room temperature or replaced with one that is at normal room temperature.

(e) *Laundering.* If the carpet or rug has had a fire-retardant treatment, or is made of fibers which have a fire-retardant treatment, the selected sample or oversized specimens thereof shall be washed, prior to cutting of test specimens, either 10 times under the washing and drying procedure prescribed in Method 124–1967 of the American Association of Textile Chemists and Colorists [washing procedure 6.2 (III) with a water temperature of 60±2.8° C. (140±5° F.) drying procedure 6.3.2(B), maximum load 3.64 kg. (8 pounds)][3], or such number of times under such other washing and drying procedure as shall previously have been found to be equivalent by the Federal Trade Commission. Alternatively, the selected sample or oversized specimens thereof may be washed, dry cleaned, or shampooed 10 times, prior to cutting of test specimens, in such manner as the manufacturer or other interested party shall previously have established to the satisfaction of the Federal Trade Commission is normally used for that type of carpet or rug in service. Under the rules and regulations which may be established by the Federal Trade Commission, the laundry requirement may be modified or waived by FTC where it is shown that laundering does not affect the flame-retardant treatment.

.6 *Labeling requirements.* If the carpet or rug has had a fire-retardant treatment or is made of fibers which have had a fire-retardant treatment, it shall be labeled with the letter "T" pursuant to conditions established by the Federal Trade Commission.

[FR Doc.73–4269 Filed 3–2–73;10:40 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[FAP 1B2682]

ALLIED COLLOIDS, INC.

Withdrawal of Petition for Food Additives

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409 (b), 72 Stat. 1786); 21 U.S.C. 348(b)), the following notice is issued:

In accordance with § 121.52 *Withdrawal of petitions without prejudice* of the procedural food additive regulations (21 CFR 121.52), Allied Colloids, Inc., 1 Robinson Lane, Ridgewood, NJ 07450, has withdrawn its petition (FAP 1B2682), notice of which was published in the FEDERAL REGISTER of June 29, 1971 (36 FR 12246), proposing that § 121.2526 *Components of paper and paperboard in contact with aqueous and fatty foods* (21 CFR 121.2526) be amended to provide for the safe use of sodium polyacrylate as a dispersant of pigments used in the manufacture of paper and paperboard for contact with aqueous and fatty foods.

Dated: February 26, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73–4332 Filed 3–6–73;8:45 am]

[3] Technical Manual of the American Association of Textile Chemists and Colorists, Vol. 45, 1969, published by AATCC, Post Office Box 12215, Research Triangle Park, NC 27709.

[Docket No. FDC–D–589; NADA No. 30–704V]

BEECHAM-MASSENGILL PHARMACEUTICALS

Daribiotic Improved; Notice of Withdrawal of Approval of New Animal Drug Application

Beecham-Massengill Pharmaceuticals, Division of Beecham, Inc., Bristol, Tenn. 37620 was informed that the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 512(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(3)) withdrawing approval of NADA (new animal drug application) No. 30–704V with respect to the use of Daribiotic Improved. The drug is administered by intramammary infusion to cows for the treatment and prevention of acute or chronic mastitis; each 25 cc. dose contains 200 milligrams of neomycin sulfate (equivalent to 140 milligrams of standard neomycin base) and 50,000 units of polymyxin B sulfate in an aqueous milk-miscible base. Labeling includes a statement that milk taken from animals during treatment and within 72 hours (6 milkings) after treatment not be used for food.

The Commissioner, on the basis of new information before him with respect to such drug evaluated together with the evidence available to him when the application was approved, concludes that the drug is not shown to be safe under the conditions of use upon the basis of which the application was approved.

Information available to the Commissioner has established that residues of neomycin exceeding the tolerance of 0.15 part per million (negligible residue provided by 21 CFR 135g.25) are present in milk taken from animals in which the drug has been used as directed in the labeling. Available evidence also established that residues of neomycin are present 120 hours following treatment. Section 135.103 (21 CFR 135.103), which provides for label requirements for new animal drugs intended for intramammary use in milk-producing animals, limits the maximum milk discard period to 96 hours. Accordingly, there cannot be approved for the subject drug labeling which would ensure the absence of neomycin residues in milk when the drug is labeled for use in lactating animals.

Beecham-Massengill Pharmaceuticals upon being informed of the Commissioner's intent to issue a notice of opportunity for a hearing proposing issuance of an order to withdraw approval of the subject new animal drug application waived the right to such a hearing and requested that the application be withdrawn.

Based on the firm's request and the findings set forth above, the Commissioner concludes that approval of new animal drug application No. 30–704V should be withdrawn. Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 512(e), 82 Stat. 345–47; 21 U.S.C. 360b(e)) and under the authority delegated to the Commissioner (21 CFR 2.120), approval of new animal drug application No. 30–704V including all amendments and supplements thereto is hereby withdrawn effective on February 26, 1973.

Dated: February 26, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.73–4326 Filed 3–6–73;8:45 am]

[GRASP 2G0005]

FISHER, CHRISTEN, AND SABOL

Notice of Filing of Petition for Affirmation of GRAS Status

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784–1786; 21 U.S.C. 321(s), 348, 371(a)) and the regulations for affirmation of GRAS status (21 CFR 121.40), published in the FEDERAL REGISTER of December 2, 1972 (37 FR 25705), notice is given that a petition (GRASP 2G0005) has been filed by Fisher, Christen, and Sabol, Suite 507–511, 1000 Connecticut Avenue NW., Washington, DC 20036, and placed on public display at the office of the Hearing Clerk, Food and Drug Administration, proposing affirmation that magnesium acetate (350 mg. magnesium per 40 fluid ounces) and zinc acetate (10 mg. zinc per 40 fluid ounces) used in a vitamin—mineral food supplement, are generally recognized as safe (GRAS).

Interested persons may, on or before May 7, 1973, review the petition and/or file comments (preferably in quintuplicate) with the Hearing Clerk, Department of Health, Education, and Welfare, Food and Drug Administration, Room 6–88, 5600 Fishers Lane, Rockville, MD 20852. Comments should include any available information that would be helpful in determining whether the substance is, or is not, generally recognized as safe. A copy of the petition and received comments may be seen in the office of the Hearing Clerk, address given above, during working hours, Monday through Friday.

Dated: February 25, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73–4327 Filed 3–6–73;8:45 am]

[GRASP 3G0010]

FOREMOST-McKESSON, INC.

Notice of Filing of Petition for Affirmation of GRAS Status

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784–1786; 21 U.S.C. 321(s), 348, 371(a)) and the regulations for affirmation of GRAS status (21 CFR 121.40), published in the FEDERAL REGISTER of December 2, 1972 (37 FR 25705), notice is given that a petition (GRASP 3G0010) has been filed by Foremost-McKesson, Inc., Crocker Plaza, One Post Street, San Francisco, CA 94104, and placed on public display at the office of the Hearing Clerk, Food and Drug Administration, proposing affirmation that addition of l-cysteine to yeast-leavened bakery

products at a level not to exceed 0.009 part for each 100 parts flour for reducing fermentation time and improving the dough is generally recognized as safe (GRAS) for use in food.

Interested persons may, on or before May 7, 1973, review the petition and/or file comments (preferably in quintuplicate) with the Hearing Clerk, Department of Health, Education, and Welfare, Food and Drug Administration, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852. Comments should include any available information that would be helpful in determining whether the substance is, or is not, generally recognized as safe. A copy of the petition and received comments may be seen in the office of the Hearing Clerk, address given above, during working hours, Monday through Friday.

Dated: February 25, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-4328 Filed 3-6-73;8:45 am]

[GRASP 3G0011]

FOREMOST-McKESSON, INC.

Filing of Petition for Affirmation of GRAS Status

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201 (s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1786; 21 U.S.C. 321(s), 348, 371(a)) and the regulations for affirmation of GRAS status (21 CFR 121.40), published in the FEDERAL REGISTER of December 2, 1972 (37 FR 25705), notice is given that a petition (GRASP 3G0011) has been filed by Foremost-McKesson, Inc., Crocker Plaza, One Post Street, San Francisco, CA 94104, and placed on public display at the office of the Hearing Clerk, Food and Drug Administration, proposing affirmation that whey fractions consisting of demineralized whey, delactosed whey, and demineralized-delactosed whey used in food products are generally recognized as safe (GRAS) for use in food.

Interested persons may, on or before May 7, 1973, review the petition and/or file comments (preferably in quintuplicate) with the Hearing Clerk, Department of Health, Education, and Welfare, Food and Drug Administration, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852. Comments should include any available information that would be helpful in determining whether the substance is, or is not, generally recognized as safe. A copy of the petition and received comments may be seen in the office of the Hearing Clerk, address given above, during working hours, Monday through Friday.

Dated: February 25, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-4329 Filed 3-6-73;8:45 am]

[FAP 3B2878]

HAZLETON LABORATORIES, INC.

Filing of Petition for Food Additive

Pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5), 72 Stat. 1786; 21 U.S.C. 348(b)(5)), notice is given that a petition (FAP 3B2878) has been filed by Hazleton Laboratories, Inc., 9200 Leesburg Turnpike, Vienna, VA 22180, proposing that § 121.2520 *Adhesives* (21 CFR 121.2520) be amended to provide for the safe use of trisnonyl phenyl phosphite/formal dehyde polymer as a stabilizer in food-packaging adhesives.

Dated: February 26, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-4333 Filed 3-6-73;8:45 am]

[GRASP 2G0004]

OLIN CHEMICALS

Filing of Petition for Affirmation of GRAS Status

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1786; 21 U.S.C. 321(s), 348, 371(a)) and the regulations for affirmation of GRAS status (21 CFR 121.40), published in the FEDERAL REGISTER of December 2, 1972 (37 FR 25705), notice is given that a petition (GRASP 2G0004) has been filed by Olin Chemicals, 120 Long Ridge Road, Stamford, CT 06904, and placed on public display at the office of the Hearing Clerk, Food and Drug Administration, proposing affirmation that 0.5 p.p.m. calcium hypochlorite used in live oyster-conditioning water is generally recognized as safe (GRAS).

Interested persons may, on or before May 7, 1973, review the petition and/or file comments (preferably in quintuplicate) with the Hearing Clerk, Department of Health, Education, and Welfare, Food and Drug Administration, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852. Comments should include any available information that would be helpful in determining whether the substance is, or is not, generally recognized as safe. A copy of the petition and received comments may be seen in the office of the Hearing Clerk, address given above, during working hours, Monday through Friday.

Dated: February 25, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-4330 Filed 3-6-73;8:45 am]

[Docket No. FDC-D-607; NADA No. 8-689V]

PFIZER, INC.

Oxytetracycline With or Without Vitamin A; Withdrawal of Approval of New Animal Drug Application

In the FEDERAL REGISTER of August 25, 1970 (35 FR 13542, DESI 8689B), the Commissioner of Food and Drugs announced the conclusions of the Food and Drug Administration following evaluation of a report received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group on Terramycin Animal Formula Tablets and Terramycin Bolus with Vitaman A, new animal drug application (NADA) No. 8-689V; marketed by Pfizer, Inc., 235 East 42d Street, New York, NY 10017.

Pfizer, Inc., responded to the announcement by waiving an opportunity for a hearing and requesting that approval of NADA No. 8-689V be withdrawn.

Based on the grounds set forth in said announcement and the firm's response, the Commissioner concludes that approval of said new animal drug application should be withdrawn. Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 512, 82 Stat. 343-351; 21 U.S.C. 360(b) and under authority delegated to the Commissioner (21 CFR 2.120), approval of NADA No. 8-689V, including all amendments and supplements thereto, is hereby withdrawn effective on March 7, 1973.

Dated: February 23, 1973.

WILLIAM F. RANDOLPH,
Acting Associated Commissioner for Compliance.

[FR Doc.73-4331 Filed 3-6-73;8:45 am]

Food and Drug Administration

[Docket No. FDC-D-448; NDA 5-933; DESI-5933]

COOPER LABORATORIES, INC.

Bistrimate; Final Order on Objections and Request for a Hearing Regarding Withdrawal of Approval of New Drug Application

In an announcement published in the FEDERAL REGISTER of August 25, 1970 (35 FR 13541), the Commissioner of Food and Drugs announced his conclusions pursuant to the evaluation of a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on Bistrimate Tablets (NDA 5-933) containing bismuth sodium triglycollamate. The holder of the new drug application at that time was Smith, Miller and Patch, Inc., 401 Joyce Kilmer Avenue, New Brunswick, New Jersey 08902. The present holder of the new drug application is Cooper Laboratories, Inc., 2900 North 17th Street, Philadelphia, Pennsylvania 19132.

The announcement stated that there is a lack of substantial evidence that the drug Bistrimate is effective for its labeled indications, and that the Commissioner intended to initiate proceedings to withdraw approval of the new drug application for the drug. Interested persons were invited to submit any pertinent data bearing on the proposal within 30 days following publication of the announcement. Material submitted

by Smith, Miller and Patch in response to the announcement was reviewed and found not to provide substantial evidence of effectiveness.

As a result of this review, on September 13, 1971, Smith, Miller and Patch, Inc., was notified by letter that the Commissioner intended to initiate proceedings to withdraw approval of the new drug application.

Subsequently, on June 6, 1972, there was published in the FEDERAL REGISTER (37 FR 11284), a notice to Smith, Miller and Patch, Inc., holder of NDA 5-933 for Bistrimate Tablets, and to any interested person who may be adversely affected, that the Commissioner of Food and Drugs proposed to issue an order withdrawing approval of said application, and all amendments and supplements thereto, on the ground that new information before him with respect to the drug, evaluated together with the evidence available to him when the application was approved, shows there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. The notice provided an opportunity for hearing on withdrawal of the new drug application for Bistrimate (NDA 5-933). Thirty days were allowed for filing a written appearance requesting a hearing by the applicant or any interested person who would be adversely affected by an order withdrawing approval of the application, giving the reasons why approval of the new drug application should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data they were prepared to prove in support of their opposition.

On July 5, 1972, a written appearance and request for a hearing was submitted by Cooper Laboratories, Inc., the current holder of the new drug application (NDA 5-933). Submitted with the request was a statement of grounds including the medical documentation relied upon, legal arguments, and an affidavit.

The medical presentation of Cooper Laboratories, Inc., has been considered, and the Commissioner of Food and Drugs concludes that there is no genuine and substantial issue of fact requiring a hearing and that the legal arguments offered are insubstantial, all as explained in more detail below.

I. *The drug.* Bistrimate is the sodium bismuth salt of triglycollamic acid combined with three equivalents of disodium triglycollamate to form a double salt-like compound. It contains 18.3 percent metallic bismuth.

II. *Recommended uses.* Bistrimate is a prescription drug recommended for use in treatment of chronic sore throat and syphilis. It is recommended for administration in tablets equivalent to 75 mgs. of metallic bismuth each. The administration of two tablets three times a day is recommended, but it is cautioned that care be exercised, and that the drug be taken only as prescribed.

III. *Medical documentation to support claims of effectiveness.* In response to the notice, Cooper Laboratories, Inc., has submitted an affidavit and several literature reprints. None of this submission concerns or refers to the effectiveness of Bistrimate as a treatment for chronic sore throat. No evidence whatever has been submitted that Bistrimate is effective for the treatment of chronic sore throat. Previously, on January 22, 1971, the holder of the new drug application (Smith, Miller and Patch, Inc.), informed the Commissioner by letter that it would not be opposed to deleting chronic sore throat as an indication for Bistrimate.

A. *The affidavit.* Included as a part of the July 5, 1972 submission, is the affidavit of Dr. Herbert J. Spoor, a physician who has prescribed Bistrimate for syphilis and has found it to be effective for this condition. Dr. Spoor's affidavit states that it is his opinion that Bistrimate is an effective treatment for syphilis. He makes no reference to any adequate and well-controlled clinical investigations having been conducted to support his opinion, but relies only upon general clinical experience to justify his conclusion.

Of the 45 articles authored or coauthored by Dr. Spoor, cited in the bibliography attached to the affidavit, none deal with syphilis or any form of bismuth treatment.

In addition to his affidavit, Dr. Spoor had a meeting with representatives of the Food and Drug Administration on February 9, 1971, to discuss Bistrimate. At that time, Dr. Spoor told the Food and Drug Administration personnel about a group of patients treated at the New York Eye-Ear Infirmary Syphilis Clinic between 1967-70. His report of that treatment consisted of a list of patients who had a positive serologic test for syphilis and were treated with a variety of drugs; no controls of any kind were employed in this group of patients. In addition, only six of 136 patients were treated with bismuth tablets. Of those patients, according to Dr. Spoor's summary sheet which was supplied to the FDA, the results were: "Claims improvement "1; "Not known "2; "Improved? "1; "No change "1; "Still not happy "1. The efficacy of Bistrimate cannot be evaluated on the basis of these six patients. Moreover, this is the only specific basis the Commissioner has been given to support Dr. Spoor's opinion that Bistrimate is effective in the treatment of syphilis. It does not constitute substantial evidence of efficacy.

B. *Four cited articles.* Cooper submitted reprints of four articles which it contends establish Bistrimate's effectiveness. The Commissioner has reviewed these articles and concludes that none of these constitute substantial evidence of efficacy, as follows:

1. Elmer R. Gross, M.D., and James K. Howles, M.D., "Non Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate." This is the text of an unpublished paper read before an American Medical Association section meeting in 1947. It is a report of the treatment of 354 patients with a variety of dermatoses (lupus erythematosus, scleroderma, lupus vulgaris, alopecia areata, etc.). There were no controls. Of the 354 patients, 222 with syphilis in various stages were treated with Bistrimate, 450 mg. daily, for periods up to 6 months. There were various treatment regimes used throughout the study. Some patients received other medications including penicillin. The criterion used by the authors was inappropriate in that they state that "for clinical purposes, patients demonstrating visible lesions are the best index of therapeutic response." This is a poor index of infection. At that time, and now, it is known that visible syphilitic lesions disappear without any treatment, although the disease continues (William Boyd, "Textbook of Pathology," 5th ed., p. 174-8 Phila., 1947). Apparently the only patients in whom serological (i.e., blood) testing was used to evaluate response were those who received both penicillin and Bistrimate.

The authors conclude that Bistrimate is the drug of choice in patients who have had major arsenical reaction, or in patients whose physical status precludes the use of arsenic. They find Bistrimate useful where parenteral bismuth therapy produced local reactions, or in geriatric syphilology where passive specific therapy is indicated. However, it is difficult to tell from the paper what percentage of patients were believed to have benefited from Bistrimate. No individual case reports are described in any detail whatever. The authors themselves realized that their conclusions were "a bit premature" and that the series was a small one.

This paper is not an adequate and well-controlled clinical study. Specifically, it fails to meet the statutory requirement as spelled out in 21 CFR 130.12(a)(5).

2. Arthur C. DeGraff, M.D. et al., "Report on the Pharmacology and Toxicology of Bistrimate" (1946). This unpublished paper consists of five parts: Part 1 relates to acute toxicity of Bistrimate in experimental animals; part 2 relates to chronic toxicity in experimental animals; part 3 concerns the urinary excretion of bismuth following administration of Bistrimate in man; part 4 concerns the effect of Bistrimate on blood clotting time; and part 5 is a report of five case histories of treatment of patients with syphilis using Bistrimate.

This paper contains no human clinical documentation of effectiveness for syphilis. The vast majority of it deals with nonpertinent data compiled from administration to animals.

The only section of the paper which is at all pertinent to the efficacy of Bistrimate on humans is a report of five case histories of treatment of patients with syphilis using the drug. No definite conclusions can be made regarding the efficacy of oral Bistrimate from only case reports without controls. Dosages of Bistrimate varied among the five patients, as did duration of administration. No statistically valid conclusion could be

drawn from this small a study, and the report itself admits that the group is small. This report does not contain any adequate and well-controlled clinical studies. Specifically, the five case histories fail to meet the criteria set forth at 21 CFR 130.12(a)(5).

3. Arthur C. DeGraff, M.D., and Robert A. Lehman, Ph. D. "Oral Sodium Bismuth Triglycollamate in the Treatment of Syphilis." This is an unpublished paper which was apparently written in 1946. Included in this paper is a short description of animal toxicity studies.

The authors state that Bistrimate was given three times daily to 13 subjects at various dosage levels for a period from 1 to 16 weeks. Twenty-four hour urine specimens were analyzed for bismuth and examined for evidence of renal irritation. The authors used a daily excretion of at least 2 mgs. of bismuth in a 24-hour specimen as an "adequate excretion level." The authors point out that some subjects achieved this level, some did not.

The authors describe two patients treated with Bistrimate, one with primary syphilis, the other with multiple gummata of late syphilis. The authors made no attempt to conduct an adequate and well-controlled investigation and do not represent their report to be one. These two patients were among the five previously discussed in Dr. DeGraff's "Report on the Pharmacology and Toxicology of Bistrimate." The entire study was totally uncontrolled. In the first patient the chancre improved after 29 days, but there is no indication that the drug was responsible, since, as earlier stated, chancres heal without treatment although the disease may continue. Further, the paper is not explicit on whether the positive serologic test was repeated or not. In the second patient, similarly uncontrolled, the gummata are reported improved but again, since the serology was not repeated it cannot be concluded that the treatment with Bistrimate had any effect.

4. Elmer R. Gross, M.D. and Carroll S. Wright, M.D., "Bistrimate in Dermatology and Syphilogy." This is an unpublished article which was apparently written in 1945. Of the 34 cases in the study, Bistrimate was not the only drug given in 26. The authors pointed out that in these 26 cases "Bistrimate was given only simultaneously with other therapy and hence cannot be used to judge therapeutic efficacy." In the eight cases where Bistrimate was administered alone it was administered alone only during the first period of treatment. Thereafter, additional therapy was used in conjunction with the Bistrimate treatment. With the eight cases where Bistrimate was initially used alone to treat syphilis, it is not possible to evaluate the therapeutic efficacy of the drug because there had not been sufficient time for followup at the time of the writing of the paper. No subsequent article has been submitted by Cooper. Although the lesions cleared up during the period of treatment, there may have been subsequent relapses, when the treatment was discontinued. Further, as previously discussed, lesions will clear up without treatment. In addition, in seven out of the 34 patients, there were symptoms definitely referable to bismuth intoxication. There were no controls used in treating the patients in this report.

These studies are not adequate and are not well-controlled investigations in accordance with the statutory requirements, as set forth in 21 CFR 130.12(a)(5). No plan or protocol for any of the studies, or the report of the results of the effectiveness of Bistrimate in any of the studies provide adequate assurance that the subjects were always suitable for the purposes of the study [(ii)(a)(2)(i)], or that the subjects were assigned to test groups in such a way as to minimize bias [(ii)(a)(2)(ii)], or that comparability or pertinent variables in test and control groups were assured [(ii)(a)(2)(iii)]. Furthermore, these studies do not adequately explain the methods of observation of subjects and recording of results [(ii)(a)(3)]. They fail to provide a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. No controls were employed [(ii)(a)(4)]. Finally, the summaries of the methods of analysis and evaluation of data derived from the studies, including appropriate statistical methods are inadequate [(ii)(a)(5)]. The most that may be said of these studies is that they are merely clinical impressions.

IV. *Legal arguments.* Cooper contends that Bistrimate is not a new drug, relying on long usage of bismuth to make the product "not a new drug." However, no evidence is presented to establish that Bistrimate is not a new drug within the meaning of the statute.

Cooper states that Bistrimate was once listed as effective by a number of medical texts. It is now indisputable that the product is not regarded as effective. There is no mention of Bistrimate in the publication of the American Medical Association's Council on Drugs, "Drug Evaluations—1971." Nor is it listed in any of the official drug compendia. A leading medical text, Goodman and Gilman, "The Pharmacological Basis of Therapeutics" (3d ed. 1965) states that it is difficult to justify the use of bismuth in any of its forms, and the current fourth edition (1970) states that "Although it was the last of the group V metals to be introduced into medicine (1785), it should be the first to be abandoned, since there is little reason to recommend its continuance in a modern therapeutic armamentarium." Moreover, because of its inefficaciousness with respect to treatment of syphilis, Bistrimate is not only a hazard to the diseased patient who is denied proper treatment; it constitutes a public health hazard, for that patient may infect others.

Finally, it is immaterial whether Bistrimate was generally recognized as safe on October 10, 1962. The Drug Amendments of 1962 require that every drug which was the subject of an NDA between 1938 and 1962 is required to be proven effective for its labeled uses. 76 Stat. 780, 788–789; USV Pharmaceutical Corp. v. Richardson, 461 F. 2d 223 (C.A. 4, 1972); Hynson, Wescott and Dunning, Inc. v. Richardson, 461 F.2d 215 (C.A. 4, 1972). Because Bistrimate was the subject of an NDA during that period of time, the act requires that it be shown by Cooper to be effective for its claimed uses. Pfizer, Inc. v. Richardson, 434 F.2d 536 (C.A. 2, 1970; Upjohn Co. v. Finch, 422 F.2d 944 (C.A. 6, 1970); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del., 1970).

Cooper's contentions that the Commissioner has no authority to establish criteria for adequate and well-controlled clinical investigations necessary to demonstrate effectiveness of drug products on the market, and to condition the holding on an evidentiary hearing on a showing that reasonable grounds exist therefore, have been ruled upon adversely to the firm. Diamond Laboratories, Inc., v. Richardson, 452 F. 2d 803 (C.A. 8, 1972); Ciba-Geigy Corp. v. Richardson, 446 F. 2d 466 (C.A. 2, 1971); Pfizer, Inc. v. Richardson, supra; Upjohn v. Finch, supra; Pharmaceutical Manufacturers Association v. Richardson, supra. Thus, the objections of Cooper on these grounds are unfounded.

V. *Findings.* The Commissioner, based on the information before him and a review of the medical documentation, affidavit, and legal arguments offered to support the claims of effectiveness for Bistrimate, finds that there is a lack of substantial evidence that Bistrimate has the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling, that the legal arguments are insubstantial, and that Cooper Laboratories, Inc. has failed to set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing.

The Commissioner finds that no evidence whatever has been submitted regarding the effectiveness of Bistrimate for chronic sore throat, and thus it cannot be found to be effective for this indication. The evidence submitted to support effectiveness is wholly lacking in both quantity and quality, and does not even purport to meet the statutory standard of substantial evidence of effectiveness.

The Commissioner further finds that, because Bistrimate has not been shown to be effective in the treatment of syphilis, it permits a contagious patient to continue to transmit venereal disease. Bistrimate is thus a public health hazard in that its use exposes the public to needless risk of disease. Therefore, the new drug application heretofore approved for Bistrimate (NDA 5–933) is hereby withdrawn on the basis of a lack of substantial evidence of effectiveness and the public health hazard such ineffectiveness creates.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 701, 52 Stat. 1052–1053, 1055–1056, as amended, and 76 Stat. 781–785, as amended; 21 U.S.C. 355, 371),

and under authority delegated to the Commissioner (21 CFR 2.120), the request for an evidentiary hearing is denied. Notice is given that the approval of the new drug application for Bistrimate (NDA 5-933) and all amendments and supplements thereto is withdrawn effective on March 7, 1973.

Dated: March 2, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.73-4447 Filed 3-6-73;8:45 am]

[DESI 10240; Docket No. FDC-D-273, NDA 12-718]

MESULFIN TABLETS

Final Order on Objections and Request for a Hearing Regarding Withdrawal of Approval of New-Drug Application

In the FEDERAL REGISTER of September 27, 1969 (34 FR 14907), the Food and Drug Administration announced its evaluation of a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the preparation Mesulfin tablets, containing 250 milligrams sulfamethizole and 250 milligrams methenemine mandelate per tablet; Ayerst Laboratories, 685 Third Avenue, New York, NY 10017 (NDA 12-781; DESI 10240).

The announcement stated the conclusion of the Food and Drug Administration that on an overall basis there is a lack of substantial evidence that the drug will have the effect it purports to have or is recommended to have. The Commissioner further stated that he intended to initiate proceedings to withdraw NDA 12-718. However, before initiating such proceedings, the holder of the new drug application was invited to submit, within 30 days of the date of publication of the announcement in the FEDERAL REGISTER, any pertinent data bearing on the proposal. The Commissioner stated he would only consider well-organized material consisting of adequate and well-controlled studies bearing on the efficacy of Mesulfin tablets that had not previously been submitted. On October 27, 1969, Ayerst Laboratories submitted information concerning Mesulfin tablets to the FDA. The information received (discussed below) together with information previously available, did not provide substantial evidence of effectiveness of the drug for use in man for the conditions for which it is recommended in its labeling.

A notice was thereafter published in the FEDERAL REGISTER of February 18, 1971 (36 FR 3146), which provided an opportunity for hearing on withdrawal of the new drug application for Mesulfin tablets (NDA 12-718). Thirty days were allowed for filing a written appearance requesting a hearing by an interested person, giving the reasons why approval of the new drug application should not be withdrawn, together with a well-organized and full factual analysis of the clinical and other investigational data they were prepared to prove in support thereof.

On March 15, 1971, American Home Products Corp., on behalf of Ayerst Laboratories, Inc., requested an extension of time to respond to the notice, and also requested the Commissioner, pursuant to 21 CFR 130.14(a), to explain the reasons for his actions, enumerating six particular inquiries. By letter of March 24, 1971, an extension of time to April 6, 1971, was granted and a full explanation of the basis for the Commissioner's action was provided.

On April 6, 1971, American Home Products filed a response which consisted of a request for a hearing and written notice of appearance, including a statement of reasons why the firm contended that a hearing was in order, and the firm's medical documentation.

This submission has been considered, and the Commissioner of Food and Drugs concludes that there is no genuine and substantial issue of fact requiring a hearing, and that the legal arguments offered are insubstantial, all as explained in more detail below.

I. *The drug.* Mesulfin tablets is a fixed combination preparation containing, in each tablet, sulfamethizole (250 milligrams) and methenamine mandelate (250 milligrams).

II. *Recommended uses.* Mesulfin tablets are offered for use in the treatment of cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis due to bacterial infection amendable to sulfonamide therapy. It is also offered for prophylaxis of patients with indwelling catheters, ureterostomies, urinary calculi, urinary stasis, and neurogenic bladders. It is also indicated to be of value in genitourinary surgery and instrumentation, and for the treatment of many infections due to organisms resistant to antibiotics, sulfonamides, and other chemotherapeutic agents. The usual dose is two tablets four times daily.

III. *The data to support claims of effectiveness.* In support of its request for hearing, American Home Products submitted numerous studies on the use of Mesulfin tablets. These consisted of two new studies, one long-term study, and 11 studies originally submitted with NDA 12-718, and arguments presented why these studies should be considered "controlled." Proposed revised labeling for Mesulfin tablets was also submitted. Also submitted were the testimonial affidavits of eight physician-investigators who have worked with Mesulfin.

A. *The recent studies.* 1. *Whalley, The Effects of Treatment or Non-Treatment of Asymptomatic Bacteriuria of Pregnancy, unpublished.* The purpose of this study was to determine the effect of treating asymptomatic bacteriuria on the course of the bacteriuria and on the incidence of ante-partum, intra-partum and post-partum complications.

The 139 patients studied were divided into three groups; the first group, consisting of 62 patients, was untreated from the date the bacteriuria was diagnosed until parturition; the second group, consisting of 52 patients, was treated with Mesulfin for a 2-week period; and a third group, consisting of 25 patients, was treated with Mesulfin from the time of diagnosis to the end of pregnancy. Of the 25 patients on continuous Mesulfin therapy, all had bacteriologically negative urine cultures throughout the study. Of the 52 treated for 2 weeks, 29 (55 percent) obtained bacteriologically negative urine cultures for the remainder of their pregnancy; three patients (5.8 percent) had no improvement with Mesulfin; reinfection occurred in 20 (38.5 percent) of this group; and of these latter 23, eight developed symptomatic urinary tract infections. All of the 62 untreated patients continued to show evidence of urinary tract infection as evidenced by consistent bacteriologically positive cultures.

The conclusion was reached that Mesulfin therapy is markedly superior to no treatment in asymptomatic bacteriuria of pregnancy.

However, for the following reasons, the Commissioner concludes that the Whalley study is not adequate and well-controlled and does not constitute substantial evidence of the effectiveness of Mesulfin. The study was not designed in a manner which leads to the collection of data capable of demonstrating the specific effects of each active ingredient, as required by 21 CFR 3.86. As the title of the study indicated, it was conducted to compare the effect of the fixed dose combination therapy versus no treatment in pregnant women with asymptomatic bacteriuria. The results of the study thus could not provide evidence as to the potential benefit or risk attributable to each active component of Mesulfin. Furthermore, the Whalley study does not appear to be well controlled. Had random allocation been applied to the three treatment groups, one would have expected 46 patients in each group. The random occurrence of 25 for continuous treatment, 52 for 2 week treatment and 62 for no treatment could be expected less than 1 time in 100 by chance. It is unlikely that randomization would have produced a distribution as uneven as the one reported. The result implies that randomization has failed to produce comparable groups with regard to numbers.

The statistical analysis of the Whalley study is clearly in error. The author concludes that there is an almost perfect correlation between the group with positive urine cultures and symptomatic urinary tract infection. However, in the untreated group, 62 patients had positive urinary cultures but only 27 had symptomatic urinary infections, less than 44 percent; this is clearly less than the 100 percent suggested by the investigator's and the company's analysis.

Finally, testing was not done to identify the microorganisms present in positive cultures before beginning medication in order to determine drug susceptibility of these microorganisms. Susceptibility tests of microorganisms to the testing

drug was performed only in case of initial treatment failure or relapse. Thus, it was not possible to evaluate the final results for drug susceptibility.

2. *McGanity and LeBlanc, Asymptomatic Bacteriuria in Pregnancy, unpublished.* The purpose of this study was to determine the effects of treatment of bacteriuria on development of urinary tract disease such as pyelonephritis and on prematurity. The methodology is described in Texas Reports on Biology and Medicine, 22:336, summer, 1964. Thirteen hundred patients were used in this study. All prenatal patients had urine cultures done on their initial visits and those having colony counts of greater than 10^5 per ml. of a single organism were placed on randomized therapy. This therapy was not based on bacteriological sensitivity studies. Drugs were initially used in therapeutic dosages and then reduced to prophylactic dosages when the urine cultures became negative. Patients were given Mesulfin, methenamine mandelate, furadantin, or no treatment. No patients were administered sulfamethizole or a sulfa drug alone. In their protocol, the investigators stated that they were using Mesulfin as a representative of the sulfa group, yet Mesulfin is a combination of a sulfa and methenamine mandelate.

Patients were followed throughout the remainder of pregnancy; delivery cultures and 6-week post-partum cultures were done. The investigators concluded that the results of the study demonstrated an incidence of asymptomatic bacteriuria of 6.5 percent; the incidence of subsequent pyelonephritis in the initially negative culture group was 2 percent. A selected group of patients with initial negative cultures who were placed on long-term drug therapy had an incidence of acute pyelonephritis of 0.9 percent, leading the investigators to conclude that continuous drug therapy appeared to diminish the risk of catheterization. In those patients with initial positive cultures receiving continuous but randomized drug therapy, the incidence of acute pyelonephritis was 4.3 percent, whereas in those without continuous therapy, the incidence of subsequent acute pyelonephritis was 20 percent. It was concluded that antibiotic [sic] therapy used continuously throughout pregnancy in patients with asymptomatic bacteriuria reduced the incidence of acute pyelonephritis to that of a normal population.

For the following reasons, the Commissioner concludes that the McGanity and LeBlanc study is not adequate and well-controlled and therefore does not constitute substantial evidence of the efficacy of Mesulfin. Like the Whalley study, this study was not designed in a manner which would lead to the collection of data capable of demonstrating the specific effects of each active ingredient, as required by 21 CFR 3.86. The comparable analysis and report suggest a reduction in bacteriuria and urinary tract infections but these results do not provide evidence as to the potential benefit or risk attributable to each active component of Mesulfin.

The study has a multipurpose protocol which does not have as its aim the evaluation of the relative importance of the components of Mesulfin in the treatment or prevention of urinary infections. It is unclear if the study was based on randomization and conducted in a double blind fashion. Both of these would be necessary for a properly controlled study. Of the 110 patients with positive cultures only nine were reported to have been administered methenamine mandelate compared to 23 for no drug, 41 for Mesulfin and 34 for Furadantin; three are unaccounted for. None were administered sulfamethizole or another sulfa drug alone. Adequate randomization would have resulted in more patients having taken methenamine mandelate, thus making any statistical conclusion both more accurate and more reliable.

The chi-square analyses on pages 6, 7, and 8 of the McGanity and LeBlanc study, although providing a summary of the data, are insufficient to support a claim that the components are contributing to the efficacy of the combined product, since there is no data comparing the sulfa component to the methenamine mandelate and in turn comparing the components individually to the composite drug and to no treatment. Moreover, four times as many patients were treated with Mesulfin than methenamine mandelate. This statistical variation questions the reliability of the results.

A criterion for bacteriuria was not stated although "negative culture" was defined as "colony count less than 10^5" in the clinical protocol. The criterion of "negative culture" is questionable since the count is much too high to be considered as such, especially when the organism is of the same species, strain, or serotype. The clinical protocol and summary presented are not coherent. It is therefore difficult to arrive at a meaningful evaluation.

B. *The Long-Term Study.* Zinsser, et. al., Comparative Drug Study in Chronic Urinary Infections Using Computer Definition of Patient Disease Patterns and Quantitative Measures of Drug Efficacy by Sequential Analysis and Patient Derived Autodefinition of a Disease: Pyelonephritis. This long-term study together with the submitted analysis of the data by Dr. Hyman Menduke clearly reveal that the study was designed primarily to investigate the diseases involved rather than the drug efficacy. The study comprises a retrospective analysis of a patient population covering the past 20 years. Dr. Menduke's letter points out that the subjects were not assigned on a random basis, nor were the treatments specified for certain durations with specific intervals per treatment. In his analysis, Dr. Menduke only addresses those patients with a "usable episode," whose condition at the beginning and at the end is unknown. Dr. Menduke also redefined the sampling unit to a per-patient basis. Moreover, this set of observations suggests that at least one component is not contributing to the drug's effect; Dr. Menduke's analysis reveals that methanamine mandelate has a success rate equivalent to the no treatment group. The clinical protocol for the study included a bacteriological evaluation but Dr. Menduke did not mention a bacteriological evaluation at all. The study was not controlled as required by section 505 of the Act nor designed to evaluate the effectiveness of each component as required by 21 CFR 3.86. For these reasons, the Commissioner finds that the data as presented do not constitute an adequate and well-controlled investigation and are not substantial evidence of the effectiveness of Mesulfin.

C. *The studies contained in the New Drug Application file.* 1. John P. Colmore, M.D., and Barbara F. Branden, M.D., University of Oklahoma Medical Center, evaluated the effectiveness of Mesulfin in patients with pyelonephritis and bacteriuria of pregnancy. Quantitative urine bacteriology was obtained at each visit and CBS's, urinalysis, SGOT, and BUN determinations were obtained before initiation of therapy and monthly thereafter. The principal infecting organisms were E. coli or an Escherichia species and Klebsiella-Aerobacter, 63 and 14 cases respectively. A total of 110 patients were treated with two tablets q.i.d. and of these 84 were evaluated. Results are reported that "Mesulfin was shown to be highly effective (79.8 percent success) and safe in the eradication of bacteria due to gram-negative bacilli (particularly E. coli, other Escherichia species and Klebsiella-Aerobacter)".

This study fails to investigate the effectiveness of each individual active component of the combination drug Mesulfin; hence it is not determined which component is effective or the overall effect of the sulfamethizole or methenamine mandelate in the combination formulation, as required by 21 CFR 3.86. Nor was the study controlled as required by section 505 of the Act.

The drug is reported safe and effective when used as the treatment of bacteriuria in the third trimester of pregnancy with exception of one case of hemolytic anemia with recovery following discontinuance of therapy. The time involved for return to normal is not given, nor are followup reports of urine cultures given. The Commissioner finds that, based on the data submitted, this study is not adequate and well-controlled and does not constitute substantial evidence of the effectiveness of Mesulfin.

2. Fred K. Garvey and Harold L. Murray: A Clinical Report on the Use of Combined Mandelamine and Thiosulfil in Resistant Urinary Tract Infections, N.C. Med. J., 22(5) May 1961. These doctors investigated the effectiveness of Mesulfin for the treatment of chronic bacillary urinary tract infections resistant to antibiotic therapy. Twenty-five patients meeting this criterion were selected for study. Before initiating therapy, the infecting organism was identified by culture technique and the degree of pyuria noted for each patient. The dosage used

was two tablets four times a day except in a few cases when only one tablet was given four times daily. The main duration of therapy was 3 to 4 months. In 21 of the 25 patients Mesulfin effectively relieved the symptoms and cleared the urine of microscopic evidence of pyuria and bacteriuria. The authors concluded the product is superior to other antimicrobial agents in that it is relatively free from toxicity, continuous in its action, and has the advantage of waging a two-fold attack on bacteria—that is, in both the tissues and the urinary stream.

The Commissioner finds that this study was not adequate for the following reasons: Microscopic examination alone is not acceptable criterion used for cure of urinary tract infection. Culture of urine and repeated cultures that remain normal varying in time based on the site of infection in the urinary tract are required. Cultures were not done on most patients as a follow-up and no culture reports are presented. Furthermore, there was no clinical study conducted to show the effectiveness of each drug (methenamine mandelate and sulfamethizole) compared to the overall effectiveness of the combination as required by 21 CFR 3.86. No controls were employed as required by section 505 of the Act.

Early in their experience the investigators noted a frequently occurring turbidity of the urine which varied from a milk cloudiness to a buttermilk flocculence. Turbidity was greater at lower pH levels and qualitative analysis of the sediment showed ammonium, uric acid, oxalate, calcium and phosphate ions. They reported no sulfa crystals large enough to be morphologically evident under microscope. They concluded that apparently, the flocculency was due to amorphous deposits of the varying ions resulting from a lower pH in the urine, and became more marked after the urine cooled. The pH of urine was not recorded even though it is well known that most of the sulphonamide compounds have a low solubility in water and in urine, unless the latter is alkaline. This requirement for alkaline urine for sulfa solubility is in direct conflict with acid urine required for methenamine to be effective.

In Zinsser, et al., "Formation of an Insoluble Condensation Product from Sulfamethizole and Formaldehyde" appearing in January 1963, Journal of Pharmaceutical Sciences, the composition of the sediment found in human urine after the ingestion of a combination of sulfamethizole, methenamine, and mandelic acid using the Bratton and Marshall assay procedure was more than 50 percent sulfonamide. The sediment was also said to contain ammonium and urate salts. Their in vitro studies showed sulfamethizole, methenamine, and mandelic acid in the pH range of 4.5 to 6.0, and that precipitation of the sulfonamide Since methenamine is hydrolyzed to formaldehyde in acidic solution, the aldehyde was tested in the same manner, and the formaldehyde precipitated the sulfamethizole from solution. Zinsser reported that other investigators have independently discovered that sulfamethizole formed the same insoluble condensation product with either formaldehyde or methenamine. Helv Druery, J. Chim. Acta., 31, p. 179 (1948); U. P. Basu, J. Indian Chem. Socy., 26, p. 125 (1949). The findings of these investigators are in contradistinction to the conclusions as to the etiology and composition of the precipitate as described by Garvey and Murray.

3. Fred K. Garvey and Harold L. Murray, "A Clinical and Laboratory Study of Combined Mandelamine and Thiosulfil in Resistant Urinary Tract Infections", North Carolina M.J. 21:183, May, 1960.

The authors conducted an in vitro study of the comparative effect of methenamine mandelate and sulfamethizole, alone and in combination, and Mesulfin, against Proteus, Aerobacter, and Pseudomonas bacilli isolated from patients who were resistant to previous therapy. The isolates were used to inoculate urine of four nonmedicated healthy male subjects to establish a normal growth of the bacteria. The four males were given 0.5 gm. of each test drug every 6 hours for a total of four doses, allowing at least 4 days between each course. On the morning following administration of the test drug, their first voided specimens were collected, combined and filtered through porcelain candles and used as diluent for the culture. After incubation, the effect of each dosage regimen on growth of the test bacteria was determined turbidometrically. All organisms grew well in normal urine. In urine containing methenamine mandelate alone, growth of all these organisms were substantially inhibited. Aerogenes and Pseudomonas growth was inhibited but Proteus growth was simply delayed in urine containing Thiosulfil (sulfamethizole). Growth of these organisms in the presence of urine containing both drugs was satisfactorily inhibited and compared favorably with Mesulfin.

The size of the group is so small that the study cannot be considered adequate and results are statistically insignificant. There is no data on patient tolerance for the drug, side effects, or problems encountered in connection with other body processes. None of the investigation methods are outlined, making an objective statistical evaluation impossible. Furthermore, there is no data to indicate at what level the drugs obtained their desired effect. For these reasons, the Commissioner finds that this study is not adequate and it does not constitute substantial evidence of the effectiveness of Mesulfin.

4. Drs. S. A. Wolfson, G. M. Kalmanson, M. E. Rubini, and L. B. Guz, Wadesworth Hospital, Veterans' Administration Center and Department of Medicine U.C.L.A. did an epidemiological survey of 521 consecutive admissions to the medical service of the VA hospital. Fifteen percent of the male patients presented asymptomatic significant bacteriuria, 100,000 organisms per ml. of urine. Fifty-nine percent of these elderly male patients were selected for treatment with 4 grams divided doses of Mesulfin daily for 10 days. Pretreatment urine cultures identified the infecting organisms as Escherichia Coli, Pseudomonas, Proteus or Klebsiella-Aerobacter. Followup cultures were obtained 10 days, 1 month, and 3 to 6 months after cessation of therapy. The cure rate was 59 percent based on the criterion that the original organisms found prior to therapy were eradicated and did not recur within the followup period.

This study is not adequate since the individual components of Mesulfin were not tested individually, as required by 21 CFR 3.86. Furthermore, it is obviously not controlled since there is no indication that any controls were used at all, as required by section 505 of the Act. Thus, there is no basis upon which to compare the patients treated with Mesulfin and those who would have been untreated. The Commissioner finds that this study does not constitute substantial evidence of the efficacy of Mesulfin.

5. Rodger Barnes, M.D. (and Associates) of White Memorial Clinic, Los Angeles, Calif., evaluated the effectiveness of Mesulfin for the treatment of acute and chronic urinary tract infections in a series of 97 patients. Prior to initiating therapy, a complete urinalysis was done and bacteria were evaluated using gram-staining techniques. The usual dosage employed was two tablets q.i.d. In acute conditions duration of treatment was from 1 to 6 weeks and for chronic infections, therapy was extended for periods of 12 months or more. At the end of the treatment period, gram-staining techniques were again employed and urinalyses were done. Successful therapy was defined as symptomatic improvement with a negative post-treatment culture; partial success was defined as symptomatic improvement, but no post-treatment culture taken. Results showed the drug was a success or partial success in 55 patients (56 percent) and not effective in 35 patients (36 percent) who showed a positive post-treatment culture; 54 percent of the patients showed reduction of WBC in the urine after Mesulfin therapy. Adverse reactions noted consisted of dizziness, nausea, blurred vision, diarrhea, and irritation of the bladder. Dr. Barnes recommended the drug for use in treatment of chronic urinary tract infection when it is necessary to continue antibacterial medication over a long period of time.

The number of post-treatment cultures obtained per patient is not stated. Treatment was declared a success (or the drug considered successful) in 56 percent of the trials. This number includes those patients who were asymptomatic with a negative post-treatment culture and those who showed symptomatic improvement but who had positive post-treatment cultures. There is no value given for those patients who had post-treatment negative cultures alone.

This is obviously not a controlled study since there is no indication that any controls were employed, as required by section 505 of the Act. Moreover, there is no data as to the type of bacteria which were involved in the patients' infections. Finally, the individual components were not tested against the combination drug to determine if the combination was more effective than the single drug, as required by 21 CFR 3.86. The Commissioner finds that this study does not constitute substantial evidence of the efficacy of Mesulfin.

6. Bruce H. Stewart, M.D., Cleveland, Ohio, used Mesulfin to treat 26 cases of urinary tract infections in whom conventional therapy had failed. Adult dosage was two tablets q.i.d., and for children one tablet t.i.d. The organisms identified in pretreatment cultures were: *E. coli, Proteus, A. aeruginosa, Alkaligenes species, S faecalis, A. viridans* and *S. aureus*. Five patients had negative pretreatment cultures. Negative posttreatment cultures were obtained in two with recurrent cystitis and one with chronic prostatitis. Negative cultures were also obtained for one patient with urethral stenosis with infection, and one with benign prostatic hyperplasia with infection. One patient with urethritis relapsed after treatment. Three cases of chronic pyelonephritis had negative posttreatment cultures, four were positive and an additional four relapsed. Three patients with probable post operative pyelonephritis had positive posttreatment cultures as had one patient with postoperative phyloplasty.

The study was not controlled as required by section 505 of the Act and the individual components of the drug were not tested against the combination as required by 21 CFR 3.86. Moreover, the results indicate that the drug may not be effective. The Commissioner finds that this study does not constitute substantial evidence of the effectiveness of Mesulfin.

7. Cecil M. Crigler, M.D., Houston, Tex., treated urinary tract infections in 31 female patients and one male patient. Dosage of Mesulfin administered was two tablets q.i.d. from 2 to 8 weeks. The principal infecting organisms were identified as *E. coli, P. vulgaris,* and *S. aureus*. Pre- and post-treatment cultures were obtained in 16 cases and in 15 of these the post-treatment cultures were negative. In nine of the 15 cases the organism present was shown to be resistant to many of the commonly used antibiotics and sulfa drugs. An *E. coli* infection in one patient which did not respond to Mesulfin was also resistant to penicillin, bacitracin, erythromycin, and several sulfonamides. The only side effect noted was one patient reporting marked bladder cramps.

This study was not controlled as required by section 505 of the act and the individual components were not tested against the combination as required by 21 CFR 3.86. No follow-up data is provided. No data is given for the 15 patients on whom preclinical cultures were not taken. The Commissioner finds that this study does not constitute substantial evidence of the effectiveness of Mesulfin.

8. Yves Goudreau, M.D., of Montreal, Canada, treated four cases of chronic cystitis and one case of subacute pyelonephritis with Mesulfin. A divided daily dosage of 1–2 grams was used from 1 to 2 weeks. Negative postculture was obtained in the pyelonephritic patient and in three of the four chronic cystitis patients.

There is no definition as to length of followup. The report refers to one followup culture on each patient; a single followup is inadequate to document effectiveness of the drug. There were no controls used as required by section 505 of the Act and the individual components of Mesulfin were not tested against the combination as required by 21 CFR 3.86. The Commissioner finds that this study is not substantial evidence of the effectiveness of Mesulfin.

9. H. S. Everett, M.D., Baltimore, Md., treated five female patients with cystitis and a sixth with a low grade urinary tract infection with 0.5 gm. q.i.d. of Mesulfin. Organisms cultured were the usual gram negative found in the urinary tract. Only three patients had negative posttreatment cultures; two were positive. All five patients were listed as clinically improved.

Duration of followup is not given, hence the extent of effectiveness of the drug cannot be determined. This is obviously not a controlled study since there is no indication that any controls were employed, as required by section 505 of the Act. The individual components were not tested against the combination drug to determine if the combination was more effective than the single drug as required by 21 CFR 3.86. The Commissioner finds that this study does not constitute substantial evidence of effectiveness of Mesulfin.

10. Temple W. Williams, Hanna ABU-Nassau and Ellare M. Yow, "Methenamine Mandelate—Sulfamethizole Combination Evaluation in Management of Urinary Tract Infections", Tex. St. M.J. 60:149 (February 1964). The investigators evaluated the results of Mesulfin in the treatment of 37 patients with symptoms of acute or chronic pyelonephritis. Criteria for selection of patients were: Presence of symptoms referable to the urinary tract, and demonstration of pyuria and/or significant bacteriuria. Urine samples were collected before and after treatment and examined for colony count. Gram negative organisms and *E. coli* predominated. Dosage of 1 gram initially followed by 1 gram four times daily was used in acute pyelonephritis and 1–4 grams in chronic pyelonephritis. A good response was interpreted as meaning symptomatic response within 2 to 3 days, cessation of pyuria, and a significant reduction of bacteriuria when present. Fair response was interpreted as diminished pyuria and bacteriuria but with no symptomatic response until the completion of at least 1 week of therapy. Of the 15 acute pyelonephritic patients, 11 showed good response and four patients fair. Of the 22 chronic pyelonephritic patients, only two had good response and 19 fair with one patient with poor response.

This study is not a controlled study as required by section 505 of the Act. Like the other clinical studies reported above, there are no studies to determine the effectiveness of either active component individually as required by 21 CFR 3.86. The Commissioner finds that this study does not constitute substantial evidence of the effectiveness of Mesulfin.

11. H. A. Baker and A. Sidorwicz, "Therapy of Urinary Tract Infections Based on In Vitro Studies with a combination of Sulfamethylthiadiazole and Methenamine Mandelate", Clin. Med. 70:1307 July 1963.

This is an in vitro study evaluating sulfamethylthiadiazole, methenamine mandelate and the two in combination against *E. coli, Aerobacter aeruginosa, proteus sp.* and *Ps. aeruginosa*. The two drugs were tested at a concentration of 2.5 mg./ml. alone and in combination (i.e., total of 5 mg./ml.).

The authors concluded that lowering the pH increased the activity of sulfamethylthiadiazole and the methenamine mandelate was more active at pH 6.0 than at pH 9.0; sulfamethylthiadiazole was bacteriostatic while methenamine mandelate was bactericidal as well as bacteriostatic; and the combination has an antibacterial activity superior to either agent.

Absolutely no data has been provided to determine if any patients at all were used in the study. There is no data to support the conclusion of the investigators. The study is obviously inadequate and not well controlled. The Commissioner finds that this study is not substantial evidence of the effectiveness of Mesulfin.

D. *The physicians' affidavits.* American Home Products has also submitted the affidavits of eight physicians, all of whom conducted the studies on Mesulfin discussed above, and all of whom attest to the effectiveness of Mesulfin and the validity of their own studies. These affidavits are in fact testimonials to Mesulfin. They neither contain nor refer to adequate and well-controlled clinical studies. The Commissioner finds that these affidavits are inadequate to establish that Mesulfin is effective.

E. *Other medical authorities supporting the Commissioner's determination.* The AMA Drug Evaluations, 1971, does not recommend the combination of sulfamethizole and methenamine mandelate for any indication. Indeed, the AMA Drug Evaluations, 1971, at pp. 436–7 states that the "Use of Methenamine [is] usually restricted to patients with infections not cured by more effective antibacterial agents." Sulfamethizole is recommended for use (p. 47) in urinary tract infections alone, not in combination with any other drug.

Furthermore, in Goodman and Gilman, The Pharmacological Basis Of Therapeutics, Fourth Edition (1970), the authors state at page 1042 that "an incompatability between methenamine mandelate and sulfamethizole has been

noted (Lipton, 1963); the formaldehyde liberated in the urine forms an insoluble precipitate with the sulfanamide." None of the studies submitted by American Home Products addressed this problem nor offered any explanation. Finally, in Goodman and Gilman, it is stated at p. 1161 that sulfanamides are the drug of choice in treating urinary infections caused by E. coli. For treating urinary infections caused by A. aerogenes, A. faecalis, proteus and pseudomonas aeruginosa, sulfanamides are not listed at all as drugs of choice. Only for treating proteus mirabilis are sulfanamides recommended. Methenamine mandelate is nowhere listed as a drug of choice for urinary infections.

F. *Summary.* In order to establish that a drug is effective for the conditions for which it is prescribed, recommended or suggested, substantial evidence consisting of adequate and well-controlled clinical investigations must be submitted to the FDA. 21 U.S.C. 355(e); 21 CFR 130.-12(a)(5). No controls were employed in the Colmore, Wolfson, Barnes, Stewart, Cigler, Gaudreau, Everett, Williams, Baker, and the first Garvey study discussed. The deficiencies in the controls used in the other studies and the inadequacies of all the studies are discussed in detail above.

As pointed out above, Mesulfin is a fixed dose combination drug, composed of 250 mg. sulfamethizole and 250 mg. methenamine mandelate. As the Commissioner stated in the preamble to 21 CFR 3.86 (36 FR 3126, Feb. 18, 1971): "A fixed dose combination drug must have an advantage to the patient over and above that obtained when one of the individual ingredients is used in the usual safe and effective dose. No drug should be present in a fixed combination unless its inclusion clearly enhances safety or efficacy and the fixed ratio of doses is safe and effective for all indications and for patients requiring such concurrent therapy."

American Home Products claims that Mesulfin is a rational fixed combination drug. However, American Home Products has produced no adequate and well-controlled clinical investigations that support this contention. The only submitted study that compared the combination against its individual components and no treatment was the second Garvey study involving only four laboratory subjects. Both the NAS/NRC and the Commissioner have found the combination of methenamine mandelate and sulfamethizole, i.e., Mesulfin, ineffective for its intended uses. Moreover, there is evidence, cited above, that sulfamethizole and methenamine mandelate are antagonistic to one another, which evidence American Home Products has not refuted. Therefore, claimants' contention is without merit.

IV. *The NAS/NRC evaluation of Mesulfin.* American Home Products claims that the Commissioner's evaluation of Mesulfin differs substantially from that of the NAS/NRC. The NAS/NRC Panel found that indication for use of Mesulfin in the treatment of cystitis, urethritis, pyelitis, pyelonephritis and prostatis due to bacterial infection amenable to sulfonamide therapy, was ineffective unless qualified. The panel gave several examples of the qualifications that would have to be added to the label of Mesulfin: "for example patients having any one of these conditions would rarely be cured by sulfonamide therapy in the presence of obstruction; if gonorrhea is meant by "urethritis," it should be so stated, and if a claim is made in regard to pyelonephritis, it should be stated that this product is most effective against acute, nonobstructive first episode, bacterial urinary tract infections and in general is less effective against chronic infections or in the presence of anatomic abnormalities." Moreover, the NAS/NRC made no reference to combining methenamine mandelate with sulfamethizole in its discussion of the effectiveness of Mesulfin for these indications or any other indications. The panel found that American Home Products had not submitted any reference or scientific study relating to the combination of sulfamethizole and methenamine mandelate. It is apparent that the NAS/NRC did not find the fixed combination of sulfamethizole and methenamine mandelate effective for these indications, as American Home Products' claims. The Commissioner concurred in this finding. American Home Products has still not submitted any adequate and well-controlled study that supports the efficacy of Mesulfin for these indications.

Significantly, the NAS/NRC found that Mesulfin was ineffective: in genitourinary surgery and instrumentation, and that addition of methenamine mandelate to sulfamethizole would make no difference; in infections due to organisms resistant to antibiotics, sulfonamides, and other chemotherapeutic agents; and for prophylaxis of patients with indwelling catheters, ureterostomies, urinary calculi, urinary stasis and neurogenic bladders. It concluded that wide usage of methenamine does not imply effectiveness and that effectiveness should be documented.

V. *Legal objections.* The Commissioner has authority to establish criteria for adequate and well-controlled clinical investigations necessary to demonstrate effectiveness of drug products on the market and may condition holding of an evidentiary hearing on a showing by American Home Products that reasonable grounds exist therefor. Diamond Laboratories, Inc. v. Richardson, 452 F. 2d 803 (C.A. 8, 1972); Ciba-Geigy Corp. v. Richardson, 446 F. 2d 466 (C.A. 2, 1971); Pfizer, Inc. v. Richardson, 434 536 (C.A. 2, 1970); Pharmaceutical Manufacturers Ass'n v. Richardson, 318 F. Supp. 301 (D. Del., 1970).

Since American Home Products has submitted no adequate and well-controlled clinical studies establishing the effectiveness of Mesulfin for its recommended uses, no hearing on the withdrawal of the NDA for Mesulfin is justified as no genuine issue exists as to the material question of the effectiveness of Mesulfin for its recommended uses. 21 CFR 3.86, 130.12(a)(5)(ii), 130.14(b) and 130.27(b)(3); Ciba-Geigy Corp. v. Richardson, supra; Upjohn Co. v. Finch, 422 F. 2d 944 (C.A. 6, 1970).

VI. *Findings.* The Commissioner, based on the review of the medical documentation offered to support the claims of effectiveness for Mesulfin, finds that American Home Products has failed to present substantial evidence of effectiveness for this product. Therefore, pursuant to 21 CFR 130.14(b), American Home Products' request for a hearing is denied. No objection or documentation was presented by any other firms and, in accordance with 21 CFR 130.15, this failure is construed as an election by any other firm not to avail itself of the opportunity for the hearing.

The Commissioner further finds that the approval of the new-drug application heretofore approved for Mesulfin (NDA 12-718) should be withdrawn on the basis of a lack of substantial evidence of effectiveness.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 701, 52 Stat. 1052-53, 1055-56, as amended; 21 U.S.C. 355, 371), and under authority delegated to the Commissioner (21 CFR 2.120), notice is given that the approval of the new-drug application for Mesulfin (NDA 12-718) is withdrawn. The withdrawal is effective immediately.

(Secs. 505, 701, 52 Stat. 1052-53, 1055-56, as amended, and 76 Stat. 781-785, as amended; 21 U.S.C. 355, 371)

Dated: March 2, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.73-4446 Filed 3-6-73;8:45 am]

National Institutes of Health

TOBACCO WORKING GROUP, SUBCOMMITTEE ON SMOKE FILTRATION

Notice of Meeting

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the Tobacco Working Group's Subcommittee on Smoke Filtration, March 8, 1973, at 2 p.m., National Institutes of Health, Building 31, Conference Room 3. This meeting will be open to the public from 2 p.m. to 5 p.m. on March 8 to discuss current experimental data. Attendance by the public will be limited to space available.

Mr. Frank Karel, Associate Director for Public Affairs, NCI, Building 31, Room 10A31, National Institutes of Health, Bethesda, Md. 20014 (301—496-1911) will furnish summaries of the open meeting and roster of committee members.

Dr. Gio B. Gori, Executive Secretary, Building 31, Room 11A03, National Institutes of Health, Bethesda, Md. 20014 (301—496-6616) will provide substantive program information.

Dated: March 1, 1973.

ROBERT W. BERLINER,
Acting Deputy Director, National Institutes of Health.

[FR Doc.73-4271 Filed 3-6-73;8:45 am]