogen in the reviewed OTC products as approximately 1 mg per 30 grams (g) or 0.003 percent, because 0.1 microgram (ug) of crystalline estrone is equivalent to 1 I.U. (Ref. *10*). One submission stated that the natural estrogen in its hormone cream is obtained from pregnant mares' urine and consists of 95 percent estrone with 17-estradiol and 5 percent miscellaneous female hormones (Ref. *9*). Bioassay is a better way of expressing estrogenic potency than weight because equal weights of chemically different estrogens differ markedly in their biologic effect. The estrogenic potency of estradiol is 12 times that of estrone

and 80 times that of estriol (Ref. *11*). Nevertheless, recent publications give estrogen content by weight.

The concentration of 10,000 I.U./oz estrogen was selected to achieve local cutaneous effects without significant systemic effects. The lack of systemic effects of this concentration is well documented in studies by Masters (Ref. *2*), Haznam, Mahesh, and Greenblatt (Ref.*3*), Karnaky (Ref. *12*), and Greenblatt (Ref. *13*). In the 30 years that these preparations have been marketed, only 3 cases of uterine bleeding (Ref. *14*) may be ascribed to their use (Ref. *15*). Adverse effects of systemic estrogen therapy, such as thrombotic disorders, nausea, edema, and breast tenderness and enlargement, have been reported from external use, due to the fact that when these products are purchased OTC it is possible for the user to disregard the instructions and apply far larger quantities than recommended (Ref. *16*). The incidence of irritation and allergic contact dermatitis using 10,000 I.U./oz is low. The Panel recognized that the data submitted are relatively old and concludes that there are inadequate data to establish that the use of estrogen is safe when used in amounts up to 2 oz/month in cream or oil. Therefore, the Panel recommends that estrogens in topically applied estrogen-containing OTC drug products be placed in Category III for safety.

Progesterone applied to the skin in concentrations similar to estrogen concentrations in marketed OTC cream and oil products seems free of systemic effects. Goldzieher and Baker (Ref. *5*), using a combination of estrogren 10,000 I.U./oz and progesterone 25 mg/oz, demonstrated no detectable increase in urinary pregnanediol. Karnaky (Ref. *12*) found no change in vaginal smears from the once-a-day use of cream containing estrogen 10,000 I.U. and progesterone 5 mg/oz. The Panel concludes that the topical OTC daily use of progesterone in a concentration up to 5 mg/oz is safe.

2. *Effectiveness.* The Panel was not presented any evidence or photographs showing any gross change, such as more even pigmentation or less wrinkling, to demonstrate that local application of estrogens improve the appearance of the skin. The only changes demonstrated have been histologic (microscopic review of sections of tissue) (Ref. *16*).

Goldzieher (Ref. *17*) biopsied the thighs and forearms of five elderly women before and after topical application of estrogen 10,000 I.U./oz. He found upon microscopic examination that the thin, senile epidermis thickened, both because of an increased number of cell layers and also because of the increased size of individual epidermal cells, and that the dermal-epidermal junction (rete ridges) returned to normal. A similar study using estrogen 5,000 to 15,000 I.U./oz on 28 elderly women, 6 elderly men, and 4 young women showed similar changes in the elderly people of both sexes but no change in the young women (Ref. *18*). Microscopic improvement was first evident histologically 10 days after starting treatment, and by the thirtieth day of treatment the epidermis has doubled in thickness and was better differentiated. Eller and Eller (Ref. *19*) did serial biopsies on 36 adults of both sexes and various ages treated with estrogen cream containing 7,500 and 15,000 I.U./oz and reached the same conclusion. Brown (Ref. *20*) instructed women aged 30 to 75 to apply estrogen cream to one side of their faces and the cream base alone to the other side for 45 days. The cream contained either 10,000 I.U. estrogen with 5 mg progesterone per ounce or 50,000 I.U./oz estrogen. Twenty-six post-treatment facial biopsies were submitted to expert dermatopathologists, who could not detect any histologic difference between the estrogen-treated and cream base-treated sides. In this study, Brown (Ref. *20*) noted a clinical (visual) impression of moderate improvement in appearance and wrinkling on the estrogen-treated side. This was also noted by Spoor (Ref. *21*) in double-blind half-face studies on eight women aged 22 to 64 treated for 30 days with cream containing 10,000 I.U./oz estrogen and 5 mg/oz progesterone.

Peck (Ref. *22*) performed a modified McClure-Aldrich test by injecting 0.05 milliliter (mL) of normal saline intradermally and measuring the time required for the visible and palpable wheal to disappear. This test measures the ability of the dermis to absorb additional fluid and therefore the saturation of the dermis which fluid prior to the injection. Peck (Ref. *22*) tested the cheeks of 4 women who used 10,000 I.U./oz estrogen cream daily. He found that the absorption time of the saline was increased in every case after 6 weeks of treatment. He did not report McClure-Aldrich tests after using the cream base alone. The Panel believes that it is possible that the mild dermal edema, which was difficult to demonstrate histologically, may be produced equally well by a moisturizing cream which does not contain hormones.

The use of progesterone on the skin is thought to increase skin surface oil by stimulating sebaceous glands. Animal experiments have shown that progesterone increased the size and rate of secretion of sebaceous glands in castrated male and female rats (Ref. *23*). A qualitative study by Spoor (Ref. *21*) using osmic acid staining of surface fat was interpreted as showing an increase in sebum production from local application of progesterone. However, quantitative gravimetric and histologic studies by Pochi and Strauss (Ref. *24*) demonstrated no effect on sebaceous gland secretion or size from the intramuscular administration of 50 mg/day progesterone in prepubertal girls and boys, young adult women, and aged women.

The physiologic stimulus to sebaceous gland growth and secretion is testosterone (Ref. *24*). In 1961, Strauss (Ref. *25*) demonstrated an appreciable increase in sebum production in aged females after the daily administration of 100 mg of methyltestosterone orally. Accordingly, Strauss (Ref. *25*) believed that some of the synthetic progestational agents, such as 17-*alpha*-ethynyl-nortestosterone, have and rogenic activity and stimulate sebaceous glands. However, more recent medical opinion (1975 to 1980) is that progesterone has no effect on human sebaceous glands (Refs. *16* and *26*).

The Panel notes that estrogen and progesterone hormones are often included in products that make cosmetic claims only. The Panel recognizes that evidence submitted demonstrating safety of estrogens not exceeding 10,000 I.U./oz and progesterone not exceeding 5 mg/oz is relatively old data. Additionally, the Panel knows of no objective data that show these levels are effective. The Panel believes that inclusion of estrogen and progesterone in these products misleads the consumer into believing that using the ingredient will give the user a more youthful appearance when in fact the changes that occur cannot be seen with the naked eye.

3. *Evaluation.* The Panel concludes that there are inadequate data to establish the safety of topically applied estrogens in the concentration reviewed, up to 10,000 I.U./oz, and that progesterone, in a concentration up to 5 mg/oz, is safe when used on the skin daily in a quantity not exceeding 2 oz/month. These amounts of topical estrogens and progesterone do not produce systemic effects and have a low incidence of irritation or allergic local effects. Higher concentrations of topical estrogens produce systemic effects and should not be available OTC. Higher concentrations of progesterone have not been tested for safety for OTC use.

The Panel further concludes that there is no evidence that using a hormone-containing drug product at the levels which are safe for OTC use will do

anything more than using the cream vehicle alone. Therefore, the Panel concludes that these products are ineffective for OTC drug use. Further, the Panel recognizes an inherent fallacy in marketing a cosmetic product which contains a medication regardless of the nonmedical intention of the label claim. If the medication affects the structure or function of the skin, then the purported cosmetic is, in fact, a medication. If the medication is present in such small amounts that neither the structure or function of the skin is altered, then its presence in the cosmetic is misleading because of lack of effectiveness, and the product should be considered misbranded.

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(2) Masters, E. J., "The Percutaneous Absorption of Estrogen," *Proceedings of the Scientific Section of the Toilet Goods Association, No. 33, May 1960,* contained in OTC Volume 160095.

(3) Haznam, M. W., V. B. Mahesh, and R. B. Greenblatt, "Absorption of Topically Applied Estrogen Preparations," *Dermatologia Internationalis,* 4:86–91, 1965.

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PART 310—NEW DRUGS

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended in Part 310 by adding to Subpart E new § 310.530, to read as follows:

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

(a) Estrogens and progesterone have been present as ingredients in over-the-counter (OTC) drug products marketed for topical use as hormone cream. There is a lack of adequate data to establish the safety and effectiveness of these ingredients as OTC topically applied hormones. Data on any other ingredients intended for use as a topically applied hormone in OTC drug products have not been submitted to the Food and Drug Administration for review for safety and effectiveness. Therefore, 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.

(b) Any OTC drug product labeled, represented, or promoted for use as a topically applied hormone-containing drug product is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is regarded as a new drug within the meaning of section 201(p) of 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.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for use as a topically applied hormone-containing drug product is safe and effective for the purpose intended.

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

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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Tuesday
January 5, 1982

Part VI

Department of Health and Human Services

Food and Drug Administration

Mercury-Containing Drug Products for Topical Antimicrobial Over-the-Counter Human Use; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 333

[Docket No. 75N-0183]

Mercury-Containing Drug Products for Topical Antimicrobial Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would classify over-the-counter (OTC) mercury-containing drug products for topical antimicrobial use as not generally recognized as safe and effective and as being misbranded. This notice related to the development of a monograph for topical antimicrobial drug products in general, which is part of the ongoing review of OTC drug products conducted by FDA. This notice also reopens the administrative record for OTC topical antimicrobial drug products to allow for consideration of recommendations on mercury-containing drug products that have been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on October 6, 1980 a report on OTC mercury-containing drug products for topical antimicrobial use from the Advisory Review Panel on OTC Miscellaneous External Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which established conditions under which OTC mercury-containing drug products for topical antimicrobial use are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

Because mercurial ingredients are marketed in OTC drug products for topical antimicrobial use, FDA has determined that the Miscellaneous External Panel's recommendations on OTC mercury-containing drug products should be included as part of the proposed rulemaking for topical antimicrobial drug products. Development of this rulemaking has been ongoing for some time.

In the **Federal Register** of September 13, 1974 (39 FR 33103), FDA issued an advance notice of proposed rulemaking to establish the monograph for OTC topical antimicrobial drug products. In the **Federal Register** of January 6, 1978 (43 FR 1210), FDA issued a tentative final monograph (notice of proposed rulemaking) for OTC topical antimicrobial drug products. In the **Federal Register** of March 9, 1979 (44 FR 13041) FDA reopened the administrative record and announced its intent to publish an updated (amended) tentative final monograph (amended notice of proposed rulemaking) for OTC topical antimicrobial drug products. FDA advises that it is again reopening the administrative record for OTC topical antimicrobial drug products in order to allow for the consideration of the Miscellaneous External Panel's recommendations on mercury-containing drug products. An amended tentative final monograph (amended notice of proposed rulemaking) will be published in a future issue of the **Federal Register**. At that time, comments received on this advance notice of proposed rulemaking concerning mercury-containing drug products will be addressed. Also, the proceeding to develop a monograph for mercury-containing drug products will be merged with the general proceeding to establish a monograph for OTC topical antimicrobial drug products. Because the Panel has recommended that mercury-containing drug products be classified in Category II, no new sections to Part 333 are being included in this advance notice of proposed rulemaking.

The unaltered conclusions and recommendations of the Panel relating to OTC mercury-containing drug products for topical antimicrobial use are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The statement has been prepared independently of FDA, and the agency has not yet fully evaluated the Panel's recommendations. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** an amended tentative final monograph for OTC topical antimicrobial drug products, including mercury-containing drug products, as an amended notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC topical antimicrobial drug products will be restated when the amended tentative final monograph is published in the **Federal Register** as an amended notice of proposed rulemaking. In that amended notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered in the amended notice of proposed rulemaking. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC mercury-containing drug products for topical antimicrobial use. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or

reformulating; removal of unsafe or ineffective products form the OTC market; and testing necessary, if any, to elevate Category III conditions to Category I. Comments regarding the impact of this rulemaking on OTC mercury-containing drug products for topical antimicrobial use should be accompanied by appropriate documentation. Comments will not be accepted at this time on any portion of the OTC topical antimicrobial rulemaking other than that relating to mercury-containing drug products.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC mercury-containing drug products for topical antimicrobial use submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph has been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and II). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subjects to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

Statement of the Advisory Review Panel on OTC Miscellaneous External Drug Products on Mercury-Containing Drug Products for Topical Antimicrobial Use.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous external drug products was issued in the **Federal Register** on November 16, 1973 (38 FR 31697). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))) , as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure of any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the original notice with a detailed, but not necessarily all inclusive, list of ingredients in miscellaneous external drug products to be considered in the OTC drug review. The list, which included ingredients described as "mercurials," was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

Under § 330.10(a)(1) and (5) the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous external drug products:

William E. Lotterhos, M.D., Chairman

Rose Dagirmanjian, Ph. D.

Vincent J. Derbes, M.D. (resigned July 1976)

George C. Cypress, M.D. (resigned November 1978)

Yelva L. Lynfield, M.D. (appointed October 1977)

Harry E. Morton, Sc. D.

Marianne N. O'Donoghue, M.D.

Chester L. Rossi, D.P.M.

J. Robert Hewson, M.D. (appointed September 1978)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominate by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph. D., and Jon J. Tanja, R.Ph., M.S., have provided assistance to the Panel since February 1977.

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by John T. McElroy, J.D. Thomas D. DeCillis, R.Ph., served as Panel Administrator until April 1976, followed by Michael D. Kennedy until January 1978, followed by

John T. McElroy, J.D. Joseph Hussion, R. Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents in this document its conclusions and recommendations on OTC mercury-containing drug products for topical antimicrobial use. The Panel's findings on other categories of miscellaneous external drug products are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on: January 27 and 28, March 7 and 8, April 20 and 21, June 22 and 23, August 3 and 4, and October 5 and 6, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305) Food and Drug Administration (address above).

No individuals requested to appear before the Panel to discuss mercury-containing drug products for topical antimicrobial use, nor was any individual requested to appear by the Panel.

The Panel has thoroughly reviewed the literature and data submissions, and has considered all pertinent information submitted through October 6, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations set forth in § 330.10, the Panel reviewed OTC mercury-containing drug products for topical antimicrobial use with respect to the following three categories:

Category I. Conditions under which OTC mercury-containing drug products for topical antimicrobial use are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC mercury-containing drug products for topical antimicrobial use are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 18 active ingredients in OTC mercury-containing drug products for topical antimicrobial use and classified all 18 in Category II.

I. Submissions of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or in marketed products, as mercurial active ingredients. Fourteen ingredients were identified as follows: Ammoniated mercury, bichloride of mercury, calomel, mercuric salicylate, mercuric sulfide, mercurochrome, mercury, mercury chloride, mercury oleate, nitromersol, *para*-chloromercuriphenol, vitromersol, yellow mercuric oxide, and zyloxin. Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC mercurial drug products. In addition, in the **Federal Register** of September 13, 1974 (39 FR 33103), the following ingredients were deferred from the OTC Antimicrobial I Panel to the Miscellaneous Topical Panel (later renamed the Advisory Review Panel on OTC Miscellaneous External Drug Products) for review: mercuric chloride (also included in the call-for-data as bichloride of mercury), *ortho*-chloromercuriphenol, and *ortho*-hydroxyphenylmercuric chloride.

A. Submissions.

Pursuant to the above notices, the following submissions were received:

Firms and Marketed Products

Becton, Dickinson and Co., Rochelle Park, NJ 07662—Mercurochrome.

Bowman Pharmaceuticals, Inc., Canton, OH 44702—Merphol, Mercuronate, Ointment.

Corona Manufacturing Co., Atlanta, GA 30301—Corona Ointment.

Eli Lilly and Co., Indianapolis, IN 46206—Merthiolate.

Marion Health and Safety, Inc., Rockford, IL 61101—Kip Ointment, Merthiolate Swabs, Mercurochrome Swabs.

Whitehall Laboratories, New York, NY 10017—Sperti.

B. Ingredients Reviewed by the Panel.

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Ammoniated mercury
Merbromin
Orthohydroxyphenylmercuric chloride
Phenylmercuric nitrate
Thimerosal

2. *Other ingredients reviewed by the Panel.*

Calomel (mercurous chloride)
Mercuric chloride (bichloride of mercury)
Mercuric salicylate
Mercuric sulfide
Mercury
Mercury chloride
Mercury oleate
Nitromersol
Ortho-chloromercuriphenol
Para-chloromercuriphenol
Vitromersol
Yellow mercuric oxide
Zyloxin

C. Classification of Ingredients.

1. *Active ingredients.*

Calomel (mercurous chloride)
Merbromin
Mercuric chloride (bichloride of mercury)
Mercury, ammoniated (ammoniated mercury)
Ortho-hydroxyphenylmercuric chloride
Phenylmercuric nitrate
Thimerosal

2. *Inactive ingredients.*

None.

3. *Other ingredients.* Mercury oleate was submitted to this Panel for the treatment of psoriasis only and will be included in the Panel's recommendations on dandruff, seborrheic dermatitis, and psoriasis drug products to be published in a future issue of the **Federal Register.**

Mercuric oxide, yellow (yellow mercuric oxide) was reviewed as an ophthalmic anti-infective by the Advisory Review Panel on OTC Ophthalmic Drug Products in its report published in the **Federal Register** of May 6, 1980 (45 FR 30002).

The Panel was not able to locate nor is it aware of data demonstrating the safety and effectiveness of the following ingredients when used as OTC mercurial topical antimicrobial active ingredients. The Panel, therefore, classifies these ingredients as Category II, not generally recognized as safe and effective for this use, and they will not be discussed further in this document.

Mercuric oxide, yellow (yellow mercuric oxide)
Mercuric salicylate
Mercuric sulfide, red (mercuric sulfide)
Mercury
Mercury chloride
Mercury oleate
Nitromersol
Ortho-chloromercuriphenol
Para-chloromercuriphenol
Vitromersol
Zyloxin

D. Referenced OTC Volumes.

The "OTC Volumes" cited in this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All of the information included in

these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

Mercury is a silver-white, heavy, liquid metal with an atomic weight of 200.59. It forms alloys with most metals except iron and combines with sulfur at ordinary temperatures.

Mercury has been known to humans perhaps longer than any other metal, and humans have used it in various ways for treating illness. With the advent of the science of chemistry, new compounds of mercury were developed and used in treatment of different pathological conditions. With the advent of the science of bacteriology, mercury compounds were among the preparations chosen for antimicrobial therapy.

It has been the general course of events that, whenever a mercury compound has been tried for a particular therapeutic function, it has been used enthusiastically at first, only to be replaced eventually by a safer or more effective drug.

Elemental mercury, especially when vaporized, is toxic and readily absorbed through intact skin, the respiratory tract, and the gastrointestinal tract (Ref. *1*). The mercury compounds exhibit varying degrees of toxicity, and sensitivity to these compounds is not unusual. The literature includes a number of cases of sensitivity to mercury-containing preparations ranging from topical salves and solutions to amalgam tooth fillings (Refs. *2* and *3*). Both organic and inorganic mercury compounds produce allergic contact dermatitis, and cross-sensitivity has been noted (Ref. *3*).

The decline in the importance of mercury in antimicrobial therapy since midcentury can be attributed more to the discovery of its lack of effectiveness for this purpose than lack of safety, however. Work done in the field of enzyme chemistry clarifying the mode of action of mercury against bacterial and fungal cells has shown that mercury compounds as a class are of dubious value for antimicrobial use (Ref. *4*).

Mercuric ions combine with free sulfhydryl groups in the bacterial cells and thus deprive the cells of these sulfhydryl groups which are necessary to insure that metabolism and growth take place. The action of mercury is primarily bacteriostatic, but it may act slowly as a bactericide (Ref. *5*). That is to say, mercury inhibits the growth of bacteria, but does not act swiftly to kill them (Ref. *6*).

In late 1939 and early 1940, important discoveries were made showing that the bacteriostatic action of mercury can be reversed by many types of sulfur-containing compounds. Brewer (Refs. *7* and *8*) formulated a culture medium, thioglycollate, which allowed the growth of anaerobic microorganisms by the use of aerobic techniques. Marshall, Gunnison, and Luxen (Ref. *9*) demonstrated that the thioglycollate medium was capable of inactivating the bacteriostatic action of thimerosal and supported the growth of contaminants. Morton, North, and Engley (Refs. *10* and *11*) demonstrated that inhibited bacteria are not completely killed by mercury-containing compounds. When these inhibited bacteria are cultured in sodium thioglycollate solution, growth resumes because the solution chemically removes the mercury and eliminates any residual bacteriostatic activity (Ref. *12*). Intraperitoneal injections of the sodium thioglycollate culture proved fatal to mice and hemolytic streptococci were isolated from the heart's blood after death of the mice (Ref. *11*). These discoveries made it necessary to reexamine all previous reports in the literature claiming a killing activity for mercurial compounds.

It has been found that, if mercury is first allowed to combine with the sulfhydryl groups in bacterial cells, growth is inhibited, but the introduction of additional sulfhydryl groups to the cell-mercury complex neutralizes this action, and growth again takes place (Ref. *6*). Brewer (Ref. *13*) examined a hospital's stock of sutures, some of which had been stored for up to 10 years. Some of the sutures were nonsterile even though they had been stored in a solution containing a high concentration of mercury. Viable *Staphylococcus aureus* were recovered from sodium thioglycollate solution after exposure to a phenylmercuric nitrate preparation for 24 hours (Ref. *14*).

The presence of serum has also been shown to reduce the antibacterial action of mercury compounds. Three hundred times more mercuric chloride, 800 times more merbromin, and 14,000 times more thimerosal were required to inactivate half the *Salmonella typhosa* cells suspended in 10 mL of an 80-percent serum solution than were required to achieve comparable results in the same period of time when the microorganisms were suspended in a salt solution (Ref. *15*). Thus, the activity of mercury preparations as topical antimicrobial agents would be markedly affected if the microorganisms on the skin or the surface of a wound were in contact with serum, pus, or other body fluids.

In 1933 Birkhaug (Ref. *16*) calculated extremely high phenol coefficients (measurements of the killing power of a compound compared to that of phenol) for mercury compounds. The method of measurement, however, was imprecise so that one could not distinguish between the bacteriostatic and bactericidal activity. Today, measurement techniques for bactericidal activity have demonstrated that the phenol coefficient for OTC mercury-containing topical antimicrobial preparations is nonexistent when their bacteriostatic action is neutralized. This has been demonstrated by Morton, North, and Engley (Ref. *11*) in studies demonstrating the effect of merbromin and thimerosal on *Streptococcus pyogenes* and by Engley (Ref. *17*) in additional studies of the effect of mercuric chloride, phenylmercuric borate, and other mercurial compounds on this strain of bacteria.

After reviewing all data and information submitted on mercury-containing products for which topical antimicrobial activity is claimed, and after a careful review of the literature, the Panel concludes that some mercury-containing preparations are not effective and others are not safe and effective for OTC topical antimicrobial use. A bacteriostatic action that is capable of being reversed by contact with body fluids and other organic matter does not constitute an effective topical antimicrobial action, and the Panel has therefore placed all mercury compounds in Category II for topical antimicrobial use.

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III. Categorization of Data

A. Category I Conditions.

These are conditions under which active ingredients used as OTC mercury-containing drug products for topical antimicrobial use are generally recognized as safe and effective and are not misbranded. This document contains no Category I conditions.

B. Category II Conditions.

These are conditions under which active ingredients used as OTC mercury-containing drug products for topical antimicrobial use are not generally recognized as safe and effective or are misbranded.

1. *Category II ingredients.*

Inorganic mercury compounds:
Calomel
Mercuric chloride
Mercury, ammoniated
Organic mercury compounds:
Merbromin
Thimerosal
Ortho-hydroxyphenylmercuric chloride
Phenylmercuric nitrate

a. *Inorganic mercury compounds*—(i) *Calomel.* Calomel (mercurous chloride) is practically insoluble in water and therefore relatively nonpoisonous for humans unless it remains in the body for a long enough time to be oxidized. Once oxidized to mercuric chloride, it is highly toxic (Ref. *1*). It has been used in the past by inunction (rubbing into the skin) as a prophylactic against venereal disease and internally as a cathartic. The Panel concludes calomel may be safe as a topical antimicrobial agent, but is not effective for this purpose.

(ii) *Mercuric chloride.* Mercuric chloride (bichloride of mercury) is a bivalent mercury salt that exhibits a high toxicity for tissue cells, a low lethal action for microorganisms, and an inability to protect against infection (Ref. *1*). The Panel concludes that mercuric chloride is not safe and not effective as a topical antimicrobial agent.

(iii) *Mercury, ammoniated.* Ammoniated mercury is insoluble in water and alcohol, but readily soluble in warm hydrochloric, nitric, and acetic acids. If ingested, it causes epigastric pain, nausea, and purging.

Ammoniated mercury has been used topically in the treatment of impetigo, ringworm, psoriasis, pruritus ani, pinworm, and infestations with pubic lice (Refs. *2* and *3*). Prolonged use may cause chronic mercury poisoning, local pigmentation of skin and eyelids (Ref. *4*), and/or hypersensitivity to mercury (Ref. *5*).

Of 70 patients treated for psoriasis with ammoniated mercury, 33 showed signs of mercury poisoning (Ref. *6*). The Panel concludes that ammoniated mercury is not safe for use as a topical antimicrobial agent.

b. *Organic mercury compounds.* Organic mercury compounds were first synthesized in an attempt to decrease the toxicity of the mercuric ion. That the attempt was not wholly successful is shown by the fact that, while merbromin and phenylmercuric nitrate have been found to be less toxic than bichloride of mercury for human epithelial cells in vitro, thimerosal was found to be more toxic (Ref. *7*). The toxicities of these compounds were not in proportion to their mercury content.

Some microorganisms have exhibited a tolerance to organic mercury compounds. For example, a strain of *Penicillium roqueforti* resistant to phenylmercuric acetate was shown to incorporate mercury in its hyphae, thus reducing the amount of biologically active mercury in its environment and permitting other microorganisms to grow that would have been inhibited by the mercury (Ref. *8*).

(i) *Merbromin.* Merbromin is soluble in water and alcohol but practically insoluble in acetone, chloroform, and ether. This compound produces a carmine red solution that stains the skin a deep red, not a desirable property for an antimicrobial agent, as this can mask inflammation, and inflammation is a warning sign of infection.

In a 1928 study Simmons (Ref. *9*) pointed out that most of the killing action of merbromin in an alcohol-acetone vehicle was due to the vehicle. Aqueous merbromin, 2 percent, failed to kill two strains of *Staphylococcus aureus* in an exposure of 10 minutes and one strain of hemolytic streptococci in an exposure of 5 minutes. The cultures were killed under similar conditions by merbromin, 2 percent, in an alcohol-acetone vehicle and by the alcohol-acetone vehicle alone, which was included as a control. It was shown in 1942 that a 1:20 dilution of merbromin failed to kill *Staphylococcus aureus* and *Escherichia coli* during an exposure of 10 minutes at room temperature (Ref. *10*). A 1:20 dilution is two and one-half times more concentrated than the 2-percent aqueous solution of merbromin that is marketed OTC for topical antimicrobial use.

The Panel concludes that merbromin is safe for topical use but lacks a bactericidal action and is not an effective topical antimicrobial active ingredient.

(ii) *Thimerosal.* Thimerosal is a cream-colored crystalline powder that is stable in air, but not in sunlight. One gram (g) is soluble in approximately 1 milliliter (mL) water and in 8 mL alcohol, but is practically insoluble in ether and benzene. At the cellular level, thimerosal has been found to be more toxic for human epithelial cells in vitro than mercuric chloride, phenylmercuric nitrate, and merbromin (Ref. *7*). It was found to be 35.3 times more toxic for embryonic chick heart tissue than for *Staphylococcus aureus* (Ref. *11*).

Moller and Trofast (Ref. *12*) demonstrated that 10 of 20 guinea pigs sensitized to thimerosal developed a delayed hypersensitivity. This production of a hypersensitivity condition in 50 percent of laboratory animals demonstrates that the substance is very allergenic and it is reasonable to expect that thimerosal will act similarly in humans.

In Sweden, where thimerosal is used mainly as a preservative in vaccines and test materials and is not sold as an OTC skin disinfectant, Moller (Ref. *13*) reported a mean frequency of thimerosal allergy of 3.7 percent among dermatologic patients throughout a 5-year period during which 600 to 800 patients were treated for contact allergy each year. Moller classified thimerosal a medium stong allergen in comparison to nickel and balsam of Peru, which showed an incidence of reactions of 9 percent and 7 percent, respectively. Moller also found that among healthy subjects 10 percent of school children, 16 percent of military recruits, 18 percent of twins, and 26 percent of medical students had hypersensitivity to thimerosal. He concluded that the periodic tuberculin testing of individuals in Sweden with vaccines containing thimerosal as a preservative affords an opportunity for the development of delayed hypersensitivity to thimerosal in this population.

Underwood et al. (Ref. *14*) patch tested over 400 patients in which 160 patients (40 percent) showed a positive reaction to one or more of the remedies which had been applied before an initial visit to a dermatologist. Of the 160 patients, 56 (35 percent) reacted to a mercury compound, and thimerosal was responsible for 90 percent of these reactions. The North American Contact Dermatitis Group (Ref. *15*) tested 1,200 subjects with 16 allergens. Thimerosal produced an incidence of 8 percent reactions and ranked third highest of the 16 allergens. Epstein, Rees, and Maibach (Ref. *16*) tested a group of private dermatological patients in the western United States with 26 substances. Thimerosal had a 13.4-percent incidence of sensitivity, which was the third highest incidence of sensitivity.

It has been suggested that hypersensitivity to thimerosal may be due to the thiosalicylate portion of the molecule and not the mercury (Ref. *5*); however, this has not been confirmed. Based on the above data, the Panel concludes that thimerosal is very allergenic.

A comprehensive study of several mercury compounds in 1950 (Ref. *1*) showed that these compounds were bacteriostatic rather than bactericidal and that thimerosal was no better than water in protecting mice from potential fatal streptococcal infection under the conditions of the study. The streptococcal culture was added to the various mercury antimicrobial preparations; the mixture held at the temperature of skin (32° to 34° C) for 10 minutes; subcultured into dextrose broth, dextrose broth with 0.1 percent thioglycollate, and dextrose broth with 10 percent blood serum; and then injected intraperitoneally into mice. The latter two culture media neutralized the bacteriostatic action of the mercury compounds (Ref. *1*).

The Panel concludes that thimersal is not safe for OTC topical use because of its potential for cell damage if applied to broken skin and its allergy potential. It is not effective as a topical antimicrobial because its bacteriostatic action can be reversed.

(iii) *Ortho-hydroxyphenylmercuric chloride.* Ortho-hydroxyphenylmercuric chloride occurs as white to faint pink feathery crystals that are soluble in water, alcohol, and benzene (Ref. *2*). It is used in burn preparations. The Panel concludes that this compound is safe for topical use in the concentration marketed for OTC use (0.056 percent). However, as a topical antimicrobial, this compound is not effective because its action is bacteriostatic rather than bactericidal (Ref. *17*).

(iv) *Phenylmercuric nitrate.* Phenylmercuric nitrate occurs as pearly, lustrous scales that are soluble in water (1 part to about 1,250 parts water) and slightly soluble in alcohol. Against human epithelial cells in vitro, phenylmercuric nitrate was found to be less toxic than bichloride of mercury and thimerosal, but it was still very toxic (Ref. *7*). Solutions of phenylmercuric salts in concentrations of 1:1,500 and greater tend to cause blistering of human skin and may act as primary skin irritants and allergens (Ref. *18*). The Panel finds phenylmercuric nitrate in the concentration submitted (1:10,000) (Ref. *19*) safe for topical application, but there is no evidence that this compound is an effective topical antimicrobial at this concentration.

2. *Category II labeling.* The Panel concludes that labeling of any OTC mercury-containing product for topical antimicrobial use is Category II because all mercury ingredients are placed in Category II.

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C. Category III Conditions.

These are conditions for which the available data are insufficient to permit final classification at this time. This document contains no Category III conditions.

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance

notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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federal register

Tuesday
January 5, 1982

Part VII

Department of Health and Human Services

Food and Drug Administration

Drug Products for Over-the-Counter Human Use for the Treatment of Acute Toxic Ingestion; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0050]

Drug Products for Over-the-Counter Human Use for the Treatment of Acute Toxic Ingestion; Establishment of a Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) drug products used for the treatment of acute toxic ingestion are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on June 24, 1978 a report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6))provide that the agency issue in the **Federal Register** a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC drug products for the treatment of acute toxic ingestion are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC drug products used for the treatment of acute toxic ingestion as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency notes that the Panel has included in its report a series of labeling recommendations for the use of ipecac syrup as an emetic. (See part III. paragraph A.1.b. below—Ipecac Syrup.) The Panel was aware that ipecac syrup had already been reviewed by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products and requested that its recommendations regarding ipecac syrup be incorporated in the tentative final monograph (notice of proposed rulemaking) for emetic drug products rather than in the advance notice of proposed rulemaking for drug products for the treatment of acute toxic ingestion which is included in this document. Unfortunately, the report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products was received too late for the recommendations to be considered in the development of the emetic tentative final monograph (notice of proposed rulemaking) which was published in the **Federal Register** on September 5, 1978 (43 FR 39544). Therefore, FDA will consider that portion of this document which deals with ipecac syrup in promulgating the final rule for emetic drug products.

Ipecac syrup is frequently an integral part of acute toxic ingestion therapy. Additionally, ipecac syrup is marketed with activated charcoal in a kit for acute toxic ingestion. The Panel's recommendations regarding the labeling of ipecac syrup by itself are not incorporated into this advance notice of proposed rulemaking. Rather, this advance notice of proposed rulemaking refers to the tentative final monograph (notice of proposed rulemaking) for OTC emetic drug products (43 FR 39544) for required labeling of ipecac syrup. This advance notice of proposed rulemaking will deal with ipecac syrup only to the extent that it is used in conjunction with other drug products for the treatment of acute toxic ingestion.

The agency's position on OTC drug products for the treatment of acute toxic ingestion will be stated initially when the tentative final monograph is published in the **Federal Register** as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC drug products for the treatment of acute toxic ingestion. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing necessary, if any. Comments regarding the impact of this rulemaking on OTC drug products for the treatment of acute toxic ingestion should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC drug products used in the treatment of acute toxic ingestion submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person

submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to voluntarily comply with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the **Federal Register** of August 27, 1975 (40 FR 38179) a further notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of active ingredients in miscellaneous internal drug products to be considered in the OTC drug review. The list, which included ingredients for the treatment of acute toxic ingestion described as "universal antidotes," was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC review to all OTC drug products.

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous internal drug products:

John W. Norcross, M.D., Chairman
Ruth Eleanor Brown, R.Ph. (resigned May 1976)
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D.
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O.
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)
Diana F. Rodriguez-Calvert, Pharm. D. (appointed July 1976)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D. Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator. Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer. Joseph Hussion, R.Ph., served as the Drug Information Analyst unitl July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R. Ph.

To expand its medical and scientific base, the Panel called upon the following consultants for advice in areas which required particular expertise:

Carol R. Angle, M.D. (pediatrics)
Jay M. Arena, M.D. (pediatrics)
William A. MacColl, M.D. (pediatrics)
Lynn R. Brady, Ph. D. (pharmacognosy)
Arthur E. Schwarting, Ph. D. (pharmacognosy)
Ralph B. D'Agostino, Ph. D. (statistics)

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs; but due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for each drug category. The Panel presents its conclusions and recommendations for drug products used for the treatment of acute toxic ingestion in this document. The review of other categories of miscellaneous internal drug products is being continued by the Panel, and its findings are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Meetings at which drug products used for the treatment of acute toxic ingestion were discussed were held on the following dates: March 23 and 24, April 27 and 28, September 21 and 22, November 16 and 17, 1975; March 7 and 8, October 10 and 11, 1976; May 15 and 16, July 9, 10, and 11, 1977; January 28, 29, and 30, March 10, 11, and 12, May 5, 6, and 7, and June 23 and 24, 1978.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

John B. Johnson requested, and was given, an opportunity to appear before the Panel to express his views on activated charcoal used for the treatment of acute toxic ingestion. No other person requested an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and submitted data, has listened to additional testimony from an interested person, and has considered all pertinent data and information submitted through June 24, 1978 in arriving at its conclusions and recommendation for OTC drug products used for the treatment of acute toxic ingestion.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered OTC drug products for the treatment of acute toxic ingestion with respect to the following three categories:

Category I. Conditions under which OTC drug products used for the treatment of acute toxic ingestion are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC drug products used for the treatment of acute toxic ingestion are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed six active ingredients in drug products for the treatment of acute toxic ingestion and classified two ingredients in Category I, four ingredients in Category II, and no ingredients in Category III.

I. Submission of Data and Information

A. Submission by Firm

Pursuant to the notices published in the Federal Register of November 16, 1973 (39 FR 31696) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on OTC miscellaneous internal drug products, the following firm made a submission for a drug product used for the treatment of acute toxic ingestion.

Firm and marketed product

Bowman Pharmaceuticals, Inc., Canton, OH 44702—Poison antidote kit.

B. Labeled Ingredients Contained in Marketed Products

1. *Ingredients in products submitted to the Panel for review.*

Charcoal, activated
Ipecac syrup

2. *Other ingredients reviewed by the Panel.* In addition to those ingredients included in the product submitted to the Panel, the following ingredients were listed in the Federal Register notice of August 27, 1975 (40 FR 38179).

Alcohol
Magnesium hydroxide
Potassium arsenite
Tannic acid

C. Classification of Ingredients

1. *Active ingredients.*

Charcoal, activated
Ipecac syrup

2. *Inactive ingredients.* None.

3. *Other ingredients.* No submissions were received for the following ingredients. The Panel has not been able to locate, nor is it aware as a group of experts, of any data, published or unpublished, demonstrated the safety and effectiveness of these ingredients for OTC use in the treatment of acute toxic ingestion. The Panel therefore classifies these ingredients as Category II for this use, and they will not be reviewed in this document.

Alcohol
Magnesium hydroxide
Potassium arsenite
Tannic acid

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the Federal Register of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the submitted information is included in one volume which, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions of Terms

For the purpose of this document, the Panel agreed upon the following definitions:

1. *Acute toxic ingestion.* An ingestion, within a brief time, of a substance in amounts that could threaten the survival or well-being of an individual.

2. *Adjunct.* An accessory, auxiliary agent, or measure.

3. *Adsorption.* Adhesion of the molecules of a gas, liquid, or dissolved substance to a surface.

4. *Antidote.* A substance used to counteract a poison.

5. *Aspiration.* Inhalation of a foreign substance into the lungs.

6. *Emesis.* Vomiting.

7. *Emetic.* An agent that causes vomiting.

8. *Poison.* A substance ingested within a brief time in amounts that could threaten the survival or well-being of an individual.

9. *Toxic substance.* A poison.

B. General Discussion.

An estimated 2 million accidental poisonings occur in the United States each year (Ref. *1*), and about 60 percent of these poisonings involve children under 5 years of age (Ref. *2*). Therefore, it is obvious that extensive preventive measures are needed to reduce the incidence of accidental poisoning. When ingestion of a toxic substance occurs, means should be available to handle the situation until the patient can be treated by a physician.

The Panel is aware of the current OTC labeling regulation dealing with warning statements (21 CFR 330.1(g)). The Panel concurs with the warning, "Keep this and all drugs out of the reach of children," and believes that it should be incorporated in the labeling for digestive aid products. However, the Panel recommends that the other warning statement required by § 330.1(g). "In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately" be revised to read as follows: "In case of accidental overdose, contact a Poison Control Center, emergency medical facility, or physician immediately for advice." The Panel believes that this revision will be more informative to the consumer.

With the exception of corrosives such as strong acids and alkalies, the emergency treatment of poisoning is aimed at minimizing the absorption of the poison. This can be accomplished by interfering with the absorption of the

poison by the gastrointestinal tract or by removing the poison from the body as quickly as possible.

Upon discovering that a toxic substance has been ingested, a Poison Control Center, emergency medical facility, or physician should be called at once for advice. If medical consultation cannot be obtained immediately, the following procedure should be carried out:

1. The patient should be transported to the medical facility as soon as possible.

2. In most cases the poison should be removed from the patient's stomach immediately by inducing vomiting. However, vomiting should not be induced if the patient: (a) Is semiconscious or unconscious; (b) is having convulsions; (c) has swallowed strychnine, unless advised otherwise by a Poison Control Center, emergency medical facility, or physician; (d) has swallowed petroleum distillates such as kerosene, gasoline, paint thinner, or cleaning fluids, unless advised otherwise by a Poison Control Center, emergency medical facility, or physician; or (e) has swallowed a corrosive poison such as alkali (lye) or strong acid, unless advised otherwise by a physician or emergency treatment facility.

Vomiting may be induced by gently irritating the back of the patient's throat with the blunt end of a spoon or a finger or by using an emetic such as ipecac syrup. In the former method, before the vomiting reflex (gagging) is stimulated, the patient should drink one or two glasses of water (not milk or carbonated beverages) in order to dilute the toxic substance and provide a sufficient volume of gastric contents to be vomited. When retching and vomiting begin, the patient should be placed face down with head lower than hips. This position will prevent the vomitus from being aspirated into the lungs and causing further damage. Unfortunately, this mechanically induced vomiting is usually unsuccessful and incomplete (Ref. *3*).

When using ipecac syrup (not ipecac fluidextract) as an emetic, it should be given in doses of 1 to 2 teaspoonsful (5 to 10 milliliters (mL)) for children under 1 year of age (followed by ½ to 1 glass of water); children over 1 year old and adults should receive 1 tablespoonful (15mL) (followed by 1 to 2 glasses of water). Milk or carbonated beverages should not be used in place of water. If vomiting does not occur after 20 minutes, the dose should be repeated. The subject should be kept upright and ambulatory to speed emesis. A young child may be jiggled to speed emesis. If vomiting does not occur within 20 minutes of the second dose, the advice of a Poison Control Center, emergency medical facility, or physician should again be sought.

Vomiting should not be induced following the ingestion of most petroleum distillates because of the possibility of their being aspirated into the lung (Ref. *4*). However, there may be some cases of petroleum distillate ingestion in which the Poison Control Center, emergency medical facility, or physician will suggest that vomiting be induced.

Vomiting should also not be induced following the ingestion of acidic and alkaline corrosives because regurgitation would increase the damage to the esophagus. Large volumes of water of milk should be ingested to dilute the acidic or alkaline corrosive substances.

Chilling should be prevented by wrapping the patient in blankets, when necessary.

Alcohol in any form should not be given.

Activated charcoal should be given only after the patient vomits or when advised by a health professional. Activated charcoal acts by adsorbing a toxic substance and should not be given prior to the administration of ipecac syrup since it would adsorb the ipecac and negate its emetic action.

Although activated charcoal has a tremendous adsorptive capacity, it should be considered an adjunct for the treatment of an acute toxic ingestion rather than a specific antidote for any one poison. Following the administration of activated charcoal, a physician may still need to use specific antidotes to treat the particular poison.

The major drawback to the use of activated charcoal is its black color which often causes children not to want to ingest it. If spewed, it spots clothes and walls. The Panel, therefore, encourages the development of a palatable formulation which can be more easily administered to children.

Although activated charcoal is an effective, nonspecific adsorbent of a large number of materials, the Panel concurs with the general medical recognition that there is no true "universal antidote" (Ref. *5*). The so-called "universal antidote" recommended in the past consisted of activated charcoal, tannic acid, and magnesium oxide. However, it has been well established that the tannic acid and magnesium oxide have no significant effectiveness and may actually impede the effective ingredient, activated charcoal. The use of burnt toast as a homemade antidote has no merit. This material is not activated charcoal, and it has no significant adsorptive properties (Ref. *5*).

In many cases of accidental poisoning it is not possible to identify the substance ingested; but if the substance is known, the Poison Control Center, emergency medical facility, or physician will want this information along with the container in which the substance was stored to assist in determining the kind and amount of poison ingested and the appropriate treatment.

Although ipecac syrup is the primary mode of treatment of accidental poisoning in children, the Panel considers it rational to market ipecac syrup and activated charcoal in a combination package. The Panel has made specific recommendations in this document for the proper labeling of such a kit to encourage immediate home treatment under the direction of a physician or emergency medical facility.

Every physician treating children should have a supply of ipecac syrup and activated charcoal in his office.

References

(*1*) Arena, J. M., "The Treatment of Poisoning," *Clinical Symposia*, 30:1–47, 1978.

(*2*) National Clearinghouse for Poison Control Centers—Bulletin, U.S. Department of Health, Education, and Welfare, PHS, FDA, Bethesda, MD, February 1978.

(*3*) Arena, J. M., "Poisoning—Toxicology, Symptoms, Treatment," 2d Ed., Charles C. Thomas, Springfield, IL, p. 31, 1970.

(*4*) Arena, J. M., "Poisoning—Toxicology, Symptoms, Treatment," 2d Ed., Charles C. Thomas, Springfield, IL, p. 171, 1970.

(*5*) Done, A. K., "Poison Control," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol, and J. E. Hoover, Mack Publishing Co., Easton, PA, pp. 1830–1831, 1975.

C. Labeling

The Panel has reviewed the labeling claims made for ingredients offered for emergency treatment of acute toxic ingestion and has categorized them as either Category I, Category II, or Category III.

For any labeling to be acceptable, it must include the established name of the drug, an accurate statement of the pharmacological category of the drug, the net quantity of contents, the indications for use, pertinent warnings and contraindications, and the recommended dosage range. Only those indications and warnings listed under the specific ingredient discussions are generally recognized as acceptable at this time.

The Panel believes that all labeling should be clear, concise, and easily readable and understandable by most consumers, including those whose

comprehension is limited. The Panel follows this concept in the development of Category I labeling. The Panel is also concerned about the size and color of the print used in labeling of these and all drug products, and recommends that the industry design labeling which can be read easily by consumers.

The Panel believes that the label should contain the active ingredient by its established name, and the label should state the quantity of the active ingredient in the recommended dosage.

The Panel recommends that drug product labeling contain directions for use which are intended to facilitate the delivery and availability of the active ingredient, and that these directions be prominently displayed on all package labeling.

The Panel agrees with the current OTC labeling regulation on warning statements at 21 CFR 330.1(g) and recommends that labeling for drug products used to treat acute toxic ingestion contain a "Warnings" section which contains the following statement in addition to any drug-specific warnings: "Keep this and all drugs out of the reach of children." The Panel believes that the other warning required by this regulation should not be required for these products, i.e., "In cases of accidental ingestion, seek professional assistance or contact a poison control center immediately."

In order to facilitate administration in emergency situations, activated charcoal should be packaged in containers designed to deliver a minimum of 30 grams (g). The amount of contents should be conspicuously displayed on the front panel of the package label. The person administering the activated charcoal would then have a better idea of the actual amount to give to the patient.

To remove as much of the toxic substance as possible from the stomach, it is essential that vomiting, when indicated, be induced prior to the administration of activated charcoal. If activated charcoal is administered before ipecac syrup, the ipecac will be adsorbed by the activated charcoal and inactivated.

If vomiting does not occur within 20 minutes after the first dose of ipecac syrup, the dose should be repeated. If vomiting does not occur within 20 minutes after the second dose, it is imperative that medical advice be obtained to determine what further procedures should be followed to remove or detoxify the ingested poison.

Labeling for ipecac syrup must contain a warning not to give this drug product if strychnine, corrosive poisons, or petroleum distillates have been ingested unless advised otherwise by a physician or emergency medical facility. The reasons for this warning are contained in the "General Discussion." (See part II. paragraph B. above—General Discussion.)

Milk must not be administered along with ipecac syrup because its coating action on the gastrointestinal tract and its ability to inactivate the ipecac alkaloids through its protein binding action would prevent the ipecac syrup from acting. Carbonated beverages should not be administered with ipecac syrup because they may cause over-distention of the stomach.

III. Categorization of Data

A. Category I Conditions

The following are Category I conditions under which drug products for the treatment of acute toxic ingestion are generally recognized as safe and effective and not misbranded.

1. *Category I active ingredients.*

Charcoal, activated
Ipecac syrup

a. *Charcoal, activated.* The Panel concludes that activated charcoal is safe and effective for OTC use in the treatment of acute toxic ingestion as discussed below.

Wood charcoal is made by burning wood out of contact with the air—the residue obtained consists of nearly pure carbon (Ref. *1*). This process is called destructive distillation. The carbon resulting from destructive distillation can also be obtained from nut shells, animal bones, or other carbonaceous material (Ref. *2*). Charcoal made by this process results in a product with varied adsorptive properties. It is "activated" by treating it with various substances such as steam, air, carbon dioxide, oxygen, zinc chloride, sulfuric acid, phosphoric acid, or a combination of some of these substances at temperatures ranging from 500° to 900° C (Ref. *1*). This treatment produces a very porous, honeycomblike internal structure formed by removing substances previously adsorbed on the charcoal. The internal surface area of activated charcoal averages about 10,000 square feet per g (Ref. *2*).

(1) *Safety.* The Panel concludes that activated charcoal is generally recognized as a safe gastrointestinal adsorbent for ingested poisons when used in the doses noted below.

Activated charcoal has been used since 1960 in uremic patients to reduce the gastrointestinal disturbances of the patient. A dose of 20 to 50 g of activated charcoal was given daily, and no side effects were observed during continuous treatment for 4 to 20 months (Ref. *3*).

Considering the above information and the fact that activated charcoal has been in use for over 150 years (Ref. *4*), the Panel concludes that activated charcoal is generally recognized as a safe gastrointestinal adsorbent for oral administration in the treatment of acute toxic ingestion.

(2) *Effectiveness.* The Panel concludes that activated charcoal is an effective gastrointestinal adsorbent that is widely used for the emergency treatment of acute toxic ingestion of a variety of drugs and toxic agents.

In treating an acute toxic ingestion, activated charcoal should only be used after first contacting a Poison Control Center, emergency medical facility, or a physician. It should generally be restricted to administration following emesis, which is usually induced by the ingestion of ipecac syrup.

Decker, Combs, and Corby (Ref. *5*) have demonstrated in vitro that the adsorption capacity of activated charcoal varies considerably according to the chemical acted on. They found that activated charcoal very efficiently adsorbed high doses of dextroamphetamine sulfate, primaquine phosphate, chlorpheniramine maleate, colchicine, diphenylhydantoin, aspirin, and propoxyphene hyrdochloride. Iodine, phenol, and, to a lesser degree, methyl salicylate were quite well adsorbed. Quinacrine, meprobamate, chlorpromazine, quinine, chloroquine, quinidine, and glutethimide were less efficiently adsorbed by activated charcoal; and inorganic acids, certain alkalies (sodium and potassium hydroxides), and sodium metasilicate (active ingredient in many cleaning preparations) were not adsorbed to any measurable extent. It was observed that the adsorptive capacity did not seem to correlate with chemical structure, although highly ionic substances of low molecular weight, such as cupric copper, ferrous iron, and boric acid, were very poorly adsorbed by activated charcoal. Drugs which are solids and insoluble in acidic aqueous solutions were likewise not adsorbed, e.g., tolbutamide. The insecticides malathion, DDT, and *N*-methylcarbamate were quite poorly adsorbed.

Picchioni, Chin, and Laird (Ref. *6*) list about 30 toxic substances which have been demonstrated to be effectively adsorbed in vivo (in man and animals) by activated charcoal. Some of the more significant ones are aspirin and other salicylates, propoxyphene, amphetamine, acetaminophen, barbiturates (barbital, phenobarbital, pentobarbital, and secobarbital), glutethimide, ethchlorvynol,

chlorpromazine, chlordane, hexachlorophene, kerosene, malathion, mercuric chloride, methyl salicylate, phenylopropanolamine, and strychnine. In addition, Decker (Ref. *7*) mentions the usefulness of activated charcoal in adsorbing tricyclic antidepressants (nortriptyline and imipramine) by interrupting enterohepatic recycling.

Originally it was felt that the activated charcoal and toxic substance complex which was formed in the stomach may possibly dissociate as it passes through the gastrointestinal tract. Recent studies indicate that the competitive effects of other constituents of the gastrointestinal fluids and associated higher pH may cause minimal dissociation to occur during the passage through the gastrointestinal tract (Ref. *7*). However, from a practical standpoint, this effect is inconsequential since it is markedly diminished with increasing doses of activated charcoal (Ref. *7*). It has also been demonstrated that, although the absorption of salicylate, barbiturate, and glutethimide was significantly reduced in rats and dogs, the activated charcoal-drug complexes were not dissociated to any significant extent in the gastrointestinal tract (Ref. *4*).

When possible, activated charcoal should be administered within 30 minutes following ingestion of the toxic substance to achieve significant inhibition of the drug absorption, although it has been shown that charcoal can "catch up" and bind certain poisons which have already passed through the pylorus (the opening through which the stomach contents are emptied into the upper intestine). Considering this, activated charcoal should be administered after ipecac syrup when large amounts of toxic substances have been ingested (Ref. *7*).

Corby, Fiser, and Decker (Ref. *4*) observed that activated charcoal can be a very valuable adjunct in the initial phases of treating acute toxic ingestion of many drugs not only in the emergency room and during the course of treatment in a hospital, but also as a first aid measure in the home.

The Panel recommends that for ease of administration, the activated charcoal be packaged in premeasured units with a minimum quantity of 30 g. If the quantity of the ingested toxic substance is known, it is generally considered that an amount of activated charcoal that is 8 to 10 times the amount of toxic substance should be administered. Otherwise, the recommended dosage of 30 g (6 level tablespoonsful) should be given.

It is obviously important to get as much activated charcoal into the patient as possible and as soon as possible after administration of ipecac syrup has produced vomiting. The Panel is aware of the difficulties in administration of this powdery substance and, therefore, encourages the development of a palatable form, such as a combination of activated charcoal and an inactive vehicle, e.g., carboxymethylcellulose, a highly activated charcoal requiring a lower dose, or coated charcoal particles. If such forms are developed, the adsorption capacity of the labeled dose must be expressed in terms of activated charcoal and determined in vivo.

The Panel recognizes that activited charcoal varies in its adsorptive capacity, but concludes that it is generally recognized as effective in the treatment of acute toxic ingestion.

(3) *Dosage.* The minimum effective dose of activated charcoal varies with the toxic dose of each substance and with several other variables, e.g., retained food, gastric emptying, and solubility. For most compounds, 5 to 10 g of activated charcoal are needed to adsorb 1 g. A theoretical dose of 20 g is required to adsorb the fatal adult dose of 2 g of phenobarbital; 30 g would be required to adsorb the toxic dose of 3 g of salicylates in a preschool child; and 500 g would be required for the fatal adult dose of 50 g of acetaminophen. In view of the wide dose range of activated charcoal and the lack of literature references as to the optimum dose, the Panel recommends that activated charcoal be used in doses, of no less than 30 g (6 level tablespoonsful) mixed with ½ glassful of water. The only upper limit on the amount which can be ingested would be governed by the feasibility of administration.

(4) *Labeling.* The Panel recommends the following labeling for activated charcoal:

(i) *Indication.* "For the treatment of acute poisoning."

(ii) *Warnings.* (*a*) "Before using, call a Poison Control Center, emergency medical facility, or physician for advice." This warning should be conspicuously boxed and in red letters.

(*b*) "Do not use in semiconscious or unconscious persons."

(*c*) "If the patient has received ipecac syrup, do not administer activated charcoal until after the patient has vomited, except under the advice and supervision of a physician.

(iii) *Directions.* "Mix 6 level tablespoonsful (30 g) in ½ glassful (4 ounces) of water. Drink entire contents of glass after mixing."

References

(*1*) Swinyard, E. A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA. p. 751, 1975.

(*2*) Hawley, G. G., "The Condensed Chemical Dictionary," 8th Revised Ed., Van Nostrand Reinhold Co., New York, p. 168, 1971.

(*3*) Yatzidis, H., "Activated Charcoal Rediscovered," (letter to Editor), *British Medical Journal*, 4:51, 1972.

(*4*) Corby, D. G., R. H. Fiser, and W. J. Decker, "Re-Evaluation of the Use of Activated Charcoal in the Treatment of Acute Poisoning," *Pediatric Clinics of North America*, 17:545–556, 1970.

(*5*) Decker, W. J., H. F. Combs, and D. G. Corby, "Adsorption of Drugs and Poisons by Activated Charcoal," *Toxicology and Applied Pharmacology*, 13:454–460, 1968.

(*6*) Picchioni, A. L., L. Chin, and H. E. Laird, "Activated Charcoal Preparations—Relative Antidotal Efficacy," *Clinical Toxicology*, 7:97–108, 1974.

(*7*) Corby, D. G., and W. J. Decker, "Management of Acute Poisoning with Activated Charcoal," *Pediatrics*, 54:324–328, 1974.

b. *Ipecac syrup.* The Panel is aware that ipecac syrup has previously been reviewed by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products and that the FDA is developing the tentative final monograph (TFM) on emetic drug products. This Panel feels that the final monograph for ipecac syrup should contain the following information:

The active ingredients of ipecac syrup are the alkaloids emetine and cephaeline contained in powered ipecac. The product is packaged and marketed as ipecac syrup, United States Pharmacopeia (USP) XIX, in a 1 fluid ounce (30 mL) container or in ½ fluid ounce (15 mL) containers for use in acute toxic ingestion kits.

(1) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the phrase "to cause vomiting (emesis) in case of poisoning." This phrase should be conspicuously boxed and in red letters.

(2) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings":

(i) "Call a Poison Control Center, emergency medical facility, or physician for advice before using and if vomiting does not occur within 20 minutes after a second dose has been given." This warning should be conspicuously boxed and in red letters.

(ii) "Do not use in semiconscious, unconscious, or convulsing persons."

(iii) "This product should not be used if strychnine, corrosives such as alkalies (lye) and strong acids, or petroleum distillates such as kerosene, gasoline, paint thinner, or

cleaning fluid have been ingested, unless advised otherwise by a physician."

(iv) "Do not administer milk or carbonated beverages with this product."

(3) The warning required by the current regulation § 330.1(g) (21 CFR 330.1(g)) concerning overdoses should not be required on ipecac syrup products.

(4) *Drug interaction precautions.* The labeling of the product should contain the following statement under the heading "Drug Interaction Precautions": "Activated charcoal will adsorb the active ingredients of ipecac syrup. If both activated charcoal and ipecac syrup are used, give the activated charcoal only after vomiting has been produced by the ipecac syrup."

(5) *Directions.* The labeling of the product should contain the following statements under the heading "Directions":

(i) *Infants under 1 year of age:* Oral dosage of ipecac syrup is 1 teaspoonful (5 milliliters) to a maximum of 2 teaspoonsful (10 milliliters) followed by ½ to 1 glass of water (4 to 8 ounces) or as directed by a physician. If vomiting does not occur within 20 minutes, the dose should be repeated one.

(ii) *Infants over 1 year of age, children, and adults:* Oral dosage of ipecac syrup is 1 tablespoonful (15 milliliters) followed by 1or 2 glasses of water (8 to 16 ounces) or as directed by a physician. If vomiting does not occur within 20 minutes, the dose should be repeated once.

2. *Acute toxic ingestion kit.* The Panel recognizes that it would be in the consumer's interest to establish guidelines for the minimum components of a kit used for the treatment of acute toxic ingestion. It is suggested that the kit contain four containers of 15 mL each of ipecac syrup and two containers of 30 g each of activated charcoal. The activated charcoal containers should be of sufficient size to permit the mixing of 4 ounces of water with the activated charcoal and be equipped with a screw cap so that the mixture can be shaken without spilling.

a. *Labeling.* The following labeling is specific for the outside container of the kit alone:

(1) *Indications.* "For the treatment of acute poisoning."

(2) *Warnings.* (i) "Before using, call a Poison Control Center, emergency medical facility or physician for advice." This warning should be conspicuously boxed and in red letters.

(ii) "Do not use in semiconscious or unconscious persons."

b. *Directions.* (1) "When professional advice is not available, first give ipecac syrup to induce vomiting, after vomiting has occurred give activated charcoal to help adsorb any remaining toxic substance."

(2) In bold-faced print "READ INSTRUCTIONS AT TIME OF PURCHASE AND INSERT PHONE NUMBERS ON LABEL."

(3) "Save the container of the poison."

(4) An area of prominence should be provided to enter the telephone numbers of the Poison Control Center ———, emengency medical facility ———, personal physician ———, and ambulance ———.

B. Category II and Category III Conditions

The ingredients classified as Category II are listed in part I. paragraph C.3. above. The Panel found no Category III conditions. Therefore, Category II and III conditions will not be discussed in this document.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding to Part 357, a new Subpart A, to read as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—Drug Products for Over-the-Counter Human Use for the Treatment of Acute Toxic Ingestion

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—Drug Products for Over-the-Counter Human Use for the Treatment of Acute Toxic Ingestion

§ 357.1 Scope.

(a) An over-the-counter drug product for the treatment of acute toxic ingestion in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 357.3 Definitions.

As used in this subpart:

(a) *Acute toxic ingestion.* An ingestion, within a brief time, of a substance in amounts that could threaten the survival or well-being of an individual.

(b) *Emesis.* Vomiting.

(c) *Emetic.* An agent that causes vomiting (emesis).

§ 357.10 Active ingredients for the treatment of acute toxic ingestion.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient:

(a) Charcoal, activated.

(b) Ipecac syrup.

§ 357.14 Acute toxic ingestion kit.

The kit is a single outer package labeled according to § 357.54 that consists of two 30-gram containers of activated charcoal identified in § 357.10(a) and labeled according to § 357.50 and four 15-milliliter containers of ipecac syrup identified in § 357.10(b) and labeled according to § 357.52. The containers of activated charcoal enclosed within the kit are of sufficient size to permit the addition of 4 ounces (120 milliliters) of water and are equipped with screw top caps to facilitate mixing of the contents.

§ 357.50 Labeling of drug products containing activated charcoal identified in § 357.10(a) for the treatment of acute toxic ingestion.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "adsorbant."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the

phrase: "For the treatment of acute poisoning."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "Before using, call a poison control center, emergency medical facility, or physician for advice." This warning should be conspicuously boxed and in red letters.

(2) "Do not use in semiconscious or unconscious persons."

(3) "If the patient has received ipecac syrup, do not administer activated charcoal until after the patient has vomited, except under the advice and supervison of a physician.

(4) The warning required by § 330.1(g) concerning overdoses is not required on products containing activated charcoal.

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": "Mix 6 level tablespoonsful (30 grams) in ½ glassful (4 ounces) of water. Drink entire contents of glass after mixing."

§ 357.52 Labeling of drug products containing ipecac syrup identified in § 357.10(b) for the treatment of acute toxic ingestion.

The product contains the labeling identified in proposed § 337.50 for emetic drug products. (See the **Federal Register** of September 5, 1978 (43 FR 39546).)

§ 357.54 Labeling of acute toxic ingestion kit identified in § 357.14 for the treatment of acute toxic ingestion.

In addition to the labeling identified in § 357.50 required on containers of activated charcoal and the labeling identified in § 357.52 required on containers of ipecac syrup, the outer label of the acute toxic ingestion kit bears the following:

(a) *Statement of identity.* The labeling on the outside of the kit contains the established names of the drugs, if any, and identifies the product as an "acute toxic ingestion treatment kit."

(b) *Indications.* The labeling on the outside of the kit contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "For the treatment of acute poisoning."

(c) *Warnings.* The labeling on the outside of the kit contains the following warnings under the heading "Warnings":

(1) "Before using, call a Poison Control Center, emergency medical facility, or physician for advice." This warning should be conspicuously boxed and in red letters.

(2) "Do not use in semiconscious or unconscious persons."

(3) The warning required by § 330.1(g) concerning overdoses is not required on products containing activated charcoal and ipecac syrup.

(d) *Directions.* The labeling on the outside of the kit contains the following information under the heading "Directions":

(1) "When professional advice is not available, first give ipecac to indice vomiting, after vomiting has occurred give activated charcoal to help absorb any remaining toxic substance."

(2) (In bold-faced print) "READ INSTRUCTIONS AT TIME OF PURCHASE AND INSERT PHONE NUMBERS ON LABEL."

(3) "Save the container of the poison."

(e) *Other required statements.* An area of prominence should be provided to enter the telephone numbers of the following: "Poison Control Center ," "emergency medical facility ," "personal physician ," "ambulance ."

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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