[4110–03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 344]

[Docket No. 77N–0334]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Topical Otics

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This is a proposal to establish conditions under which over-the-counter (OTC) topical otic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-the-Counter (OTC) Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products.

DATES: Comments by March 16, 1978, and reply comments by April 14, 1978.

ADDRESSES: Written comments to the Hearing Clerk (HFC–20), Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: Pursuant to Part 330 (21 CFR Part 330), the Commisioner of Food and Drugs received on August 23, 1977, a report of the Advisory Review Panel on Over-The-Counter (OTC) Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing: (1) A proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC topical otic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; and (3) the conclusions and recommendations of the Panel to the Commissioner: The summary minutes of the Panel metings are on public display in the office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, but has concluded that the Panel's findings should first be issued as a formal proposal to obtain full public comment before any decision is made on the recommendations of the Panel. The findings of the Panel represents the best scientific judgment of the members. The findings have been prepared independently of FDA and do not necessarily reflect the agency's position on any particular matter contained therein. After careful review of all comments submitted in response to this proposal, the Commissioner will issue in the FEDERAL REGISTER a tentative final regulation establishing a monograph for OTC topical otic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC topical otic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before January 16, 1978, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to William E. Gilbertson, Pharm.D., FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD–510), 5600 Fishers Lane, Rockville, Md. 20857.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

The Commissioner has reviewed the potential environmental impact of the recommendations and proposed monograph for OTC topical otic products of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products and has concluded that the Panel's recommendations and proposed monograph will not significantly affect the quality of the human environment and that an environmental impact statement is not required. A copy of the environmental assessment is on file with the office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

In the FEDERAL REGISTER for January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 (formerly § 130.301) published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations, the Commissioner issued in the FEDERAL REGISTER of December 12,1972 (37 FR 26456) a request for data and information on all topical analgesic, including antirheumatic, otic, burn, sunburn prevention and treatment active ingredients in drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC topical analgesic, including antirheumatic, otic, burn, sunburn prevention and treatment products pursuant to § 330.10(a)(1):

Thomas G. Kantor, M.D., Chairman
John Adriani, M.D.
Col. William A. Akers, M.D.
Maxine Bennett, M.D.
Minerva S. Buerk, M.D.
Walter L. Dickison, Ph.D.
Jerry Mark Shuck, M.D.

For purposes of this review, the Panel grouped the active ingredients and labeling into four major pharmacologic groups, i.e., topical analgesics, topical protectants, topical otics, and topical sunscreens. The Panel presents its conclusions and recommendations for topical otic active ingredients in this document. The Panel's conclusions and recommendations for topical analgesic, topical protectant and topical sunscreen active ingredients will be presented in a later issue of the FEDERAL REGISTER.

The Panel was first convened on March 6, 1973 in an organizational meeting. Working meetings were held on May 8 and 9, July 12 and 13, September 27 and 28, November 3 and 4, November 26 and 27, 1973; January 30 and 31, March 6 and 7, April 10 and 11, May 8 and 9, June 10 and 11, July 17 and 18, September 24 and 25, October 22 and 23, November 26 and 27, 1974; January 21 and 22, March 13 and 14, April 17 and 18, May 21 and 22, July 15 and 16, September 30 and October 1, November 12 and 13, 1975; March 4 and 5, May 19 and 20, June 22 and 23, September 27 and 28, November 18 and 19, 1976; February 23 and 24, May 25 and 26 and August 22, 23, and 24, 1977.

Six nonvoting liaison representatives served on the Panel. Mrs. Jacqueline Pendleton (at the initial meeting), Mrs. Valerie Howard (from May 8, 1973 until September 28, 1973), Lynn Berry (from November 3, 1973 until April 27, 1976) and Kathleen A. Blackburn (from March 5, 1976 until August 24, 1977), each nominated by an ad hoc group of consumer organizations, served as the consumer liaison, and Joseph L. Kanig, Ph.D., nominated by the Proprietary Association, and Ben Marr Lanman, M.D.,

nominated by the Cosmetic, Toiletry, and Fragrance Association, served as the industry liaisons.

The following FDA employees served: C. Carnot Evans, M.D., served as Executive Secretary. Lee Geismar, served as Panel Administrator. Lee Quon, R. Ph., served as Drug Information Analyst until July 1973, followed by Thomas H. Gingrich, R. Ph., until July 1975, followed by Timothy T. Clark, R. Ph., until July 1976, followed by Victor H. Lindmark, Pharm. D.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or the Panel's request on the issues before the Panel:

Joseph P. Armellino, M.D.
Charles Bluestone, M.D.
Stuart Ericksen, Ph. D.
Alexander A. Fisher, M.D.
J. M. Glassman, M.D.
Thomas Fitzpatrick, M.D., Ph. D.
Peter Hebborn, Ph. D.
Howard Maibach, M.D.
Edward Marlowe, M.D.
Kenneth L. Milstead
John Parrish, M.D.
Madue Pathak, M.D.
Robert Sayre, Ph. D.
Joseph P. Soyka, M.D.
Garrett Swenson, Esq.
Stephen M. Truitt, Esq.
Frederick Urbach, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through August 23, 1977 in arriving at its conclusions and recommendations for OTC topical otic drug products.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to topical otic active ingredients are set forth in three categories:

Category I. Conditions under which topical otic drugs are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which topical otic drugs are not generally recognized as safe and effective or are misbranded.

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

The Panel recommends the following for each group of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in a drug's being not generally recognized as safe and effective or misbranded (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. The Panel identified no conditions for which available data were insufficient to permit final classification at this time. In other words, no topical octic active ingredient was classified as Category III.

I. SUBMISSION OF DATA AND INFORMATION

Pursuant to notice published in the FEDERAL REGISTER of December 12, 1972 (37 FR 26456) requesting the submission of data and information on OTC topical otic drugs, the following firms made submissions related to the indicated products:

A. SUBMISSIONS BY FIRMS

Firms	*Marketed products*
Calhoun's Laboratory, Baxley, Ga. 31513.	Ear-Chek Drops.
International Pharmaceutical Corp., Warrington, Pa. 18976.	Debrox Drops.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Emardon Ear Drops.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL

Anhydrous glycerol, Antipyrine, Benzocaine, Carbamide peroxide, Glycerine.

C. CLASSIFICATION OF INGREDIENTS

1. *Active Ingredients.*
Antipyrine, Benzocaine, Carbamide peroxide in glycerin (carbamide peroxide in anhydrous glycerol), Glycerin (Glycerin, anhydrous glycerol).

2. *Inactive Ingredients.*
None.

3. *Ingredients deferred to other OTC advisory review panels or other experts.*
None.

D. REFERENCED OTC VOLUME SUBMISSIONS

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of December 12, 1972 (37 FR 26456). The volumes shall be put on public display on or before January 16, 1978, in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

II. TOPICAL OTICS

A. GENERAL DISCUSSION

1. *Introduction.* As part of its review, the Panel was charged to evaluate data and information on the safety, effectiveness, and labeling of OTC topical otic active ingredients. The Panel received three submissions pertaining to three different OTC marketed products. Each of the products contains ear wax softening agents (discussed below) with various labeling claims for use in "wax removal," "ear hygiene," and "wax prevention". One of the products also contains an anesthetic (benzocaine) and an analgesic (antipyrine) with additional labeling claims "to relieve minor irritation caused by wax, itching and other discomforts." The Panel also reviewed a submission deferred from the OTC Miscellaneous External Drug Products Panel for one of the ear wax softening products noted above. In this case, the product, which contains carbamide peroxide, is promoted ethically (not to the general public) for the treatment and prophylaxis of otitis externa (e.g., swimmer's ear), furunculosis, otomycosis, minor cuts, burns, and abrasions or exudative otitis media.

As will be discussed more fully below, the Panel concluded that ear (otic) symptoms such as "earache", "infected ear," "running ear", and "cold in the ear" are usually caused by some underlying disease process that requires diagnosis and treatment by a physician, and should not be self-treated. These symptoms may not only be the result of a disease process of the external and middle ear but they could also be due to referred pain from another area of the head or neck region. A traumatic or pathologic condition of the tongue, teeth, oropharynx (throat), tonsils, or paranasal (nose) sinuses may cause referred pain to the ear and may appear to the individual as an "earache". Symptoms that are caused by a disease process are usually progressive and therefore preclude the use of OTC products except under the advice and supervision of a physician.

The Panel further concluded that the topical use of OTC ingredients should be restricted to the relief of self-limiting conditions related to the external ear. The only condition the Panel considered appropriate for self-treatment with OTC otic products is cerumen (wax) accumulation in the external ear canal. For such purposes, the Panel felt that only ingredients that soften and loosen ear wax (ear wax softening agent) are safe for OTC adult use. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician. In contrast, ingredients that dissolve ear wax (cerumenolytic agents) were judged to be unsafe for OTC use. Cerumenolytic agents should be administered only by a physician in situations in which the cerumen is impacted and cannot be safely removed by self-medication. Ear wax softening agents, as distinguished from cerumenolytic agents which dissolve wax, are aids that soften and loosen obstructive ear wax which is then removed by irrigation with warm water.

To assure proper use of these products and to adequately distinguish them from use in disease conditions, the Panel recommends that the labeling of ear wax softening agents contain the following warnings: "Discontinue use if there is pain or dizziness and consult a physician" and "If symptoms of fullness persist, consult a physician". Symptoms that can safely be relieved by OTC otic products should subside within a short time after self-medication. If symptoms persist or if an adverse reaction to the medication occurs, the individual should consult a physician. The Panel has provided in the labeling for a warning to alert individuals with a possible disease condition against the use of ear wax softening agents. The warning states:

Caution: Do not use in the ear in the presence of ear drainage, ear pain or known ear drum perforation (hole) or injury.

The Panel discusses below the conditions under which OTC topical otic ingredients should not be used in the ear, conditions for which the individual should not be used in the ear, conditions for which the individual should consult a physician, e.g., pruritus, infection, ear drainage etc., and the basis for the recommended labeling.

Historical background. Man has been subject to earache and other otological symptoms since his beginning. Locally applied heat for the relief of earache has come down through the ages as the sovereign remedy (Ref. 1). Various methods of applying heat have been employed. Salt was heated and applied externally; a hot roasted onion was held against the ear; or warm liquids were poured into the ear. The physician Minyomi (described in the Talmud) taught that any kind of fluid to relieve ear pain is bad except for the juice of kidneys. He stated that "One should take the kidney of a bald buck, cut it crosswise and place it on glowing coals and pour the water which comes out of it into the ear, neither cold nor hot, but tepid" (Ref. 2).

Many remedies have been suggested for deafness. In the middle of the nineteenth century, Dr. William R. Wilde (Ref. 3) notes that variuos solutions were used to syringe the ears in the hope that the deafness was the result of a collection of hardened wax; "then setting the digestive organs to rights by purgation, and a course of bitters lest the affection might be owing to the stomach. Next in order, blistering behind the ears is tried, in order to draw away some peccant humour that had perhaps accumulated round the delicate organ of hearing. These, and such methods failing to give relief, stimulants, often of a very acrid nature, are poured into the external auditory passages, either to restore the secretion, or to excite or rouse the dormant nervous power. Hot tinctures, turpentine, creosote, and pungent oils are applied to the external surface of the tympanic membrane without mercy" (Ref. 3). Dr. Wilde also described an old popular superstition in which black wool is placed in the meatus in order to preserve the organ from cold, specifying that the wool to be effective should be "procured from the left forefoot of a six year old black ram." Some also advised placing a slice of fat bacon to be inserted into the meatus every second night. Wilde concludes that since all of these means have failed, "we need not wonder that suffering patients throw themselves into the hands of quacks and nostrum-mongers" (Ref. 3).

When bloodletting was a part of the physician's daily curriculum, leeches were applied to every painful ear. Wilde gives specific and careful instructions on local depletion by leeches. In an 1894 home treatment guide by Dessar (Ref. 4), he noted "if there is severe throbbing pain, deep in the ear, two leeches should be applied, one in front of and the other immediately behind the ear, the opening being previously plugged with cotton. In children one will be sufficient. The leeches should be left on for at least ten minutes, or until they drop off."

The Panel is of the opinion that many folklore remedies and superstitions regarding ear disease still persist. This is understandable when it is realized that scientific medical knowledge regarding the ear and the availability of special instrumentation for examining and evaluating ear function have only been acquired in recent decades. There is a great need for consumer education regarding ear care and tropical otic therapy.

2. *Definitions.* The following definitions pertain to otic products:

2. *Cerumen.* The wax-like substance found in the normal human ear canal.

b. *Cerumenolytic agent.* An agent that dissolves or disintegrates cerumen in the external ear canal.

c. *Cerumenolysis.* The dissolution or disintegration of cerumen in the external ear canal.

d. *Ear wax softening agent.* An agent that softens and loosens ear wax (cerumen).

3. *Anatomy and physiology of the external ear and ear canal.*—a. *The article or pinna.* This is a flattened, irregular, oval structure which is the external expansion of the cartilagenous canal. The skin covering the auricle is thin and vascular and therefore more reactive than anywhere else on the body. There is a distinct subcutaneous layer only on the posterior medial convex surface. There are a few small hairs in the skin. The sebaceous glands are sometimes of considerable size. The sweat glands are scarce and small. The lobule consists primarily of fatty tissue covered by skin (Refs. 5 and 6). The auricle and external auditory canal show great individual variations in size and shape.

b. *The external auditory (ear) canal.* The canal extends from the concha of the auricle to the medial terminus, the tympanic membrane (Ref. 6). The canal, which is cone shaped, ends for all purposes in a blind recess. It is the only epithelial-lined cul-de-sac in the body (Ref. 5). The canal is divided into a cartilagenous (outer one-third) and a bony (inner two-thirds of the canal) part. The long axis of these two portions of the external auditory canal is not in a straight line. The cartilagenous part is directed slightly upward and backward and the osseous canal slightly downward and forward. At the junction of the cartilagenous and osseous portions, there is a narrowing called the isthmus. Beyond the isthmus, the floor of the canal dips downward to the junction of the annulus with the tympanic membrane to form a depression termed the tympanic recess. Water or liquids may be retained in this recess and give the feeling of fullness in the ear until removed.

c. *The skin of the external auditory (ear) canal.* The canal is lined with skin which is much thicker in the cartilagenous portion (0.5 to 1.0 mm) than in the bony canal (0.2 mm). There are also other differences. The skin of the outer one-third of the canal (cartilagenous) has definite dermal papillae and a well developed subcutaneous layer. The skin of the inner two-thirds of the canal (osseous portion) has no subcutaneous layer, is devoid of papillae, is firmly attached to the periosteum, and is directly continuous with the external layer of the tympanic membrane. The hairs of the external auditory canal are confined to the cartilagenous meatus and vary greatly in their development and stiffness. Their function appears to be protective in character by trapping some of the larger foreign bodies in their waxy mesh.

Sebaceous glands and apocrine glands are found in large numbers in the skin of the cartilagenous canal, but are absent from the skin of the osseous canal. The oily secretion of the sebaceous glands is secreted into the follicular canal of the hair in the superficial part of the dermis. The apocrine glands are not active until puberty. They occur more abundantly on the superior and inferior walls in the canal, and the ducts can open both into the upper part of the follicular hair canal or freely onto the skin surface.

d. *Secretions.* The highly viscous sebaceous secretions from the large sebaceous glands of the hair follicles and the watery pigmented secretions from the apocrine glands combine with the exfoliated surface cells of the horny layer of the epidermis to form a protective, waxy, water repellent coating for the external auditory canal. This is known as cerumen or ear wax (Ref. 7). The number of glands in each ear is between one and two thousand. They derive their blood supply from the anterior auricular branch of the superficial temporal artery and their nerve supply from the auricular branch of the vagus nerve or Arnold's nerve (Ref. 8). Cerumen has been investigated as to its composition by several workers (Refs. 6, 8, and 9). It contains variable amounts of water, fats, fatty acids, carbohydrates, protein, free amino acids, ash, pigment (yellow) and some unknowns. The odor is noted as being acrid.

The age of the individual has no definite effect on the color, consistency, or amount of wax. The dryer the wax present, the darker is its color and the harder its consistency (Refs. 6 through 12).

e. *The tympanic membrane.* The membrane, commonly known as the ear drum, rests at the end of the external auditory canal. It serves as a protection to the middle ear from external foreign material and also functions in transmitting the airborne sound waves to the middle ear.

f. *The acid mantle.* The skin of the normal ear canal is one the acid side. Fabricant and Perlstein (Ref. 13) measured the pH of the cutaneous surface of the external auditory canal in 131 subjects (27 infants, 44 children, and 60 adults) and found little difference in all the various groups. The pH values fall chiefly within the acid range at or around pH 6.0. This "acid mantle" defends against bacterial and fungal invasion (Refs. 14 and 15).

g. *Natural cleansing.* The external ear is equipped with a "self-cleansing" process. Accumulated wax and other desquamated keratin are continuously being moved externally from the cartilagenous canal by the movement of the jaw in the process of chewing (Ref. 15). Alberti

(Ref. 16) demonstrated the growth, migration, and desquamation of the skin covering of the tympanic membrane and deep external auditory canal in man in a dramatic experiment. Dye and ink were used to mark 62 human tympanic membranes on their outer surfaces. The dye spots were carried to the canal wall and were only shed in the cartilagenous portion of the canal. The rate and pattern of movement were gauged by means of sketches and serial photography. The most rapid migration took place on the anterior wall of the external auditory canal.

h. *Endogenous organisms.* A number of microbial species populate the skin of the healthy or normal external ear canal. *Staphylococcus epidermidis,* corynebacteria, and micrococci are the organisms usually found (Refs. 15 and 17).

In a study of normal ear canals in over 50 subjects, Saunders (Ref. 17) noted no fungi, and conspicuously absent were coagulase-positive staphylococci, *Pseudomonas aeruginosa, alpha* and *beta* hemolytic streptococci and *Proteus vulgaris.*

4. *Predisposing factors which lead to a breakdown of natural defenses.* There are natural barriers in the normal ear canal, e.g., hairs in the external meatus, size of the canal and isthmus, and cerumen, which prevent the introduction of foreign material that may lead to infection. These have been discussed in the anatomy and physiology section above. Once the protective layer of skin is broken, and the normal acid pH is altered, the way is paved for the introduction of infection (external otitis). Predisposing factors to be considered are:

a. *Genetic factors.* The individual may have inherited a narrow ear canal, abundant tragal hair at the meatus, or have inefficient mastication due to mandibular malformation. These are factors which would impair the natural cleansing mechanism. He may have excessive wax production due to hyperactivity of the glands (Ref. 18). There are also racial variations. External otitis is rarely seen in blacks, perhaps because the auditory canal is shorter, straighter and wider (Refs. 5 and 19). There may be genetic traits leading to diseases such as eczema and seborrheic dermatitis which may also involve the skin of the ear and auditory canal (Reg. 20).

b. *Enviromental factors.* These factors have been discussed in several references (Refs. 21 through 25). The most important factors in the environment are intense heat with sweating and humidity, found in warmer climates and in the tropics, and exposure to water in swimming and diving (Ref. 26). There is the occupational condition of acute otitis externa known as "swimmer's ear" among professional and recreational diving personnel. Wright and Alexander (Ref. 27) noted the disappearance of cerumen from the ear canal in a study of divers and swimmers. Senturia (Refs. 6 and 24) has suggested that the exposure to water results in tissue maceration and aborption of water by the stratum corneum which may be of importance in predisposing the ear canal to infection. This concept is supported by the fact that there appears to be a positive correlation between the degree of water exposure in the ear canal and the incidence of external otitis (Ref. 27).

Seasonal incidence of external otitis has been observed. Branca (Ref. 14) noted that external otitis occurs in the summer months and documented it month by month over a 4-year period, noting the greatest number of cases occurring in July, August, and September in southern Florida.

c. *Traumatic factors.* Trauma plays an important part in the breakdown of natural defenses which predisposes to external ear infection. Poorly fitting hearing aid ear molds may be traumatic as well as sensitizing. Improperly cleaned and poorly fitting ear plugs or ear protectors may be at fault (Ref. 23). Many patients will confess to wielding some implement in addition to their own fingers to relieve itching or to clean their ears (Ref. 28). Syverton (Ref. 25) studied 50 men with external otitis. He found that picking or insertion of a finger, usually the index finger, into the external auditory meatus was common, having been indulged in by approximately 50 percent of the group (23 of 50). Of these 23, 8 were "lifetime" habitual pickers, 3 were "lifetime" occasional pickers and 12 picked at their ears only when having ear trouble.

McKelvie (Rf. 22) conducted a study of external otitis patients, and to elicit maximum information, asked them to leading question "How do you clean your ears out?", thereby implying approval. Of a total of 113 patients questions, 58 used matches usually carrying cotton wool on the wooden end; 2 used the striking end without cotton wool; 7 used hairpins; and 4 used commercial wool covered wooden probes. Dudley (Ref. 29) reported 5 cases of traumatic tympanic membrane perforations due to self-cleansing of the ears with cotton applicators. He makes a plea for the nonuse of cotton applicators in the ear.

The cotton applicator, or any instrument, can be a traumatic tool to the ear. In addition, it can push wax deeper into the ear canal, thus making removal more difficult. The question is asked by Dudley, "Is there any need for self-cleaning of the ear canals? There seems to be doubt that any real good is accomplished by these maneuvers" (Ref. 30).

Schramm (Ref. 31) noted that 15 percent of first office visits in an otolaryngology office practice stem from therapeutically induced disease. Patient-induced diseases accounted for 8.6 percent of the 1,000 consecutive patients seen. Of these patient-induced diseases, external otitis associated with cotton applicator cleansing was noted in 2.9 percent of the cases. In his discussion, Schramm stated that it is unfortunate that cerumen has a color reminiscent of an unkempt child. The desire to be clean apparently provides motivation to remove cerumen. Cotton applicator cleansing may remove fluid cerumen, abrade skin and induce epithelial atrophy. Dry cerumen generally is impacted tightly. The resultant removal or modification of protection provided by cerumen provides the underlying etiology for bacterial or fungal infection. Seventy percent of all the patients with external otitis had an antecedent history of cotton applicator cleansing. The pracice of canal cleansing is to be condemned. The Panel concurs with this condemnation.

d. *Infective factors.* Once the protective layer of skin is broken, the way is paved for the introduction of infection. In response to a feeling of fullness, associated with the preinflammatory stage, a patient may scratch the ear canal or rub the auricle vigorously. These maneuvers abrade or fissure the skin of the cartilaginous part of the ear canal. An inflammatory process is set up, further disturbing the already compromised secretary mechanisms of the skin. In most cases, the organisms recovered tend to be Gram-negative bacilli, although Gram-positive organisms are found. These organisms include *Pseudomonas aeruginosa, Enterobacter aerogenes, Proteus mirabilis, Klebsiella pneumoniae, Streptococcus hemolyticus beta, Streptococcus viridans, Staphylococcus epidermidis* and *Corynebacterium species.* In the microbiology of "swimmer's ear," *Pseudomonas aeruginosa* occupies a central role (Refs. 15 and 32).

e. *Stress factors.* The cerumenous (apocrine) glands of the ear canal begin to function only at puberty, and are thought to respond like sweat glands to sympathetic stimulation. Under conditions of emotional tension and excessive heat, they presumably can malfunction. This can alter the chemical composition of the surface pH "acid mantle". The patient may also experience a vague itching or fullness which he attempts to relieve by rubbing, scratching, or some form of digital manipulation. This is often diagnosed as a neurogenic dermatitis, seen particularly in middle aged women (Refs. 7 and 15).

f. *The experimental production of external otitis.* Shelley and Perry (Ref. 19) were able to produce experimental otitis externa consistently in 79 normal adult male volunteers with no evidence of disease of the ears or ear canals. They produced and confirmed by ear canal biopsy a maceration dermatitis using ear plugs and tape, a primary irritancy dermatitis from formalin, and Halowax 1014, and an allergic dermatitis from penta-decylcatechol.

Senturia and Liebmann (Ref. 24) studied the problem of various etiologic factors in the etiology of external ear disease utilizing cats. They were interested in: (1) Infection with pseudomonas bacilli; (2) trauma; (3) lipid removal; (4) high temperature; and (5) high humidity, both singly and in combination. They were able to produce fairly consistently an infection of the external ear. No single factor, evaluated in this study, would produce morphologic or pathologic changes in the skin lining. It was shown, however, that infection with pseudomonas organisms was a necessary factor

when combined with trauma or lipid removal. High temperature and elevated humidity alone or in combination could not be shown to produce or to increase the degree of inflamatory changes produced by the other factors.

5. *Otic symtoms for which topical medications may be used.* The skin of the auricle and external auditory canal are accessible to topical medication. These may include creams, lotions, ointments, powders, wet dressings, and solutions. The topical medications used (both prescription and OTC) for the relief of otic symptoms are shown in the table below:

Topical Otc and Rx Drugs for Otic Symptoms

Otic symptoms	*Topical otic drugs (pharmacologic groups)*
1. Earache or ear pain.	Analgesics, anesthetics.
2. Ear drainage.	Anti-infective and acute anti-inflammatory.
3. Itching or pruritus.	Antipruritic, anti-inflammatory, acidifiers to restore "acid mantle".
4. Fullness or hearing impairment due to obstructive cerumen.	Cerumenolytics and cerumen (ear wax) softening agents and hygroscope vehicles.
5. Ear noises (tinnitus).	No topical optics.
6. Dizziness (vertigo).	No topical optics.

The Panel again emphasizes that the only indication it concludes appropriate for self-treatment with OTC topical otic products is for removal of ear wax accumulation in the external ear canal.

a. *Earache or ear pain.* These otic symptoms may be due to many causes: (1) Local pathology in the ear itself, such as an external otitis, foreign material against the tympanic membrane, a middle ear infection (otitis media), and a complication or extension of otitis media (mastoiditis, labyrinthitis, brain abscess); and (2) a referred pain to the ear from diseases involving the maxillary sinus, the nasopharynx, the base of the tongue, the hypopharynx, the larynx, the temporomandibular joint or the muscles of mastication and the lower molars (Refs. 33 and 34). It is evident that appropriate treatment is dependent upon accurate diagnosis. Improper treatment may delay diagnosis, and alter the prognosis or therapy response by temporarily masking the symptoms. The Panel concludes that for earache or ear pain due to the causes described above, self-medication is inappropriate and not safe.

b. *Ear drainage.* The drainage or discharge may be bloody, watery, purulent or mucoid, or even may be cerebral spinal fluid. Topical otic therapy is contraindicated without medical diagnosis. Drainage from the ear may be due to an infection in the external ear, a ruptured tympanic membrane, a middle ear infection, chronic mastoiditis, a tumor or a skull fracture. The Panel concludes that for the drainage due to any cause, self-medication is inappropriate and not safe.

c. *Itching or pruritus.* This is one of the most prevalent ear symptoms and may mask the preinflammatory stage of acute external otitis. In chronic external otitis, which is almost always present in dry ears (absence of cerumen), itching is often the chief complaint. The itching may also be a consequence of an eczematous process, whether it be of infectious or allergic origin, seborrheic dermatitis, psoriasis, contact dermatitis or neurodermatitis. Whatever its origin, itching commonly sets in motion an itch-scratch-itch cycle that culminates in trauma, infection, epidermal excoriation and incipient inflammation. The extraordinary and specific sensitivity of the area is appreciated. Kellmen in discussing a paper by Fowlar notes that the Japanese have a custom of producing pleasant sensations by gently striking the walls of the external canal with a feather or a single beaver hair. It can become a real addiction, like drinking or smoking (Ref. 35). Itching can occur with no visible lesion in the ear. The use of OTC products for otic itching is not recommended. Appropriate medical diagnosis is necessary to correct the cause and afford symptomatic relief.

d. Fullness or hearing impairment. Obstructive cerumen in the external auditory canal is only one of many causes of this symptom. To produce a sensation of fullness or hearing impairment, accumulated cerumen must occlude the canal and impair the route of airborne sound waves to the tympanic membrane. It is not uncommon to experience a hearing impairment after getting water in the ear canal. The cause is usually due to the absorption of the water by the cerumenous mass which thereby occludes the canal. Obstructive cerumen which totally obscured the tympanic membrane was noted in about 25 percent of the ears of 1,000 normal young men in a report by Carpendale (Ref. 36). Obstructive cerumen may be an aggravation and contribute to a hearing impairment, but it is not the cause of deafness nor presbycusis as sometimes claimed. A hearing loss may occur in external otitis due to edema of the skin and accumulated debris. The Panel recommends the use of an OTC ear wax softening agent as an aid in the removal of cerumen (ear wax) for individuals who have hypercerumenosis.

e. *Ear noises (tinnitus).* This is a symptom which may be associated with a hearing impairment, exposure to high noise levels or acoustic trauma, one of the symptoms of intracranial or systemic disease, and drug toxicity. Appropriate medical evaluation and diagnosis are indicated. Topical otic therapy is contraindicated.

f. *Dizziness (vertigo).* This is a symptom of dysequilibrium which may be of otic origin. It may be due to drug toxicity or intracranial or neurologic disease, of vascular origin or induced by hyperventilation. Appropriate medical evaluation and diagnosis are indicated. Topical otic therapy is contraindicated, either by the use of prescription or OTC drug products.

6. *Pharmacologic activities of topical otic ingredients. a. Analgesics and anesthetics.* Topical analgesics placed in the ear canal are not absorbed from the skin surface of the ear canal or tympanic mebrane sufficiently to provide analgesia or anesthesia (Refs. 1 and 37). Gray (Ref. 38) in 1900 stated that in acute inflammation of the middle ear, no satisfactory local anesthetic had been found. He used 10 percent cocaine in aniline oil and found it to be an improvement over aqueous solutions. Many other drugs have been used over the years but none is effective and many are not safe (Ref. 37).

The Panel recommends that analgesics by the oral route be used in preference to analgesics in topical otic products for the symptomatic relief of ear pain. Oral analgesics provide symptomatic relief from ear pain. The Panel recommends that otic products containing anesthetics and analgesics should not be available OTC. The topical otic analgesic drugs reviewed by the Panel are discussed below. (See part II. paragraph B.2. below—Category II Active Ingredients.)

b. *Anti-infectives.* The use of topical ear medications in the treatment of inflammatory ear conditions was considered by the Panel. The Panel concluded that self-medication for any type of infection in the ear canal is not appropriate.

c. *Antipruritics.* Itching may be caused by many different conditions. Chronic external otitis, eczematous reactions and other allergic conditions are merely a few of the causative factors. The Panel concluded that self-medication for any type of otic itching is not appropriate.

d. *Acidifiers.* The importance of the pH "acid mantle" has been discussed. (See part II. paragraph A.3.f. above—The Acid Mantle.) It is for this reason that many products used in the external ear canal have an acid pH.

e. *Ear wax softening agents and cerumenolytic agents.* The Panel concludes that ear wax softening agents are safe and effective for OTC use to relieve the symptoms of fullness due to the accumulation of ear wax (not impacted) in the external ear canal. All other symptoms involving the ear such as, earache or ear pain, ear drainage, itching, hearing impairment due to impacted, i.e., excessive, hardened or tightly packed cerumen (ear wax), ear noises (tinnitus) and dizziness (certigo), require diagnosis and treatment by a physician and should not be self-medicated. To remove impacted ear wax, cerumenolytic agents may be required and/or instrumentation which should only be performed by a physician. The Panel finds cerumenolytic agents not safe for OTC use.

Ear wax softening agents differ from cerumenolytic agents in that softening agents are used as an aid in the removal of accumulated ear wax by mechanically softening and loosening the ear wax so that it can be washed out of the ear canal by irrigation with warm water. In contrast to the mild mechanical action of ear wax softening agents, cerumenolytic agents are used to dissolve impacted ear wax.

After a review of the submitted otic ingredients and the claimed indications

for their use, the Panel concludes that only ear wax softening agents are safe for OTC use and only "To aid in the softening and loosening of cerumen (ear wax".

The normal production of cerumen, its composition and natural removal have been described elsewhere in this document. (See part II. paragraph A.3.d. above—Secretions and part II. paragraph A.3.g. above—Natural cleansing.) The protection of the normal skin in the external auditory canal by this waxy secretion has also been discussed by the Panel. The removal of cerumen may lead to infection. Daily self-cleaning of the ears is not necessary, and probably results in more harm than good. The best form of ear hygiene is wiping the external ear with a wash cloth. There is a certain group of individuals who do have a tendency to accumulate cerumen which necessitates occasional removal. Carpendale (Ref. 36) observed obstructive cerumen in about 25 percent of 1,000 normal young men. It is for these individuals that a wax softening and loosening agent is helpful in removing the obstructive cerumen. There is no safe and effective agent for dissolving cerumen (cerumenolysis) (Refs. 4, 11, 18, and 39 through 49). These are reports and studies, both in vitro and in vivo, of cerumenolytic agents. Carbamide peroxide reviewed under Category I ingredients is an aid both in the removal of cerumen by softening the wax and in the looosening of it by the mechanical action resulting from the release of oxygen. (See part II. paragraph B.1. below—Category I Labeling.) It is usually necessary to remove the softened cerumen by gentle irrigation with warm water (Ref. 6). Simple as this operation may appear and frequently as it is resorted to, it is one which requires some degree of tact, caution, and dexterity in its performance. It is not possible for anyone to syringe his own ear effectively. These latter statements were made by Wilde in 1853 (Ref. 3). The Panel concludes that the use of OTC ear wax softening agents is helpful, but if the wax is impacted or tightly packed and is not removed by gentle irrigation, a physician should be consulted. Impacted cerumen which necessitates loosening by instrumentation should be removed only under the direct supervision of a physician.

7. *Labeling and direction for use.* In the discussion above, the Panel has summarized the pharmacological activities (indications) of topical otic ingredients analgesic, anesthetic, anti-infective, anti-inflammatory, antipruritic, acidifying, cerumenolytic, and as ear wax softening agents.

In the statements below for the ingedients that have been classified as Category I or Category II, the Panel has specified the indications, directions for use and the warnings for the labeling of topical OTC otic products. (See part II, paragraph B.1. below—Category I Labeling and part II. paragraph B.2. below—Category II Labeling.) The Panel has not classified any topical otic ingredient or labeling as Category III.

The Panel concludes that only topical otic ingredients for use as aids in the removal of cerumen (ear wax softening agents) are safe for OTC use. Topical otic ingredients for all other indications should be used only under the advice and supervision of a physician.

8. *Consumer education (ear care and ear hygiene).* (Refs. 15, 29, 31, and 50 through 52.) Advertising directed to the consumer regarding the ear is often misleading. Deafness is not caused by ear wax. Presbycusis, the normal loss of hearing acuity accompanying advancing age cannot be relieved by removing ear wax. The presence of ear wax does not imply "poor hygiene". Daily cleansing of the ears with cotton applicators can be traumatic and injurious to the hearing mechanism.

The Panel would urge that greater effort be made in educating the consumer regarding the ear and how it functions.

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E. CATEGORIZATION OF DATA

1. *Category I conditions under which topical otic ingredients are generally recognized as safe and effective and are not misbranded.—Category I Active Ingredients.* The Panel has classified the following topical otic active ingredients as generally recognized as safe and effective and not misbranded:

Glycerin.
Carbamide peroxide in glycerin.

a. *Glycerin.* The Panel concludes that glycerin is safe and effective for OTC use as a topical ear wax softening agent as specified in the dosage section discussed below.

Glycerin is used in topical otic products as an aid in the softening and removal of cerumen, as a vehicle because of its solvent properties, and as a hygroscopic agent. Its viscosity makes it useful as an ingredient in both liquid and ointment forms of medication (Ref. 1).

Glycerin was discovered in 1779 by Scheele (Ref. 2). In 1865, Hartshorne published a monograph on glycerin and its uses (Ref. 2). The "Glycerin Cure for Deafness" by Wakley was noted. The popularity of such treatment, however, was short because of its lack of success. Wilde (Ref. 3) condemned the therapy. Glycerin has been widely used both alone and as a vehicle for other drugs in the treatment of inflammatory conditions of the external auditory canal (Ref. 4).

(1) *Safety.* Clinical use and marketing experience have confirmed that glycerin is safe in the dosage range used as an OTC topical ear wax softening agent.

Glycerin is widely accepted as a vehicle of choice in otic products (Refs. 1 and 5). It is safe for topical application. Glycerin (100 percent) is used in the eye as a hydroscopic agent with virtually no side effects. The mild local irritating effects of concentrated glycerin solutions, sometimes noted when the skin barrier is not intact, are due to the dehydrating property. The topical absorption of glycerin leads to formation of glucose and glycogen. When taken orally it is completely innocuous unless the dose is large enough to exert osmotic effects (Ref. 4). Fourteen adults ingested 30 ml three times daily for 50 days with no harmful effects (Ref. 5). Johnson and Carlson (Ref. 6) fed daily doses of 9 g/kg to dogs for a period of 1 year and reported no evidence of ill effects.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of glycerin as an OTC topical ear wax softening agent. However, clinical use and marketing experience have confirmed that glycerin is effective in the dosage range used as an OTC topical ear wax softening agent.

Glycerin when in contact with cerumen acts as a softening agent (Ref. 7). It may be combined with ureau hydrogen peroxide as anhydrous glycerin to aid in the softening and removal of cerumen. Glycerin used as a vericle serves the purpose of controlling and sustaining the local action of the medicament (Ref. 8). Anhydrous glycerin extracts water and is, therefore, of great value in reducing edema of the stratum corneum. It will not remove water from the stratum corneum when the epidermis is intact (Ref. 9).

Senaturia and Doubly (Ref. 7) investigated the in vitro action of various substances on ear wax to determine which substances might best facilitte the removal of ear wax from the external ear canal. One ml of various test substances was added to approximately 0.5 g of ear wax, obtained from normal subjects, in the bottom of a vial. After allowing the vials to stand at room temperature without agitation for periods of 5, 10, 15, 30, 60 minutes and 24 hours, the time required to produce an observable effect on the ear wax and the type of action was recorded. The actions of the test substances on the ear wax were described as softening, dissolving, disintegration, or swelling. The substances varied in their action on the ear wax in vitro. Distilled water, hydrogen peroxide (1.5 and 3 percent), and saline solutions (1 and 2 percent) showed immediate reaction with the ear wax and total disintegration occurred in 60 minutes. A much slower rate of disintegration occurred with aqueous solutions of sodium bicarbonate (1 and 1.5 percent), sodium hydroxide (4 percent), sodium carbonate (1.5 percent) and sodium carbonate (5 percent), in 50 percent glycerin. Most of these alkaline solutions showed little or no action in 60 minutes but disintegrated one-half to three-fourths of a piece of ear wax in 24 hours. Ethyl alcohol and normal hydochloric acid showed very little action in 24 hours. Acidolate showed a surface softening and a slight dissolving action in 24 hours. Glycerin and glycerin with benzalkonium chloride (0.1 percent) showed only surface softening in 24 hours. Propylene glycol showed an immediate swelling action without any apparent softening effect. Mineral oil and castor oil had little effect after 24 hours.

The Panel recommends that glycerin be used as an ear wax softening agent in an aqueous solution containing a concentration of 95 percent glycerin or above. Dehydrated glycerin ($C_3H_8O_3$) is no less than 99.5 percent glycerin. Glycerin U.S.P. contains no less than 95 percent $C_3H_8O_3$ (Ref. 4).

(3) *Dosage.* Adult otic dosage: Place sufficient drops into affected ear and allow to remain at least 15 minutes by tilting head. Remove wax by gentle washing with lukewarm water using a soft rubber syringe. May be repeated a second time, if necessary. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for ear wax softening active ingredients. (See part II. paragraph B.1. below—Category I Labeling.)

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b. *Carbamide peroxide in glycerin.* The Panel concludes that carbamide peroxide in anhydrous glycerin is safe and effective for OTC use as a topical ear wax softening agent as specified in the dosage section as discussed below.

Carbamide peroxide (urea hydrogen peroxide), dissolved in anhydrous glycerin is used in the external ear as an aid in the removal of cerumen. Carbamide peroxide is a solid stable complex of urea and hydrogen peroxide (H_2O_2) which contain 35 percent of H_2O_2. In contact with tissues which contain the enzyme catalase, hydrogen peroxide solution releases its oxygen. The mechanical effect of effervescence loosens tissue debris and aids in cleansing the ear canal (Refs. 1 and 2). Brown et al. (Ref. 3) first suggested the use of carbamide peroxide in glycerin in 1946, as a new topical anti-

septic solution which was not toxic, irritating or allergenic. Brown later advocated its use in the treatment of inflammatory ear conditions (Ref. 4).

Hydrogen peroxide is an unstable oxidizing agent. The germicidal activity is generally overestimated (Ref. 2). Goodman and Gilman (Ref. 1) stress that hydrogen peroxide is an active germicide only as long as it releases oxygen. It has long been used as an aid in ear wax removal, usually diluted with 3 parts of water and used as an irrigant (Ref. 5). Senturia (Ref. 6) warns against the indiscriminate use of the aqueous preparation because it may cause maceration of the skin and predispose to a diffuse external otitis.

Urea is a product of protein metabolism which aids in debriding necrotic tissue. It is found as an excretion product in human urine in a concentration of about 2 percent. A pure white crystalline material, odorless and nontoxic, it was the first organic substance ever synthesized. This was accomplished by Wohler in 1828 (Ref. 7). Robinson (Ref. 7) recommended the use of a 2 percent solution of urea in chronic external suppurating wounds. In some countries today, urine is still used on wounds to prevent infections and to stimulate cleansing and healing.

The stable complex of carbamide peroxide was a logical combination for use in the ear. Prior to the use of antibotics, it was used in chronic inflammatory conditions. However, it is no longer the drug of choice in the treatment of such conditions, and its present use is primarily to aid in cleansing the ear canal of cerumen.

(1) *Safety.* Clinical use and marketing experience have confirmed that carbamide peroxide in glycerin is safe in the dosage range used as an OTC topical ear wax softening agent.

Carbamide peroxide, 6.5 percent by weight, is safe. It has had a long and extensive marketing experience when combined with anhydrous glycerin with no reported adverse reactions (Refs. 8 and 9). There are reported clinical studies (Refs. 4 and 10) in which the combination was used in inflammatory otic conditions. It was found to be nontoxic, nonirritating, and nonsensitizing. No adverse reactions were reported. Carbamide peroxide has been used in animals (veterinary medicine) with no reported toxicity or irritation (Ref. 11).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of carbamide peroxide as an OTC topical ear wax softening agent. However, clinical use and marketing experience have confirmed that carbamide peroxide is effective in the dosage range used as an OTC topical ear wax softening agent.

The Panel recommends carbamide peroxide as an ear wax softening agent for OTC use to aid in cleansing the ear canal when obstructed by ear wax. There are no safe and effective OTC cerumenolytics for use in dissolving ear wax.

Senturia and Doubly (Ref. 12) observed, in vitro, the action of different vehicles on cerumen. After the cerumen had been removed from the human ear canal the reaction and rate of disintegration of the cerumenous mass was recorded. They reported that distilled water, hydrogen peroxide (1.5 and 3.0 percent) and saline solutions (1 and 2 percent) showed immediate reaction, and that total disintegration of the cerumen occurred in 60 minutes. A much slower rate of disintegration was seen with an aqueous solution of sodium bicarbonate (1.0 and 1.5 percent). Using ethyl alcohol (95 percent) and normal hydrochloric acid, there was very little reaction in 24 hours.

There have been few specific studies as to efficacy using carbamide in glycerin as an ear wax softening agent. Cunningham (Ref. 13) reported on 57 patients who required removal of cerumen. He used carbamide peroxide glycerin ear drops for 3 days followed by irrigation of the ear canals with warm water. Treatment was successful in all cases, and there was no sensitization or irritation encountered. This was not a controlled study.

The reported clinical studies have been primarily concerned with the use of carbamide peroxide and glycerin for inflammatory ear conditions and were primarily involved with safety issues (Refs. 4 and 10). The Panel is of the opinion that ear infections should be treated by a physician and that OTC drug therapy is inappropriate.

Amjad and Scheer (Ref. 14) compared a new cerumenolytic drug (triethanolamine polypeptide oleate condensate) to carbamide peroxide in glycerin in 80 patients. They found that the test agent was an effective cerumenolytic in 88 percent and that the combination was effective in 17 percent. The test drug used was not an OTC drug. It is a sensitizing agent and a skin irritant (Refs. 15 through 25).

Marlow (Ref. 26) recommends carbamide peroxide in glycerin as a softening agent for use prior to irrigation.

The Panel concludes that carbamide peroxide dissolved in anhydrous glycerin is safe and effective as an aid in ear wax removal by loosening the ear wax. The latter effect being accomplished by the mechanical action of hydrogen peroxide released on contact with water.

(3) *Dosage.* Adult otic dosage: Place sufficient drops (6.5 percent carbamide peroxide solution in anhydrous glycerin) into affected ear and allow to remain at least 15 minutes by tilting head. Remove wax by gentle washing with lukewarm water using a soft rubber syringe. May be repeated a second time, if necessary. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for ear wax softening active ingredients. (See part II. paragraph B.1. below—Category I Labeling.)

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CATEGORY I LABELING

The Panel recommends the following Category I labeling for ear wax softening active ingredients to be generally recognized as safe and effective and not misbranded.

a. *Indication.* "To aid in the softening and removal of obstructive ear wax".

b. *Warnings.* (1) "If symptoms of fullness persist, consult a physician".

(2) "*Caution.* Do not use in the ear in the presence of ear drainage, ear pain or known ear drum perforation (hole) or injury".

(3) "Do not use this product if there has been any kind of ear surgery".

(4) "Discontinue use if there is pain or dizziness, and consult a physician".

(5) "For external use only, not to be swallowed".

(6) "Avoid contact with the eyes".

(7) "Discontinue use if irritation or rash appears".

(8) "Do not use in children under 12 years without consulting a physician".

2. *Category II conditions under which topical otic ingredients are not generally recognized as safe and effective or are misbranded.—Category II Active Ingredients.* The Panel has classified the following topical otic active ingredients as not generally recognized as safe and effective or as misbranded:

Antipyrine
Benzocaine

a. *Antipyrine.* The Panel concludes that antipyrine is not safe and not effective for OTC use as a topical otic analgesic and anesthetic.

Antipyrine is a phenylpyrazolone derivative which was first synthesized in 1883 in a search for more effective antipyretics containing the quinoline nucleus of quinine.

It occurs as colorless crystals or as a white crystalline powder which is odorless, has a slightly bitter taste, and is very soluble in water. The two main systemic effects of antipyrine by oral administration are analgesia and antipyresis (Refs. 1 and 2). In 1912, Von Issekutz reported that "the local anesthetic of cocaine, eucaine and novocaine on the leg of a frog is enhanced when antipyrine is applied simultaneously" (Ref. 3). This property probably accounted for its use in ear drops as a topical analgesic.

(1) *Safety.* Antipyrine, used topically, is a primary irritant (Ref. 4). Ersner and Saltzman (Ref. 5) cite an experiment in which 10 normal ears were treated with ear drops (a proprietary preparation consisting of antipyrine and benzopyrine in a glycerin solvent) for 24 to 48 hours to determine its action on normal tissue. Four of these cases were terminated as a result of "bullae which were followed by pain and which did not subside until the blebs ruptured spontaneously or were ruptured mechanically." The remaining 6 cases showed no ill effects. Ersner and Saltzman reported local irritating effects in at least 35 percent of their patients after the use of topical ear preparations containing antipyrine.

The Panel concludes that antipyrine is not safe for OTC use as a topical otic analgesic and anesthetic. The Panel recommends that ear symptoms requiring the use of topical otic analgesics and anesthetics should only be administered under the advice and supervision of a physician.

(2) *Effectiveness.* Greenberg (Ref. 3) noted that antipyrine has long been observed clinically to exercise a mild local anesthetic effect. There has been little experimental investigation of this property. Ersner and Saltzman (Ref. 5) in 1942 noted that "the employment of antipyrine as a local anesthetic has been abandoned. It was found to be a primary irritant, and cocaine has always been incorporated with it so that antipyrine might be tolerated. The anesthetic powers and antiseptic powers are feeble." In a study of 142 children with acute otitis media (Ref. 6), the control group received symptomatic therapy consisting of topical ear drops containing antipyrine and benzocaine in glycerin, aspirin orally and decongestant nose drops while the treatment groups received antibiotics as well as symptomatic treatment. The authors concluded that "Topical analgesics for instillation into the ear canal appear to be effective in reducing pain." The Panel believes that the beneficial effect of analgesia in this study is probably due to the oral aspirin given concurrently rather than to the topical analgesic activity of the antipyrine and/or benzocaine.

The Panel concludes that ear symptoms that require treatment with topical otic analgesics and anesthetics should only be treated under the advice and supervision of a physician.

(3) *Evaluation.* The Panel is aware that FDA has previously taken the position, (regulatory letter issued October 29, 1973) that preparations used as ear drops, which contain antipyrine as a topical anesthetic and/or analgesic regardless of minimal claims (for softening wax), should be labeled and sold on prescription only (Ref. 7). It is the agency's view that the inclusion of a topical anesthetic or analgesic in an OTC ear drop preparation may mask acute infections.

The Panel fully concurs with the position of FDA that antipyrine should be sold on prescription only. Therefore, the Panel concludes that antipyrine is not safe for OTC use as a topical otic analgesic and anesthetic.

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b. *Benzocaine.* The Panel concludes that benzocaine is not safe and not effective for OTC use as a topical otic analgesic and anesthetic.

Benzocaine is an ester of aminobenzoic acid and ethyl alcohol. It is only slightly soluble in water, and must be in the form of the base to be effective on intact skin. It is used as a topical analgesic and/or anestic in the ear canal to lessen ear pain.

(1) *Safety.* Benzocaine possesses a relatively low degree of toxicity due to its lack of solubility. Sensitization may occur in approximately 5 percent of susceptible individualls (Ref. 1).

The Panel is aware that FDA has previously taken the position (regulatory letter issued October 29, 1973) that preparations used as ear drops, which contain benzocaine as a topical anesthetic and/or analgesic regardless of minimal claims (for softening wax), should be labeled and sold on prescription only (Ref. 2). It is the agency's view that the inclusion of a topical anesthetic or analgesic in an OTC ear drop preparation may mask acute infections.

The Panel concludes that benzocaine is not safe for OTC use as a topical otic analgesic and anesthetic. The Panel recommends that ear symptoms requiring the use of topical otic analgesic and anesthetics should only be administered under the advice and supervision of a physician.

(2) *Effectiveness.* Benzocaine is a local anesthetic and its action is almost entirely at the nerve endings. The Panel doubts that benzocaine is effective topically as an analgesic and/or anesthetic on the tissues of the tympanic membrane and the ear canal. The capacity for the absorption of liquids by the intact ear drum is poor (Refs. 3 and 4).

Benzocaine used as a topical otic anesthetic can be locally sensitizing. The absorption from the skin of the ear canal and tympanic membrane is minimal if at all (Ref. 4). There are no well-controlled clinical studies to support its effectiveness as a topical otic analgesic or anesthetic. Ear pain can be due to many causes, and appropriate treatment necessitates accurate diagnosis (Refs. 5 and 6). The Panel recommends that preparations used as ear drops, which contain a topical or local anesthetic and/or analgesic should not be marketed OTC.

The Panel concludes that benzocaine is not effective for OTC use as a topical otic analgesic and anesthetic. The Panel recommends that ear symptoms that require treatment with topical otic analgesics and anesthetics should only be treated under the advice and supervision of a physician.

(3) *Evaluation.* The Panel fully concurs with the position of FDA that benzocaine as a topical otic analgesic and anesthetic should be sold on prescrip-

tion only. Therefore, the Panel concludes that benzocaine is not safe or effective for OTC use as a topical otic analgesic and anesthetic.

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CATEGORY II LABELING

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following claims to be misleading and unsupported by scientific data. The Panel has previously discussed such labeling. (See part II. paragraph A. above—General Discussion.)

a. "For ear hygiene". The ear canals are clean. The daily habit of cleansing the ear canals is to be condemned.

b. "Wax prevention or prophylaxis". Ear wax is a normal protective in the ear canal and should be present.

c. "That gently dissolves wax". Cerumenolytic agents should be administered by a physician.

d. "For deafness". Impacted cerumen may impair hearing but does not cause deafness.

e. "For itching and other discomforts". This is misleading. The only known appropriate topical antipruritics for use in the ear are prescription drugs.

f. "For ringing ears". This is misleading and inaccurate. Topical medication is not indicated. This is a symptom thought to be possibly due to cerumen against the tympanic membrane. There is nothing to support this theory. The symptom is usually an accompaniment of a sensory neural hearing-impairment.

g. "Aids healing". This is misleading and inaccurate. A product to aid in the removal of wax has no proven effect on healing.

h. "For local treatment of burns and abrasions of the ear". Burns in the ear canal are usually due to molten metal in industry. The extent of damage and appropriate treatment should be determined by a physician. Any minor abrasion will heal without local treatment. The application of inappropriate or contaminated otic medication can be a source of contamination and result in more extensive injury.

i. "Relieves pain". This is inappropriate. There are no analgesics in cerumen softening drugs.

The Panel is of the opinion that the inclusion of a topical anesthetic or analgesic in an OTC product whose primary function is to loosen wax is irrational and may mask acute infections. Self-medication without a diagnosis of cause is inappropriate. Treatment for these conditions should be under the direction of a physician and by prescription drug only.

The Panel includes there is no safe and effective cerumenolytic OTC drug at this time.

The Panel classifies the following claims for otic analgesics and anesthetics as Category II:

1. "Removal and softening of ear wax".
2. "Relieves minor irritation caused by wax".
3. "Itching and other discomforts".
4. "Anesthetizes affected area".
5. "Relieves pain".
6. "For raw, inflamed tissues".

j. "Swimmer's ear". The Panel is opposed to the OTC use of otic ingredients for the self-treatment of ear infections. Such conditions need the diagnosis and continuous supervision of a physician. External otitis, an infection of the skin lining the external auditory canal is one of the most common diseases of the ear. The Panel has discussed the various factors that may be involved in predisposing the ear canal to infection. (See part II. paragraph A.4. above—Predisposing factors which lead to a breakdown of natural defenses.) One type of external otitis is called "diffuse external otitis" or "desquamative external otitis." This type of ear infection is commonly known as "swimmer's ear". It occurs with greater frequently during hot, humid weather and has been reported to occur in divers and swimmers. The underlying basis for this disease entity is not entirely understood but some factors, such as high environmental humidity, high temperature, prolonged exposure of the ears to moisture, and local trauma with infection are recognized as important.

"Swimmer's ear" is apparently due to excessive moisture in the external auditory meatus which may be the result of various causes. The external auditory canal is a cul-de-sac, well suited for the collection of moisture providing a basis for infection. Disruption of the skin lining of the external auditory canal by the action of the accumulated moisture, or by the use of instruments to clear the ear canal of water after bathing or swimming may cause maceration, fissuring, or laceration of the skin lining and provide a favorable environment for the growth of bacteria.

The Panel concludes that ear infections, such as "swimmer's ear," which may have a complex of symptoms such as pain, inflammation, ear drainage, etc., require diagnosis, treatment, and continuous supervision by a physician. Self-treatment may lead to further aggravation of the condition and, therefore, should be strongly discouraged.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.—Category III Active Ingredients.* The Panel concludes that the available data are insufficient to permit final classification of the following claimed topical otic active ingredients:

None.

Category III Labeling.

None.

C. DATA REQUIRED FOR EVALUATION

None of the topical otic ingredients reviewed in this document for OTC use has been classified by the Panel as Category III. Therefore, studies to bring Category III topical otic ingredients into Category I have not been developed by the Panel.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that Subchapter D be amended by adding new Part 344, to read as follows:

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

Subpart A—General Provisions

Sec.
344.1. Scope.
344.3. Definitions.

Subpart B—Active Ingredients

344.10. Ear wax softening agents.

Subpart C—[Reserved]

Subpart D—Labeling

344.50. Labeling of ear wax softening agents.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 344.1 Scope.

An over-the-counter topical otic drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 344.3 Definitions.

(a) *Age (dosage) usage.* Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

(b) *Cerumen.* The wax-like substance found in the normal human ear canal.

(c) *Ear wax softening agent.* An agent that softens and loosens ear wax (cerumen).

(d) *Otic drug.* An agent used in the external ear canal.

Subpart B—Active Ingredients

§ 344.10 Ear wax softening agents.

The active ingredients of the product consist of the following within the concentration established for each ingredient:

(a) *Glycerin.* Adult otic concentration is a 95 percent or greater concentration in aqueous solution.

(b) *Carbamide peroxide in glycerin.* Adult otic concentration is a 6.5 percent carbamide peroxide solution in anhydrous glycerin.

Subpart C—[Reserved]

Subpart D—Labeling

§ 344.50 Labeling of ear wax softening agents.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as an "ear softening agent".

(b) *Indications.* The labeling of the product shall contain a statement of the indication under the heading "Indications" that shall be limited to the following: "To aid in the softening and removal of obstructive ear wax".

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

(i) "If symptoms of fullness persist, consult a physician".

(ii) "*Caution:* Do not use in the ear in the presence of ear drainage, ear pain, or known ear drum perforation (hole) or injury".

(iii) "Do not use this product if there has been any kind of ear surgery".

(iv) "Discontinue use if there is pain or dizziness, and consult a physician".

(v) "For external use only, not to be swallowed".

(vi) "Avoid contact with the eyes".

(vii) "Discontinue use if irritation or rash appears".

(viii) "Do not use in children under 12 years without consulting a physician".

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": Place sufficient drops into affected ear and allow to remain at least 15 minutes by tilting head. Remove wax by gentle washing with lukewarm water using a soft rubber syringe. May be repeated a second time, if necessary. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before March 16, 1978). Such comments should be addressed to the Office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before April 14, 1978. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an economic impact statement under Executive Order 11821 (as amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: December 2, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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