

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 from 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 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 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 9484). 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 31897). (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 1978, 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 zyxolin. 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 07882—Mercurochrome.

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

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

Eli Lilly and Co., Indianapolis, IN 46208—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
Zyxolin

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
Zyxolin

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.

References

- (1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, N.J., pp. 766-767, 1976.
- (2) Fisher, A., "Contact Dermatitis," 2d Ed., Lea & Febiger, Philadelphia, p. 299, 1973.
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- (4) Harvey, S. S., "Heavy Metals," in "The Pharmacological Basis of Therapeutics," 6th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 975-976, 1980.
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- (6) Fildes, P., "The Mechanism of the Antibacterial Action of Mercury," *British Journal of Experimental Pathology*, 21:67-73, 1940.
- (7) Brewer, J. H., "Clear Liquid Media for the 'Aerobic' Cultivation of Anaerobes," *Journal of Bacteriology*, 39:10, 1940.

(8) Brewer, J. H., "A Clear Liquid Medium for the 'Aerobic' Cultivation of Anaerobes," (Abstract), *Journal of the American Medical Association*, 115:598-600, 1940.

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(10) Morton, H. E., L. L. North, Jr., and F. B. Engley, Jr., "In Vivo and In Vitro Studies on the Bacteriostatic and Bactericidal Actions of Mercurial Disinfectants on Hemolytic Streptococci," (Abstract), *Journal of Bacteriology*, 50:125-126, 1945.

(11) Morton, H. E., L. L. North, Jr., and F. B. Engley, Jr., "The Bacteriostatic and Bactericidal Actions of Some Mercurial Compounds on Hemolytic Streptococci. In Vivo and In Vitro Studies," *Journal of the American Medical Association*, 136:37-41, 1948.

(12) Smith, A., "Organomercurial Compounds, Report to the Council on Pharmacy and Chemistry," *Journal of the American Medical Association*, 138:36, 1948.

(13) Brewer, J. H., "The Present Status of the Sterility of Catgut Sutures on the American Market," *Journal of the American Medical Association*, 108:722-727, 1937.

(14) Richards, J. P., and A. E. E. El Khouly, "The Recovery of Phenylmercuric Nitrate-treated Bacteria Using Sodium Thioglycollate," *Journal of Pharmacy and Pharmacology, (Supplement)*, 19:209S-215S, 1967.

(15) Smith, D. E., E. J. Czarnetzky, and S. Mudd, "The Mechanism of Inactivation of Mercurial Antiseptics by Serum, and Its Implications Regarding the Possibility of Intravenous Antiseptics," *American Journal of Medical Sciences*, 192:790-808, 1936.

(16) Birkhaug, K. E., "Phenyl-mercuric-nitrate," *Journal of Infectious Diseases*, 53:250-261, 1933.

(17) Engley, F. B., Jr., "Mercurials as Disinfectants. Evaluation of Mercurial Antimicrobial Action and Comparative Toxicity for Skin Tissue Cells," *Soap and Chemical Specialties*, 30:199-205 and 223-225, 1956.

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. 19) 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 strong 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 28 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 28 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 thimerosal 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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(19) OTC Volume 180271.

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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