DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 344

[Docket No. 77N-334S]

Topical Otic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph To Include Drug Products for the Prevention of Swimmer's Ear and for the Drying of Water-Clogged Ears

AGENCY: Food and Drug Administration.

ACTION: Further notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that amends the tentative final monograph for over-the-counter (OTC) topical otic drug products by including conditions under which OTC topical otic drug products are generally recognized as safe and effective and not misbranded for the prevention of "swimmer's ear" and for the drying of "water-clogged" ears. "Swimmer's ear" is the common name for external otitis, a bacterial or fungal infection of the external ear canal that may occur following the retention of water in the ear; "water-clogged" ears refers to the retention of water in the ears after swimming, showering, or bathing. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. FDA issued a notice of proposed rulemaking on OTC topical otic drug products in the **Federal Register** of July 9, 1982 (47 FR 30012). However, the tentative final monograph only included topical otic drug products used as earwax removal aids. Topical otic drug products used for the prevention of swimmer's ear and the drying of water-clogged ears are addressed in this tentative final monograph. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by September 29, 1986. New data by July 30, 1987. Comments on the new data by September 30, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by November 28, 1986.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 16, 1977 (42 FR 63556), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC topical otic drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in topical otic drug products. Interested persons were invited to submit comments by March 16, 1978. Reply comments in response to comments filed in the initial comment period could be submitted by April 14, 1978.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

In the December 16, 1977 advance notice of proposed rulemaking on OTC topical otic drug products, the Panel discussed the treatment of swimmer's ear (42 FR 63565), but did not address the prevention of swimmer's ear or the drying of water-clogged ears.

In response to the advance notice of proposed rulemaking, two comments were received concerning both the prevention and the treatment of swimmer's ear. The agency responded to the comments in the notice of proposed rulemaking on OTC topical otic drug products, published in the **Federal Register** of July 9, 1982 (47 FR 30017). The agency stated that, because no clinical data had been submitted, there was no basis for including the prevention of swimmer's ear as an indication for OTC topical otic drug products.

In response to that notice of proposed rulemaking, comments were submitted by one health professional regarding the prevention of swimmer's ear and by one drug manufacturer regarding the prevention of swimmer's ear and the drying of water-clogged ears. Copies of the comments received are on public display in the Dockets Management Branch.

Because active ingredients and claims for the prevention of swimmer's ear and the drying of water-clogged ears were not included in the Panel's report, or substantively addressed by the agency in the tentative final monograph on OTC topical otic drug products, this tentative final monograph is being published to obtain public comment on such ingredients and claims.

The advance notice of proposed rulemaking, which was published in the **Federal Register** of December 16, 1977 (42 FR 63556), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the notice of proposed rulemaking, which was published in the **Federal Register** of July 9, 1982 (47 FR 30012), was designated as a "tentative final monograph." The present documentis also designated as a "tentative final monograph." The legal status of the tentative final monographs, however, is that of a proposed rule. In this tentative final monograph (proposed rule), FDA states for the first time its position on the establishment of a monograph for OTC topical otic drug products for the prevention of swimmer's ear and the drying of water-clogged ears. Final agency action on this matter will occur with the publication at a future date of a final rule for OTC topical otic drug products.

This proposed rule amends Part 344 (as set forth in the tentative final monograph on OTC topical otic drug products (earwax removal aids) that was published in the **Federal Register** of July 9, 1982 (47 FR 30012)) in Subpart A by adding in § 344.3, new paragrpahs (c), (d), (e), and (f); in Subpart B by revising the heading of § 344.10 and adding new §§ 344.12 and 344.14; and in Subpart C by revising the heading of § 344.50 and adding new §§ 344.52 and 344.54.

This proposal constitutes FDA's tentative conclusions on OTC topical otic drug products for the prevention of swimmer's ear and the drying of water-clogged ears. The agency emphasizes that no topical otic drug products for these conditions have been determined to be generally recognized as safe and effective and not misbranded. However, the agency is proposing Category I labeling in this document in the event that data are submitted that result in the

upgrading of any ingredient(s) to monograph status in the final rule.

The OTC procedural regulations (21 CFR 330.10) 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. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead 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 at the tentative final monograph stage.

In the previous tentative final monograph (47 FR 30012), the agency advised 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 12 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that 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 unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is 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.

In the event that new data submitted to the agency during the allotted 12-month comment and new data period are not sufficient to establish "monograph conditions" for OTC topical otic drug products for the prevention of swimmer's ear and the drying of water-clogged ears, and final rule will declare these products to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which new drug applications approved under section 505 of the act and 21 CFR Part 314 are required for marketing. Such rule will also declare that in the absence of an approved new drug application, these products would be misbranded under section 502 of the act. The rule will then be incorporated into 21 CFR Part 310, Subpart E—Requirements for Specific New Drugs or Devices, instead of into an OTC drug monograph in Part 344.

I. The Agency's Tentative Conclusions on the Comments

1. One comment stated that swimmer's ear is one of the most common infections that occurs during the swimming season and requested that a solution of 2 percent acetic acid in distilled water for the prevention of external otitis (swimmer's ear) be included in the monograph for OTC topical otic drug products. The comment also stated that the use of 2 percent acetic acid in the external ear canal would maintain a safe acid pH, which is important in order to avoid swimmer's ear. In support of its request, the comment submitted a study in which 2 percent acetic acid in water was used to prevent swimmer's ear in 25 patients (Ref. 1).

As discussed in the Panel's report (42 FR 63565), external otitis, an infection of the skin lining the external auditory canal, is one of the most common diseases of the ear. One type of external otitis is called "diffuse external otitis" and is commonly known as "swimmer's ear." It occurs with greater frequency during hot, humid weather and has been reported to occur in divers and swimmers. Such factors as high environmental humidity, high temperature, prolonged exposure of the ears to moisture, and local trauma to the ear canal are recognized as important in the development of swimmer's ear.

The external auditory canal is a cul-de-sac, well suited for the collection of moisture, that provides a basis for infection. Disruption of the skin lining the external auditory canal and the action of accumulated moisture, or the use of instruments to clear the ear canal of water after bathing, showering, or swimming may cause maceration, fissuring, or laceration of the skin lining and provide a favorable environment for the growth of bacteria. The invading organism commonly found in external otitis is *Pseudomonas aeruginosa (P. aeruginosa),* a gram-negative bacillus (Refs. 2 and 3). However, *Escherichia coli, Proteus vulgaris, Staphylococcus aureus* (Ref. 2), or, rarely, a fungus (Refs. 2 and 3), may be found. Certain persons (e.g., allergic individuals) are more prone then others to develop swimmer's ear (Ref. 2). Boies (Ref. 4) notes that infections may also occur as a result of a change of the canal skin from a normal acid pH to an alkaline pH. Prolonged exposure to moisture tends to raise the normal skin pH, improving the growth medium for bacteria (Ref. 5).

Symptoms of swimmer's ear are related to the severity of the pathologic conditions. Persons with swimmer's ear complain of itching and pain. There may be a "foul-smelling discharge, and loss of hearing if the canal becomes swollen or filled with purulent (pus-containing) debris. The skin of the external auditory canal appears red, swollen, and littered with moist, purulent debris" (Ref. 2).

In its published report, the Panel discussed the treatment but not the prevention of swimmer's ear. (The Panel believed, and the agency concurs, that the "treatment" of swimmer's ear is a Category II condition because such conditions require the diagnosis and continuous supervision of a physician (47 FR 30017).) However, the Panel did review acetic acid (2 to 5 percent) and was prepared to place this ingredient in Category I for use as "an aid in restoring the normal acid mantle of the ear canal skin—as a prophylaxis or aid in preventing swimmer's ear" (Ref. 6). The Panel later decided, however, that it would not discuss acetic acid for the prevention of swimmer's ear in its report because the ingredient had not been submitted for review (Ref. 7).

The agency recognizes that there is a population that is prone to develop swimmer's ear and that the availability of an OTC drug product to prevent the occurrence of this condition would benefit the consumer. Acetic acid and other ingredients, such as alcohols, are frequently mentioned in the literature as aids in the prevention of swimmer's ear. A number of marketed OTC drug products are promoted for the prevention of swimmer's ear, but their effectiveness, and in some cases, safety, has not been proven. The agency believes that the prevention of swimmer's ear is a Category I claim; however, adequate data must be submitted to demonstrate the safety and effectiveness of any ingredient(s) making such a claim.

The agency has considered data on 2 percent acetic acid for the prevention of swimmer's ear and concludes that the data are inadequate to support this claim for this ingredient. The data reviewed by the agency consist of the Panel's interim working papers (Ref. 6) and summary minutes (Ref. 7), published references on acetic acid (Refs. 8

through 14), and data submitted by the comment (Ref. 1).

During its deliberations the Panel reviewed data on the safety and effectiveness of acetic acid (Refs. 6 through 13). The Panel concluded that 2 to 5 percent acetic acid is safe and effective for topical use in the ear canal to restore the acid mantle of the skin, which is normally pH 6 to 6.5, and as a bactericidal drug effective against the common pathogens found in external otitis (Ref. 6). The Panel made the following comments: Acetic acid is available in three concentrations: glacial acetic acid U.S.P. (99 percent), acetic acid U.S.P. (36 percent), and diluted acetic acid (household vinegar) (5 percent) (Refs. 6 and 8). Acetic acid is completely innocuous to the tissues; it is a part of body metabolism and there is no sensitization (Ref. 6). The use of vinegar (5 percent acetic acid) in medicine dates back to antiquity; most likely, "vinegar was the first antibiotic known to man." During World War I, wound infections were treated effectively with wet dressings of 1 percent acetic acid, and this solution was effective in inhibiting the growth of *P. aeruginosa* (Ref. 9).

Acetic acid is effective as a bactericidal agent against a wide range of micro-organisms, both gram-negative and gram-positive pathogens. Cultures of the bacteria found in the external ear canal in acute infectious external otitis cases were studied by Jones et al. (Ref. 10). In the cultures with acetic acid added (at concentrations of 1, 2, 3, 4, and 5 percent) there was no growth. When other acid solutions with the same pH as solutions of 5 and 25 percent acetic acid (i.e., hydrochloric acid, citric acid, and lactic acid) and when sodium acetate were used, there was heavy growth on all plates. Solutions of acetic acid weaker than 1 percent are not consistently bactericidal in vitro.

The bactericidal and therapeutic effect of 2 percent acetic acid has also been demonstrated in vivo. Ochs (Ref. 11) reported on a series of 142 successive ear cases in which 2 percent acetic acid in propylene glycol was used to treat external otitis without a single failure. Ochs (Ref. 9) also reported treating 38 patients with chronic middle-ear infections using household vinegar. In 30 of the patients, he reported that the infection was quickly and effectively eliminated.

Goffin (Ref. 11) reported on two groups of patients with external otitis. One group, with an ear canal pH over 6.3, received 2 percent acetic acid in propylene glycol. The second group complained mostly of itching and had an ear canal pH under 6.3. This group was treated with a formulation containing acetic acid in propylene glycol with hydrocortisone added. All canals cleared within 7 days in the first group and within 10 days in the second group. The author attributed the difference in the number of days required to clear the ear canals to the pH and stated that cases with a pH higher than 6.3 appeared to be primarily infectious and responded promptly to antibacterial therapy. However, in cases with a pH lower than 6.3, factors other than infection, such as neurodermatitis, seborrheic dermatitis, and eczema, were more significant; and these cases responded less promptly even when hydrocortisone was added to the medication.

The Panel reviewed a study by Garrity, Halliday, and Glassman (Ref. 13), in which the authors reported very satisfactory results using 2 percent acetic acid in propylene glycol to prevent "swimmer's ear." The investigators observed 816 campers in two summer camps. The campers were divided into control and treatment groups. Those in the control group received no medication in their ears (although in the second camp, 190 subjects with less than 6 treatments out of a possible 24 during a 2-week stay were included in the control group). Campers in the treatment group were to receive two drops of the drug prophylactically in each ear, morning and evening. The investigators reported that in the first camp the prophylactic treatment prevented the occurrence of swimmer's ear in the treated group (no cases of swimmer's ear were reported in 31 subjects). In the untreated group, 3 out of 56 subjects developed swimmer's ear. In the second camp it was reported that none of the 462 subjects in the treated group developed swimmer's ear. In the control group, 3 out of 267 subjects developed swimmer's ear.

The agency has reviewed an additional study on prevention of swimmer's ear in campers. Heilig, Heilig, and Glassman (Ref. 14) did a 2-year study (two 46- to 47-day summer camping seasons) with followup of 400 children in a camp with over 10,000 swimming pool exposures. The authors stated that because of the high density of campers using a pool that was inadequate to handle the swimming load, there was a history of an unusually high incidence of swimmer's ear in the camp (approximately 30 cases occurred annually over several years). A solution of 2 percent acetic acid in propylene glycol was used in the study. Subjects were assigned into groups and treated (or not treated) as in the study by Garrity, Halliday, and Glassman (Ref. 13) above.

During the first summer, the investigators reported that 2 out of 246 campers in the treated group developed swimmer's ear, compared with 10 out of 246 campers in the control group. During the following summer, 4 out of 221 campers developed swimmer's ear in the treated group compared with 14 out of 202 in the control group. The authors reported that a followup 3 years later revealed that the prophylactic program had been discontinued and that the number of swimmer's ear cases was again increasing. For this reason, during a third and final summer camp period, supervised instillation of the product containing 2 percent acetic acid in propylene glycol was begun in a portion of the camp population.

The results showed that 21 of 83 untreated subjects (25.3 percent) developed swimmer's ear, and 1 of 54 campers (1.9 percent) who were treated prophylactically developed swimmer's ear. After comparing these results with the number of swimmer's ear cases that had occurred during the first and second camp periods of the same year when no prophylactic treatment was given, the authors reported that the treatment regimen was successful. During the first camp period, 7 campers out of 90 (7.8 percent) developed swimmer's ear. During the second camp period, 28 campers out of 139 (20.1 percent) developed swimmer's ear.

The data submitted by the comment consisted of a study in which 25 subjects were treated prophylactically with three drops of an aqueous solution of 2 percent acetic acid in the left ear every night (Ref. 1). The right ear served as a control and received no drug treatment. The purpose of the study was to demonstrate that 2 percent acetic acid in water prevented swimmer's ear. The results indicated that 7 subjects developed external otitis in the right ear and that 18 subjects did not develop external otitis. No adverse reactions developed. No other details of the study were given.

The agency concludes that the data that were reviewed by the Panel on the bactericidal effect of acetic acid are supportive of the ability of acetic acid to inhibit the growth of bacteria. Because acetic acid creates an undesirable environment for bacteria, it is possible that the ingredient would be beneficial in preventing swimmer's ear. However, the data did not demonstrate this effect (Refs. 6 through 13).

The agency concludes that the studies conducted to demonstrate the effectiveness of 2 percent acetic acid in

propylene glycol or in water in preventing swimmer's ear are inadequate because of deficiencies in the study design, lack of adequate baseline data and controls, and insufficient information in the studies (Refs. 1, 13, and 14). None of the studies contains information on the condition of the subjects' ears at baseline (before they entered the control or treatment groups), making it impossible to determine which subjects may have had symptoms of infection before being placed in the study. Also, the studies do not provide any evidence on whether the subjects had a previous history of swimmer's ear. Knowledge of a history of swimmer's ear is important because swimmer's ear infections are known to recur in susceptible individuals. Thus, the lack of data on the past history of the subjects as well as the lack of documentation on the condition of the subjects at baseline makes it impossible to determine whether control and treatment groups were comparable.

Furthermore, the agency notes that in the study by Garrity, Halliday, and Glassman (Ref. 13), assignment of patients to control and treatment groups was not randomized, and, in fact, all of the camp staff elected not to participate in the prophylactic program and thus were included in the control group. Additionally, 190 subjects who received less than 6 treatments were included in the control group, and those who received between 6 and 24 treatments (462 campers) were included in the treatment group. The agency questions the scientific validity of this manipulation. Moreover, in that same study, records indicate that in the second camp, the nurse responsible for overseeing the record keeping and administration of the medication frequently lost contact with campers who were on exercises in the wilderness. In view of these deficiencies, the agency does not consider this study adequately controlled, and the validity of any results reported is questioned.

The results obtained in the study by Heilig, Heilig, and Glassman (Ref. 14) are also unreliable because that study, like the previously discussed studies, lacks baseline data, has questionable comparability of control and treatment groups, lacks documentation on whether or not campers had symptoms of swimmer's ear when they arrived at camp, and does not provide adequate information on whether control and treatment groups had a comparable number of swimming pool exposures.

Furthermore, the agency notes that a prescription drug product containing 2 percent acetic acid in a propylene glycol vehicle was reviewed by the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group. That group evaluated the drug as probably effective for the treatment of otitis external caused by bacterial and fungal pathogens and possibly effective for the prevention of otitis external in swimmers and susceptible subjects. (See the **Federal Register** of September 18, 1970; 35 FR 14630.) In response to the notice, substantial evidence of effectiveness for the treatment indication was submitted, but data submitted to establish the effectiveness of the prophylactic indication failed to provide substantial evidence of effectiveness. Subsequently, in the **Federal Register** of July 19, 1974 (39 FR 26462), FDA reclassified the "possibly effective" indication to "lacking substantial evidence of effectiveness," and interested persons were afforded the opportunity to request a hearing on the matter. In response to the 1974 notice, data were submitted to establish the effectiveness of the prevention indication. These data included the studies by Garrity, Hallidy, and Glassman (Ref. 13) and by Heilig, Heilig, and Glassman (Ref. 14); however, the data were found inadequate to support the claim. On March 11, 1983, the manufacturer of the product filed a supplement to its NDA providing for the deletion of the prevention claim (Ref. 15).

The study submitted by the comment (Ref. 1) does not contain information on how or under what conditions the study was conducted; how the presence or absence of swimmer's ear was determined; how subjects were selected and whether they were studied continuously for 2 years (the study is dated June 1980 through June 1982); whether subjects had a history of swimmer's ear; and whether they were exposed to similar conditions that might cause them to develop swimmer's ear. Because of the lack of details in the study, the meaning of the results cannot be determined. The agency's comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 16).

Based on the defects described above, the agency does not consider these studies adequate to establish that acetic acid should be classified as a Category I ingredient for the prevention of swimmer's ear. A study designed to measure a drug's ability to prevent an ear infection must contain provisions that ensure that (1) subjects are comparable with respect to the presence or absence of the disease at the beginning of the study and (2) both control and treatment groups receive comparable exposure to conditions that might promote the development of swimmer's ear.

After consideration of the above data, the agency concludes that 2 percent acetic acid is safe for use in the ear. However, the data are inadequate to demonstrate the effectiveness of 2 percent acetic acid in distilled water or in propylene glycol for the prevention of swimmer's ear. Therefore, 2 percent acetic acid in distilled water or in propylene glycol is classified in Category III in this tentative final monograph. Adequate data to demonstrate the effectiveness of 2 percent acetic acid in preventing swimmer's ear must be submitted in order to upgrade this ingredient to monograph status.

References

(1) Comment No. LET004, Docket No. 77N–0334, Dockets Management Branch.

(2) Berkow, R., editor, "The Merck Manual," 14th Ed., Merck and Co., Inc., Rahway, NJ, p. 1946, 1982.

(3) Goodhill, V., "Diseases, Deafness, and Dizziness," Los Angeles, p. 286, 1979.

(4) "Boies's Fundamentals of Otolaryngology," 5th Ed., W.B. Saunders Co., Philadelphia, p. 182, 1978.

(5) "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, pp. 406–407, 1982.

(6) Pertinent pages of the Interim Working Papers of the Topical Analgesic, Antirheumatic, Otic, Burn, Sunburn Treatment and Prevention OTC Drug Review Panel, OTC Volume 06CTFM, Dockets Management Branch.

(7) Summary Minutes of the Topical Analgesic, Antirheumatic, Otic, Burn, Sunburn Treatment and Prevention OTC Drug Review Panel, July 12 and 13, 1973, November 18 and 19, 1976, February 23 and 24, 1977, and May 25 and 26, 1977, Dockets Management Branch.

(8) Osol A., editor, "Remington's Pharmaceutical Sciences," 16th ed., Mack Publishing Co., Easton, PA, pp. 1256–1257, 1980.

(9) Ochs, I.L., "Use of Vinegar as an Antibiotic in the Treatment of Chronic Middle Ear Disease," *Archives of Otolaryngology*, 52:935–941, 1950.

(10) Jones, E.H., and P.G. McLain, "Does Acid pH Inhibit Bacterial Growth in the External Ear Canal?," *The Laryngoscope*, 71:928–936, 1961.

(11) Ochs, I.L., "External Otitis," *Medical Times*, 88:579–581, 1960.

(12) Goffin, F.B., "pH as a Factor in External Otitis," *The New England Journal of Medicine*, 268:287–289, 1963.

(13) Garrity, J.D., T.C. Halliday, and J.M. Glassman, "Prevention of Swimmer's Ear by Simple Prophylactic Regimen," *Current Therapeutic Research*, 16:437–441, 1974.

(14) Heilig, D., M.C. Helig, and J.M. Glassman, "Prophylactic Use of a Topical Non-Aqueous Acetic Acid Medication for the Prevention of Otitis Externa (Swimmer's Ear): A Two-year Study with Follow-up," *Current Therapeutic Research*, 26:862–873, 1979.

(15) Letter from R.D. Frawley, Carter-Wallace, Inc., to C. Kimbrough, FDA, OTC Volume 06CTFM, Dockets Management Branch.

(16) Letter from W.E. Gilbertson, FDA, to T.H. Pope, Jr., coded LET009, Docket No. 77N–0334, Dockets Management Branch.

2. One comment submitted data on a formula containing 5 percent anhydrous glycerin and 95 percent isopropyl alcohol and stated that this formula is safe and effective "for prevention of swimmer's ear and treatment of water-clogged ears" (Ref. 1). The comment requested that the monograph be amended to allow those claims for products containing the two ingredients. In addition, the comment expressed concern about the agency's reclassification of glycerin from Category I to Category III in the tentative final monograph. The comment believed that, although the evidence in support of the effectiveness of glycerin may not suffice for approval of a new drug application, the evidence is of the same caliber as that found sufficient for other OTC drug ingredients, such as eugenol for the relief of toothache (47 FR 22728).

The agency has determined that the submitted data demonstrate the safety of the combination of 5 percent anhydrous glycerin and 95 percent isopropyl alcohol, but do not provide sufficient evidence of the effectiveness of these ingredients as a topical otic drug product "for the prevention of swimmer's ear" or the "treatment of water-clogged ears." Both an in vitro study and a clinical study were submitted to demonstrate the efficacy of this product in drying excess moisture in the ears (Ref. 1). In the vitro study, known weights of water were placed in petri dishes and varying amounts of the product were then added to the water. The petri dishes were left for 5 minutes covered (serving as a control) and uncovered in a 37° C incubator (to simulate the temperature of the outer ear canal). The results indicated a higher percentage of moisture lost in the uncovered petri dishes when compared with the covered petri dishes. Although these data are supportive, an in vitro study alone cannot substitute for a well-designed clinical study to establish effectiveness.

In the clinical study, both ears of 49 patients were irrigated with water. The investigators determined the amount of water in the ears by tactilely palpating and visually inspecting the ears. A score of 0 (maximum wetness) to 5 was assigned depending on the degree of wetness of the ear. Following irrigation and scoring, the right ear of each patient received 4 or 5 drops of the product; the left ear was not treated with a drug, and served as a control. The patients' comments regarding any sensations in the ears were recorded. At the end of 5 minutes the ears of each patient again were visually inspected and palpated to determine the amount of water remaining in the ear. The results indicated that 5 percent anhydrous glycerin in 95 percent isopropyl alcohol was successful in drying more than 50 percent of the water in the ears of 42 out of 49 patients within a 5-minute period.

This clinical study provides some evidence of the product's effectiveness in drying water in the ear; however, this study did not state clearly that the test subjects had the symptoms of water-clogged ears. The ears of the test subjects were not randomized (all right ears were drug treated) and the study was not blinded. As a result, the determination of the product's effectiveness by the investigators may have been biased. The agency believes that another well-controlled clinical study is necessary to demonstrate the effectiveness of the product to help dry water in the ears or to help relieve the discomfort of water-clogged ears by drying excess water. The agency encourages the use of objective measurements to determine the decrease in the amount of water in the ears and subjective measurements to determine the decrease in the patient's degree of discomfort and to measure the relief of discomfort. The agency also believes that more than one observation at the end of a 5-minute period is necessary to evaluate the effectiveness of the product.

In addition, the study was not appropriately designed to demonstrate a claim of "prevention of swimmer's ear." The results did not show prevention of, or a reduction in, the incidence of swimmer's ear in a susceptible target population (i.e., persons with a history of recurrent swimmer's ear). (See comment 1 above.)

In the submission, the two ingredients are claimed to be a combination product, yet the data did not show the effectiveness of each ingredient alone. If therapeutic claims are made for both the anhydrous glycerin and the isopropyl alcohol, then each ingredient must be tested alone and also in combination to demonstrate the effectiveness of the combination. However, if glycerin functions only as a vehicle (and the need for it as a vehicle is shown) and no claims are made for it as an active ingredient, additional testing would not be required for this ingredient.

The agency believes that a claim of "prevention of swimmer's ear" is an acceptable OTC drug claim; however, adequate data must be provided to demonstrate the effectiveness of any ingredient(s) making such a claim. The agency acknowledges that the term "water-clogged ears" is not a recognized clinical entity and is not a term found in textbooks. However, the agency believes that consumers use the term "water-clogged ears" to refer to the temporary retention of water in the ears after swimming, showering, washing the hair, bathing, etc. It is well recognized that the retention of water in the ears is annoying and uncomfortable and can interfere with hearing. Some people experience a sensation of fullness or hearing impairment after getting water in the ear canal. Therefore, the agency believes that a claim such as "helps relieve the discomfort of water-clogged ears by drying excess water" would be acceptable because it relates to the relief of the symptoms described above. The agency believes that the phrase "helps dry water in the ears" or "helps relieve the discomfort of water-clogged ears by drying excess water" should be used in labeling instead of the comment's suggested phrase "treatment of water-clogged ears." The former phrases are more specific and better define the intended pharmacologic action of the drug. Therefore, the agency is proposing both of these claims in this tentative final monograph.

The agency is also proposing that the combination of 5 percent anhydrous glycerin and 95 percent isopropyl alcohol "for the prevention of swimmer's ear" and "for the drying of water in the ears" or "to help relieve the discomfort of water-clogged ears by drying excess water" be placed in Category III in this tentative final monograph. Adequate data must be submitted to demonstrate the efficacy of these ingredients for these proposed uses.

In response to the comment's concern about the reclassification of glycerin to Category III in the earlier tentative final monograph (47 FR 30014), the agency notes that that reclassification concerns glycerin as an earwax removal aid, not as an ingredient for the prevention of swimmer's ear or the drying of water in the ears. Glycerin and isopropyl alcohol for these conditions were not classified by the Panel in its report or by the agency in the tentative final monograph. Eugenol was classified by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products as a

Category I toothache relief agent in the advance notice of proposed rulemaking for OTC drug products for the relief of oral discomfort, published in the Federal Register of May 25, 1982; 47 FR 22712. At present, the agency cannot address the comment's statement that the supporting evidence for glycerin is comparable to that of eugenol because the agency has not completed its review of the Dental Panel's recommendations on relief of oral discomfort drug products.

The agency's comments and evaluation of the data are on file in the Dockets Management Branch (Refs. 2 and 3).

References

(1) Comment No. C00007, Docket No. 77N–0334, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA to H.W Gordon, Commerce Drug Co., Inc., coded LETS006, Docket No. 77N–0334, Dockets Management Branch.

(3) Letter from W.E. Gilbertson, FDA to H.W. Gordon, Commerce Drug Co., coded LET010, Docket No. 77N–0334, Dockets Management Branch.

II. The Agency's Tentative Conclusions on OTC Topical OTIC Drug Products

A. Summary of Ingredient Categories and Testing of Category III Conditions.

1. Summary of ingredient categories. The agency has reviewed the submitted data on 2 percent acetic acid and the combination of 5 percent anhydrous glycerin and 95 percent isopropyl alcohol used for the prevention of swimmer's ear and 5 percent anhydrous glycerin and 95 percent ispropyl alcohol used for the drying of water in the ears or for the relief of the discomfort of water-clogged ears by drying excess water, as well as other data and information available at this time, and is classifying these ingredients in Category III for these uses. (See comments 1 and 2 above.) Adequate data must be submitted to the agency in order to demonstrate the effectiveness of these ingredients for these claims. The agency is aware that topical otic drug products containing other ingredients for which no data were submitted to the Panel or to the agency are also marketed OTC for the prevention of swimmer's ear. The agency invites comments and the submission of data on any ingredient that is promoted for any claim related to the prevention of swimmer's ear, the drying of water in the ears, or the relief of the discomfort of water-clogged ears by drying excess water. If no data are submitted or the data are insufficient to establish the safety and effectiveness of any ingredient for these conditions, then any ingredient marketed OTC will be classified as a nonmonograph condition in a final rule, and upon the effective date of that final rule will require an approved NDA before continuing marketing.

2. Testing of Category III conditions. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any topical otic drug ingredient for the prevention of swimmer's ear, the drying of water in the ears, or the relief of the discomfort of water-clogged ears by drying excess water, or for any condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Recommendations.

FDA has considered the comments and other revelant information and has tentatively reached the following conclusions:

1. The agency is proposing that 2 percent acetic acid in distilled water or in propylene glycol and the combination of 5 percent anhydrous glycerin and 95 percent isopropyl alcohol be placed in Category III for the prevention of swimmer's ear. The agency is also proposing a Category III classification for the combination of 5 percent anhydrous glycerin and 95 percent isopropyl alcohol for the drying of water in the ears or for the relief of the discomfort of water-clogged ears by drying excess water.

2. Although no ingredients for the prevention of swimmer's ear, the drying of water in the ears, or the relief of the discomfort of water-clogged ears by drying excess water have been determined to be generally recognized as safe and effective and not misbranded, the agency is proposing labeling for these products in this tentative final monograph in the event that new data are submitted that result in the upgrading of any ingredient to monograph status. The proposed doses in the directions are based on the directions of some of the currently marketed swimmer's ear and ear water-drying products. However, if acceptable new data support different doses, the final monograph will reflect the new data.

3. The warnings in this tentative final monograph are based on (1) the warnings proposed for earwax removal aids in the tentative final monograph for OTC topical otic drug products but which are also applicable to products for the prevention of swimmer's ear and relief of water-clogged ears, (2) currently marketed products, and (3) the discussion of swimmer's ear drug products in the Panel's interim working papers. Additionally, the agency is proposing other warnings to provide for the safe and proper use of these drug products.

4. In the event that any ingredient for the prevention of swimmer's ear, the drying of water in the ears, or the relief of the discomfort of water-clogged ears by drying excess water is upgraded to monograph status, the agency is amending the tentative final monograph for topical otic drug products by revising the existing heading of § 344.10 ("Topical otic active ingredient") to read "Earwax removal aid active ingredient" and revising the existing heading of § 344.50 ("Labeling of topical otic drug products") to read "Labeling of earwax removal aid drug products." The agency also proposes to add definitions for the terms "water-clogged ears," "ear water-drying aid," "swimmer's ear," and "swimmer's ear prevention aid," in § 344.3 (c), (e), and (f), respectively, and to add new § 344.12 entitled "Ear water-drying aid active ingredients," new § 344.14 entitled "Swimmer's ear prevention aid active ingredients," new § 344.52 entitled "Labeling of ear water-drying aid drug products," and new § 344.54 entitled "Labeling of swimmer's ear prevention aid drug products."

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule on OTC topical otic drug products to include labeling for the prevention of swimmer's ear, the drying of water in the ears, and the relief of the discomfort of water-clogged ears by drying excess water, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act,

Public Law 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC topical otic drug products for the prevention of swimmer's ear, the drying of water in the ears, and the relief of the discomfort of water-clogged ears by drying excess water is not expected to pose such an impact on small businesses. Therefore, the agency certified that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC topical otic drug products for the prevention of swimmer's ear, the drying of water in the ears, or the relief of the discomfort of water-clogged ears by drying excess water. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC topical otic drug products for the prevention of swimmer's ear, the drying of water in the ears, or the relief of the discomfort of water-clogged ears by drying excess water should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on topical otic drug products for these conditions, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

In the **Federal Register** of April 22, 1985 (50 FR 15810) the agency proposed to change its "exclusivity" policy for the labeling of OTC drug products that has existed during the course of the OTC drug review. Under that policy, the agency had maintained that the terms used in an OTC drug product's labeling were limited to those terms included in a final OTC drug monograph.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing the exclusivity policy and establishing three alternatives for stating the indications for use in OTC drug labeling. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "**APPROVED USES**"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "**APPROVED USES**"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "**APPROVED USES**"; plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph. The proposed rule in this document is subject to the final rule revising the exclusivity policy.

Interested persons may, on or before September 29, 1986, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before November 28, 1986. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before July 30, 1987, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before September 30, 1987. These dates are consisent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on (September 30, 1987). Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register,** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 344

OTC drugs; Topical otic drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Administrative Procedure Act, and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 344 as proposed in the **Federal Register** of July 9, 1982, 47 FR 30012, as follows:

PART 344—TOPICAL OTIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR Part 344 would continue to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.11.

2. In Subpart A, § 344.3 is amended by adding new paragraphs (c), (d), (e), and (f), to read as follows:

§ 344.3 Definitions.

* * * * *

(c) *Water-clogged ears.* The retention of water in the external ear canal thereby causing discomfort and a sensation of fullness or hearing impairment.

(d) *Ear water-drying aid.* A drug used in the external ear canal to help dry water-clogged ears.

(e) *Swimmer's ear.* A bacterial or fungal infection of the skin lining the external auditory canal that may occur in susceptible individuals following the retention of water in the ears, also known as external otitis.

(f) *Swimmer's ear prevention aid.* A drug used in the external ear canal to aid in the prevention of swimmer's ear (external otitis).

3. In subpart B, by revising the section heading of § 344.10 and by adding new §§ 344.12 and 344.14 to read as follows:

§ 344.10 Earwax removal aid active ingredient.

* * * * *

§ 344.12 Ear water-drying aid active ingredients. [Reserved]

§ 344.14 Swimmer's ear prevention aid active ingredients. [Reserved]

4. In subpart C, by revising the section heading of § 344.50 and by adding new §§ 344.52 and 344.54 to read as follows:

§ 344.50 Labeling of earwax removal drug products.

* * * * *

§ 344.52 Labeling of ear water-drying aid drug products.

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

(b) *Indications.* The labeling of the product states, under the heading "Indications," one or both of the following: "Helps dry water in the ears," or "Helps relieve the discomfort of water-clogged ears by drying excess water." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(1) "Do not use if you have ear drainage or discharge, ear pain, irritation or rash in the ear, or are dizzy; consult a doctor."

(2) "Do not use if you have an injury or perforation (hole) of the ear drum or after ear surgery unless directed by a doctor."

(3) "Avoid contact with the eyes."

(4) "Discontinue use and consult a doctor if undue irritation or sensitivity occurs."

(5) *For products containing alcohol.* "Keep away from fire or flame."

(d) *Directions.* Apply 4 or 5 drops in each ear when water remains in the ear after swimming, showering, or bathing.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 344.54 Labeling of swimmer's ear prevention aid drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "swimmer's ear prevention aid."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "Aids in the prevention of swimmer's ear (external otitis)" [which may be followed by the appropriate term(s): "by helping to dry moisture in the ears" or "by restoring the normal acidity of the ears"]. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the prohibitions in section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(1) "Do not use this produce unless you have a previous history of swimmer's ear."

(2) "Do not use if you have ear drainage or discharge, ear pain, irritation or rash in the ear, or are dizzy; consult a doctor."

(3) "Do not use if you have an injury or perforation (hole) of the ear drum or after ear surgery unless directed by a doctor."

(4) "Avoid contact with the eyes."

(5) "Discontinue use and consult a doctor if undue irritation or sensitivity occurs."

(6) *For products containing alcohol.* "Keep away from fire or flame."

(d) *Directions.* Apply 4 or 5 drops in each ear after swimming, showering, or bathing or as directed by a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

Dated: May 3, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

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