DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 344

[Docket No. 77N-0334]

Topical Otic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) topical otic drug products (products for the ear) are generally recognized as safe and effective and not misbranded. 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. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by September 7, 1982. New data by July 11, 1983. Comments on the new data by September 9, 1983. These dates are consistent 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). Written comments on the agency's economic impact determination by November 9, 1982.

ADDRESS: Written comments, objections, 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. New data and comments on new data should also be addressed to the Dockets Management Branch.

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

SUPPLEMENTARY INFORMATION: In 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 this drug class. 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.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on 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 present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC topical otic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC topical otic drug products.

In response to the advance notice of proposed rulemaking, two drug manufacturer associations, one drug manufacturer, one otolaryngologist, and one consumer group submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

This proposal to establish Part 344 (21 CFR Part 344) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC topical otic drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph (46 FR 47738).

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

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions 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 they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC topical otic drug products (published in the **Federal Register** of December 16, 1977 (42 FR 63556)), the agency suggested that the

conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss but also interfere with consumers access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register.** The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments

1. Two comments urged the agency to recognize the legal status of the monographs issued under the OTC drug review as being interpretative rather than substantive regulations.

This subject was dealt with in paragraph 85 through 91 of the preamble to the procedures for classification of OTC drug products published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 17, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger,* 512 F. 2d 688, 696–98 (2d Cir. 1975); *National Associatin of Pharmaceutical Manufacturers* v. *FDA,* 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd.,* 637 F. 2d 887 (2d Cir. 1981).

2. One comment suggested that FDA should affirm its active support of the Federal Trade Commission (FTC) proposal to limit commercial advertising claims of OTC drugs to the labeling specified in the OTC drug monographs. The comment recommended several statements on OTC drug advertising for inclusion in the topical otic monograph.

In a notice published in the **Federal Register** of May 1, 1981 (46 FR 24584), the FTC announced its decision to terminate the proposal to restrict the terms used in OTC drug advertising to those labeling terms specifically permitted by the OTC drug monographs. Instead of using this across-the-board approach, FTC will review advertising for OTC drugs on a case-by-case basis, taking into consideration the OTC drug review findings on safety and effectiveness in making its decisions. It is thus no longer relevant for FDA to take a position on the FTC proposal. Further, because OTC drug advertising is regulated primarily by the FTC, it would not be appropriate for FDA to include specific statements dealing with advertising in applicable OTC drug monographs.

3. One comment noted the Panel's statement that there is a great need for consumer education regarding ear care and topical otic therapy and expressed concern that the proposed reguations alone will do little to educate the public regarding ear care. The comment recommended that FDA develop a consumer education program on ear care to be released at the same time the final monograph is published.

The comment makes a sound recommendation. FDA has Consumer Affairs Officers who implement consumer education programs in all parts of the country. Information about the OTC drug review is provided in the consumer drug education program, and the agency will develop information for consumers on ear care and topical otic therapy which will be included in this program.

B. General Comments on Topical Otic Ingredients

4. One comment stated that the Panel supported its conclusions on the safety of carbamide peroxide in anhydrous glycerin as an earwax removal aid on clinical use and marketing experience and not on well-controlled studies. This comment contended that such an approach is in violation of regulations promulgated by FDA.

The agency does not believe that the process by which the Panel concluded that carbamide peroxide in anhydrous glycerin is safe for use as an earwax removal aid is in violation of FDA regulations. The regulations at 21 CFR 330.10(a)(4)(i) state: "Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data."

The Panel's conclusion as to the safety of carbamide peroxide in anhydrous glycerin was arrived at in accordance with the above regulation. The Panel reviewed published studies, as cited in its report, and used clinical and marketing experience to corroborate these studies. The agency believes that the evidence in these studies and the Panel's expertise in evaluating the clinical and marketing experience of carbamide peroxide in anhydrous glycerin are sufficient to establish the safety of this ingredient under its recommended conditions of use as an earwax removal aid.

5. One comment stated that the Panel supported its conclusions on the effectiveness of carbamide peroxide in anhydrous glycerin as an earwax removal aid on clinical use and marketing experience and not on well-controlled studies. The comment argued that such an approach is inadequate, is in violation of FDA regulations, and sets a dangerous precedent with regard to establishing the required burden of proof for other Category I drugs.

Proof of effectiveness, as defined in 21 CFR 330.10(a)(4)(ii), "* * * shall consist of controlled clinical investigations as

defined in § 314.111(a)(5)(ii) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing."

The agency agrees that the studies on which the Panel primarily based its conclusion that carbamide peroxide in anhydrous glycerin is effective as an earwax removal aid were not double-blinded or placebo-controlled. However, all patients participating in these studies were examined professionally and found to require removal of earwax. When carbamide peroxide was instilled in affected ears over periods ranging from 3 to 5 days, subsequent irrigation of the ears with lukewarm water was shown to remove earwax from a significant number of the ears tested.

The agency is aware of an additional study, not cited by the Panel, in which 26 patients were treated for bilateral excessive or impacted earwax (Ref. 1). Ten drops of 6.5 percent carbamide peroxide in anhydrous glycerin were instilled into each ear canal twice daily, upon arising and at bedtime, for 6 days followed by syringing the ear canals twice daily for 2 days with lukewarm water and a soft rubber ear syringe. The following day the ear canals were examined by a physician for any evidence of tissue reaction and for the degree of earwax removal. Complete removal of the earwax was achieved in 22 of the 26 patients. In two cases, additional syringing by the physician resulted in complete removal of the earwax. The remaining two patients required a second course of treatment, which resulted in complete removal of the earwax. The author concluded that carbamide peroxide in anhydrous glycerin was a safe, clinically effective, and easily administered agent for the lysis and removal of earwax, without the need for pressure syringing and instrumentation.

The agency believes that the methods of investigation employed in these studies and the results obtained, along with subsequent reports of significant human experience during marketing, justify a waiver of the well-controlled study requirements. Because an earwax removal aid achieves its intended therapeutic effect by means of a mechanical action whose results are readily ascertainable, these studies are sufficient to establish the effectiveness of carbamide peroxide in anhydrous glycerin as an earwax removal aid.

Reference

(1) Dickstein, B., "A Simplified Approach to Cerumenolysis," *EENT Digest,* 26:1, 1964.

6. One comment contended that the Panel did not rely on controlled studies to support its conclusions on the safety and effectiveness of glycerin as an earwax removal aid.

Glycerin has been adequately demonstrated to be safe for topical use in the ear. However, a thorough review of the data cited by the Panel in support of the effectiveness of glycerin as an earwax removal aid indicates that the only published study referred to was an in vitro study by Senturia and Doubly (Ref. 1) of the effect different vehicles in their action on earwax removed from the human ear canal. Distilled water, hydrogen peroxide (1.5 and 3 percent), and saline solutions (1 and 2 percent) showed immediate reaction with the earwax, and total disintegration occurred in 60 minutes. Glycerin has no effect on the earwax after 60 minutes and showed only surface softening after 24 hours. The authors concluded that glycerin showed little effect upon earwax except that of surface softening. Glycerin has been used by itself in inflammations of the external auditory canal or the middle ear (Ref. 2), and "AMA Drug Evaluations" (Ref. 3) lists glycerin as one ingredient which might be instilled in the ears of patients who have chronic difficulty with impacted earwax; however, it cites no data to support this use. The agency is not aware of any well-controlled studies that demonstrate effectiveness. FDA believes, therefore, that the existing data are not adequate to support the effectiveness of glycerin as an earwax removal aid. The agency is placing glycerin in Category III so that studies may be performed to establish its effectiveness for this indication.

References

(1) Senturia, B. H., and J. A. Doubly, "Treatment of External Otitis," *Laryngoscope,* 57:633–656, 1947.

(2) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Company, Philadelphia, pp. 560–561, 1973.

(3) "AMA Drug Evaluations," 4th Ed., American Medical Association, Publishing Sciences Group, Inc., Littleton, MA, p. 435, 1980.

7. One comment suggested that it is unduly restrictive to limit the carbamide peroxide in anhydrous glycerin to a concentration of 6.5 percent in earwax removal aids. This comment proposed amending the monograph to allow for a range of 5 to 8 percent carbamide peroxide in anhydrous glycerin.

Only two products containing carbamide peroxide in anhydrous glycerin were submitted to the Panel for review, and both had a carbamide peroxide concentration of 6.5 percent. No evidence was presented to the Panel, and none has been submitted to the agency, to show that a 5- to 8-percent range of carbamide peroxide in anhydrous glycerin would be safe and effective. Thus, the agency cannot propose a concentration range for this ingredient without additional data being provided to support such a range.

C. General Comments on Topical Otic Labeling

8. One comment contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims. The comment stated that limiting the indications to the exact terminology of the monograph is overly restrictive because the Panel itself has used alternate terminology throughout the report in discussing the indications for these products. The comment stated that the following truthful claims could be made for earwax removal aids based on language not recommended by the Panel but contained in or referenced in its report: "to soften and loosen earwax," "to relieve the symptoms of fullness due to the accumulation of earwax," "aids in the removal of accumulated earwax," "mechanically softens and loosens earwax so that it can be washed out of the ear canal by irrigation with warm water," "mild mechanical action," "aids in the removal of earwax," and "topical earwax softening agent." The comment requested that more flexibility in labeling be permitted by adding to the approved indications a statement as follows: "* * * or similar indications statements which are in keeping with the Panel's report."

Since the inception of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the

review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specific time periods or through petitions to amend monographs under 21 CFR § 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by the Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA plans to conduct an open public forum on September 29, 1982 where all interested parties can present their views. The forum will be a legislative type administrative hearing under 21 CFR Part 15 that will be held in response to a request for a hearing on the tentative final monograph for nighttime sleep-aids (published in the **Federal Register** of June 13, 1978; 43 FR 25544). Details of the hearing were announced in a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002). In proposed and tentative final monographs issued in the meantime, the agency will continue to state its longstanding policy.

As discussed below in comment 12, FDA is proposing to modify the Panel's recommended indication statement in § 344.50(b). In light of the Panel's use of alternative terminology throughout its report, the agency has reviewed the other claims noted in the comment. FDA believes that a number of these statements are consistent with the labeling message that the Panel intended to convey and that these statements, with slight modifications to ensure accurate reflection of the agency's and Panel's positions on labeling of OTC topical otic drug products, will provide the consumer with meaningful information on the labeling of earwax removal aid drug products. Accordingly, a new § 344.50(b)(2) entitled *"Other allowable statements"* is being proposed in this tentative final monograph. The following statements, as included in this section, may also be made on the labeling of earwax removal aid drug products:

"Softens and loosens excessive earwax."

"Aids in the removal of accumulated earwax."

"Aids in the removal of excessive earwax."

"Topical earwax softening and loosening agent."

The phrases "mild mechanical action" and "mechanically softens and loosens earwax" have not been included in § 344.50(b). (See comment 13 below.) The claim "to relieve the symptoms of fullness due to the accumulation of earwax" also has not been included in § 344.50(b). (See comment 15 below.)

9. Comments contended that experience in mass communication was not a criterion for scientific advisory panelists participating in the OTC drug review and questioned whether some of the terminology used in the labeling for OTC topical otic products could be understood by the ordinary individual in accordance with 21 CFR 330.10(a)(4)(v). One of the comments suggested that FDA consult with behavioral scientists and linguistic experts to help translate the technical language, which is used both in the labeling and in other portions of the Panel report, into lay language that the average consumer can understand. Another comment stated that FDA should leave the implementation of labeling language to the industry, which has had years of experience developing terminology generally understood by the public.

Since its inception, the OTC drug review has focused on developing labeling of OTC drug products that can be understood by the average consumer. While the agency acknowledges that professional experience in mass communication was not a criterion for participation in the OTC drug advisory review panels, the clinical background of the physicians, pharmacists, and other health professionals on each panel involved direct experience with patients and an awareness of the terms used by them to refer to their symptoms. In addition to members of the scientific and medical communities, each panel included representatives from industry and consumer groups and thus had access to the experience of these groups in mass communication of medical terminology. Finally, any citizen interested in doing so could participate in the OTC drug review by presenting views at panel meetings, and, now that the Panels have concluded their reviews, by commenting on advance notices of proposed rulemaking or by commenting or objecting to tentative final monographs proposed by the agency. As mentioned in comment 8 above, a number of changes in the Panel's recommended labeling of topical otic drug products have been incorporated into the agency's proposed labeling as a result of comments received. The agency urges anyone having suggestions for making the labeling language used in the topical otic final monograph more understandable to the average consumer to submit these suggestions in comments responding to this document. After a final monograph for topical otic drug products is issued, such suggestions may be made in the form of a petition to amend the monograph according to the procedures described in 21 CFR 10.30.

10. One comment expressed concern about the minimal discussion on labeling in the Panel's report and stated that a position on labeling should be made explicit by FDA. The comment provided a "Labeling General Statement" which it recommended be adopted by the agency. This labeling statement contains a general discussion of Categories I, II, and III, what labeling must contain to be acceptable, the function of FDA to clarify labeling, the role of the FDA in approving labeling for OTC drug products, the use of labeling indicating superiority of one product over another, the use of extra strength claims in labeling, other misleading superiority claims, claims implying a unique action, and claims relating to time that do not actually relate to the directions or indications, e.g., claims such as "fast" or "prompt."

The "Labeling General Statement" recommended by the comment embodies many principles beyond the scope of the topical otic monograph. Section 330.10(a)(4)(v) (21 CFR 330.10(a)(4)(v)) of the general regulations for classifying OTC drugs states the agency's general labeling standards for OTC drug products. In its report, the Panel has provided a general discussion of Categories I, II, and III; specified the indications, directions for use, and the warnings for the labeling of OTC topical otic drug products; and identified those labeling claims (Category II) that it considers to be misleading and unsupported by scientific data and (in some instances) unsupported by sound theoretical reasoning. The agency believes that the labeling discussion in the Panel's report is adequate and disagrees with the comment that the labeling discussion is minimal. The agency also disagrees with the need for the "Labeling General Statement" recommended by the comment because existing FDA regulations already state the agency's labeling requirements. In addition, most panels have specifically addressed a number of the issues contained in the "Labeling General

Statement" as these issues apply to the ingredients reviewed by the respective panels. In sum, the agency believes that the labeling statements proposed in this tentative final monograph are adequate for consumers to use OTC topical otic drug products safely and effectively.

11. One comment stated that the signal word "warning" is too strong for the types of cautionary statements required in labeling of topical otic drug products and suggested that the term "caution" be used instead. This comment argued that the word "warning" should be used only on certain other types of consumer products to highlight imminent physical hazards associated with normal storage or use of products such as household cleaners, polishes, insecticides, or products marketed as aerosols. This comment suggested that the Panel's recommendation § 344.50(c) be revised to read as follows:

"*Cautions.* The labeling of the product shall contain the following cautionary statements under the heading "Cautions."

This comment also suggested that in § 344.50(c)(ii) the signal word "caution" should be deleted as redundant because in no event should two signal words be necessary.

Section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(f)(2)) states, in part, that any drug marketed OTC must bear in labeling "* * * such adequate warnings * * * as are necessary for the protection of users." Section 330.10(a)(4)(v) of the OTC drug regulations provides that labeling of OTC drug products shall state "* * * warnings against unsafe use, side effects, and adverse reactions * * *."

The agency notes that historically there has not been a consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" are both used. In some instances either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems.

12. One comment questioned whether the term "obstructive" could be understood by the average consumer.

The Panel used the phrase "obstructive earwax" in its recommended indication for topical otic drug products to indicate that these products were intended only for use by individuals who have a tendency to accumulate excessive earwax that needs to be removed occasionally and that these products were not to be used for routine ear cleansing. The agency agrees with the comment that the term "obstructive" may not be understood by the average consumer and therefore is proposing the term "excessive" instead. In keeping with the Panel's intention and with the agency's goal of providing understandable wording, the agency is proposing in this tentative final monograph to revise the indication statement in § 344.50(b) to read as follows: "For occasional use as an aid in the removal of excessive earwax."

13. One comment suggested that the phrase "mild mechanical action to soften and loosen earwax" be added to the monograph as an allowable indication for OTC earwax removal aids because the Panel itself had used this terminology in describing such ingredients in the report.

The Panel used the term "mechanically softens and loosens" to distinguish agents which dissolve earwax from those which soften and loosen earwax so that it may be removed by irrigating the affected ear. The agency believes that the use of the words "mild mechanical action" to describe the mode of action of earwax removal aids would have no meaning to consumers. Therefore, a phrase describing these products as having a mild mechanical action will not be added to the monograph. However, because the phrase "softens and loosens excessive earwax" accurately describes the action of these products, the agency will allow use of this phrase on the labeling of OTC topical otic drug products. As described in comment 8 above, a new § 344.50(b)(2), entitled "*Other allowable statements,*" has been proposed in the tentative final monograph.

14. One comment questioned why the Panel placed the indication "removal and softening of earwax" in Category II because, but for a few words, the phrase is almost identical to the allowable Category I indication.

The agency points out that the Panel included the statement referred to in the comment in its discussion of the use of anesthetics and analgesics in OTC topical otic drug products. The above indication was one of six claims the Panel classified as Category II for topical otic anesthetics and analygesics, not for earwax removal agents. The Panel concluded, and the agency concurs, that the use of analgesics and anesthetics in the ear should be restricted to prescription use, and, therefore, ingredients and claims for these uses are placed in Category II.

15. Several comments proposed that the labeling be amended to include an additional indication "To relieve symptoms of fullness due to an excessive accumulation of earwax." These comments noted that this indication was included in the general discussion of the Panel report. One comment contended that the warning "if symptoms of fullness persist, consult a physician" is only suitable if "relief of the symptoms of fullness" is allowed as an indication. Another comment stated that the term "fullness" is unclear and confusing in the context in which it is used.

As the comments pointed out, the Panel recognized that an excessive accumulation of earwax could cause symptoms of fullness in the ear canal. However, the agency believes that the word "fullness," when used to describe an ear symptom, lacks precise meaning for most consumers. The agency is concerned that consumers might consider the symptoms of ear conditions that are more serious than excessive earwax as symptoms of fullness and thus risk the consequences of nondiagnosis and mistreatment. Therefore, the agency proposes that "symptoms of fullness" not be allowed as an indication for OTC earwax removal aids, and, correspondingly, proposes that the warning, "if symptoms of fullness persist, consult a physician," be deleted.

However, the agency believes that the labeling should state that, if the wax is not removed after using the product, the user should consult a physician. In the Panel report, it is clear that impacted earwax that cannot be removed with OTC earwax softening agents should be treated by a physician who may use agents that dissolve earwax or instruments which are not suitable for OTC use. In addition, the agency believes that the word "doctor" is more commonly used and more readily understood by consumers than the word "physician." Therefore, the agency is proposing that the warning statement, "if symptoms of fullness persist, consult a physician" be replaced by the statement: "If excessive earwax remains after use of this product, consult a

doctor." (See part II. paragraph 6. below.)

16. One comment recommended that "for use as an aid in the prevention of swimmer's ear" be included in the topical otic monograph as an indication for OTC topical otic ingredients. Also, a physician requested that the ingredient propylene glycol be included in the topical otic monograph for the prevention and treatment of swimmer's ear because he had been successfully using the ingredient for this purpose for the past 2 years. The comment included dosage instructions that the physician routinely provided to patients.

The Panel reviewed treatment of "swimmer's ear" and placed this indication in Category II as inappropriate for an OTC topical otic product. The Panel considered "swimmer's ear" to be an infection of the external ear and not amenable to self-diagnosis and self-treatment. FDA concurs. The Panel did not, however, specifically address the claim of prevention of swimmer's ear, nor did it review any product containing propylene glycol as an active ingredient for this use. The Panel stated that "swimmer's ear" is apparently due to excessive moisture in the external auditory meatus, which may be the result of various causes. Because the external auditory canal is a cul-de-sac well suited for the collection of moisture, and "swimmer's ear" occurs with greater frequency during hot, humid weather and has been reported to occur in divers and swimmers, it is possible that propylene glycol may be useful in preventing swimmer's ear because it absorbs moisture. However, the agency has not received any clinical data demonstrating that propylene glycol or any other ingredient is generally recognized as safe and effective in preventing swimmer's ear. The information provided by the comment was only testimonial. Hence, currently there is no basis to include prevention of swimmer's ear as an indication for OTC topical otic drug products. If clinical data are developed, they may be submitted within 12 months after the publication of this tentative final monograph, or thereafter in the form of a petition to amend the monograph as described in 21 CFR 10.30.

17. One comment objected to the Panel's recommended use restriction in § 344.50(c)(viii), "Do not use in children under 12 years without consulting a physician," as unwarranted and recommended that the age restriction be lowered to children under 2 years of age. In support of its position, the comment submitted two journal articles describing the use of 6.5 percent carbamide peroxide in anhydrous glycerin in children (Refs. 1 and 2).

The agency notes that the studies submitted with this comment dealt with professionally supervised use of carbamide peroxide in anhydrous glycerin in children's ears. In both studies, the children were examined by physicians prior to treatment to determine that they had excessive earwax, and the parents of the children were given specific instructions by the physician on how to use the preparation. After the treatment, the children were reexamined to determine whether any further treatment was necessary. The Panel believed that if the product is used in children it should be under the advice and supervision of a physician. The Panel was concerned that some parents would use these products unnecessarily to clean their children's ears routinely, and the agency shares this concern. The agency also belives, based on the studies cited above, that an earwax removal aid should not be used in children unless a physician has made a determination that there is a need to use such a product. The Panel addressed this point by recommending that the directions section of the labeling (§ 344.50(d)) include the statement: "For children under 12 years of age, there is no recommended dosage except under the advice and supervision of a physician." The agency believes that this statement can be shortened to read as follows: "For children under 12 years of age, consult a doctor." The agency also believes that, with this statement in the directions for use, there is no need for a similar statement in the warnings in § 344.50(c)(viii). Accordingly, the agency is proposing in this tentative final monograph to delete the statement from the warnings section.

References

(1) Dickstein, B., "A Simplified Approach to Cerumenolysis," *EENT Digest*, 26:1, 1964.

(2) Cunningham, J. M., "Clinical Evaluation of a Ceruminolytic Agency," *General Practice*, 26:11–12, 1963.

18. One comment suggested that the Panel's recommended warning in § 344.50(c)(v), "For external use only, not to be swallowed," should be deleted. This comment argued that neither ingredient proposed to be classified in Category I poses a serious risk if ingested and stated that the phrase "for external use" would confuse consumers, many of whom would not consider use in the ears to be an external use.

The agency agrees with the comment that carbamide peroxide in anhydrous glycerin does not pose a serious risk if ingested and that the use of the phrase "for external use only" labeling of OTC topical otic preparations may be confusing to consumers. Accordingly, the agency is proposing in this tentative final monograph to delete the warning "For external use only, not to be swallowed," and to add the statement "FOR USE IN THE EAR ONLY" to the directions for use to state clearly that the product is to be used only in the ear. To emphasize the importance of this direction, the agency proposes that this statement should be printed in capital letters.

19. One comment questioned whether the words "drainage" and "perforation," as used by the Panel in its recommended warnings, would be understood by the average consumer since they are infrequently used in everday conversation.

The agency believes that these words would not be readily understood by the average consumer. Therefore, to explain the meanings of these terms, the agency has added to the Panel's warning the word "hole" in parentheses after "ear drum perforation," and the words "or discharge" after the term "drainage."

20. One comment recommended the addition of a warning: "Do not use whenever an (ear) infection is suspected."

The Panel did not believe that a consumer would be able to self-diagnose an ear infection. Therefore, instead of using the word "infection," the Panel listed in the warnings the common symptoms of ear infections, such as ear pain and ear drainage. The agency believes that the Panel's recommended warning in § 344.50(c)(ii) as amended in this tentative final monograph (now § 344.50(c)(1)) is adequate, and that the warning suggested in the comment would be redundant. Accordingly, FDA has not added this warning to the tentative final monograph.

21. A comment objected to the Penel's recommended warning in § 344.50(c)(iii) not to use topical otic drug products following ear surgery. This comment contended that ear surgery should not preclude the use of a topical otice drug product forever and suggested that the warning should be revised to have a time limit of 6 weeks following ear surgery.

The agency agrees with the comment that it may be unnecessary to ban forever the use of these products following ear surgery. However, the time period of restriction from use will vary depending on the type of surgery performed. Therefore, the decision when to use a topical otic drug product following ear surgery should be made by

the patient's physician. The agency believes that the warning should not be revised to state a specific time period during which these drug products should not be used following ear surgery. However, the agency is proposing in this tentative final monograph that the warning recommended by the Panel in § 344.50(c)(iii) be modified to state that these products should be used after ear surgery only if directed by a doctor. (See comment 22 below.)

22. Several comments stated that some of the phrases in the warnings were redundant. One comment suggested a statement be added to the monograph which would allow for the general warnings to be combined when the intent of the warnings is not affected. Another comment suggested that three warning statements recommended by the Panel (§ 344.50(c)(ii), (iii), and (iv)) be combined and revised to read as follows:

(1) "Do not use in the presence of ear drainage, pain, or dizziness, or whenever an infection is suspected. If these develop, consult a physician."

(2) "Do not use in the presence of known injury or perforation (hole) of the ear drum or within six weeks following ear surgery except under the advice and supervision of a physician."

The agency agrees with the comments that some of the warnings could be combined without losing their intent. However, the references to ear infection and the 6-week period following ear surgery are not being adopted, as explained above in comments 20 and 21. The agency believes that the warning recommended by the Panel in § 344.50(c)(vii), "Discontinue use if irritation or rash appears," can be incorporated into the suggested revision of § 344.50(c)(ii) (which appears in this tentative final monograph as § 344.50(c)(1)) without changing the intent. Accordingly, the agency proposes in this tentative final monograph that the firt two statements under the heading *"Warnings"* in § 344.50(c) read as follows:

(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."

23. One comment expressed a belief that the consumer should be informed of the improper uses of topical otic drug products. It suggested that because misuse can lead to harmful aftereffects a warning should be added listing the symptoms for which the consumer ought not to use topical otic drug products. The comment proposed the following warning: *"Warning:* Avoid using to relieve minor irritation or pain for raw, inflamed tissues, swimmer's ear, anethetizing, or itching."

The agency believes that the comment has misinterpreted the requirements for OTC drug labeling as set forth in § 330.10(a)(4)(v). It is not necessary or even possible for the agency to identify every improper use of a drug that could occur and to require the listing of such information on the OTC drug product label. FDA believes that the indications for use and the warnings proposed in this tentative final monograph are adequate to inform the consumer of the proper use of these products.

24. Several comments objected to the Panel's recommendation in § 344.50(d), which directs the user to "Place sufficient drops into affected ear and allow to remain at least 15 minutes." These comments contended that the term "sufficient" is too vague and could result in unnecessary underdosage or overdosage. One comment expressed the belief that it would be more meaningful and accurate to give the dosage in numbers of drops, e.g., 5 to 10 drops, and suggested revising the directions for administering the drops as follows: "Tilt head sideways and place 5 to 10 drops into ear. Tip of applicator should not enter ear canal. Keep drops in ear for several minutes by keeping head tilted or by inserting cotton."

The agency agrees with this suggestion. Stating the amount is much more precise and is safer for the consumer. Also, the use of "5 to 10 drops" is consistent with the amount used in the studies reviewed by the Panel. Therefore, the agency is proposing that the directions in § 344.50(d) be modified accordingly. For additional clarity, the agency is changing the words "inserting cotton" to "placing cotton in the ear."

25. Comments objected to the Panel's recommendation in § 344.50(d) that direct the user to "Remove wax by gentle washing with lukewarm water using a soft rubber syringe. May be repeated a second time if necessary." One comment questioned whether the average consumer would know the meaning of the term "soft rubber syringe." Another comment cautioned that the use of an irrigation syringe should be discouraged when possible and its use indicated as an adjunct only for the removal of accumulated cerumen in difficult cases. The comment stated that in the case of carbamide peroxide in anhydrous glycerin it is not always necessary to use an irrigation syringe to remove the earwax. The comment stated that the mechanical effect of effervescence of carbamide peroxide loosens debris and in many cases this mechanical effect has been shown to accomplish removal of the earwax and debris without use of an irrigation syringe. The comment recommended extending the duration of treatment to 3 or 4 days and delaying the use of an irrigation syringe until the end of the treatment period, making clear that even then the use of an ear syringe should be optional. The comment suggested the following revision in directions for use of preparations containing carbamide peroxide in anhydrous glycerin: "Repeat twice daily for at least 3 to 4 days or as directed by a physician. Any remaining wax may be removed by gently flushing with warm water, using a soft rubber bulb ear syringe."

FDA agrees that "soft rubber bulb ear syringe" is a more meaningful term for the average consumer than the term "soft rubber syringe." The agency also concurs with the comment that the use of an irrigation syringe in the ear should be limited as much as possible and that the ear drops may be used for 3 to 4 days. FDA proposes to use the phrase "for up to 4 days if needed." With this modification, the agency accepts the revision suggested by the comment and proposes to revise § 344.50(d) to include the following as part of the directions for use: "Use twice daily for up to 4 days if needed, or as directed by a doctor. Any wax remaining after treatment may be removed by gently flushing the ear with warm water, using a soft rubber bulb ear syringe."

In addition, the agency believes that the failure to obtain relief after 4 days of treatment with an earwax removal aid could indicate a more serious condition for which the patient should consult a doctor. Accordingly, the agency is proposing the following additional warning in § 344.50(c)(3): "Do not use for more than 4 days; if excessive earwax remains after use of this product, consult a doctor."

II. The Agency's Tentative Adoption of the Panel's Report

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

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's categorization of carbamide peroxide in anhydrous glycerin in Category I and antipyrine and benzocaine in Category II. The

Panel also placed glycerin in Category I. FDA is proposing reclassification of glycerin in Category III because of a lack of sufficient data to demonstrate effectiveness.

2. *Testing of Category II and Category III conditions.* The agency notes that, because the Panel did not place any ingredients in Category III, it did not recommend any testing guidelines for Category III topical otic 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 ingredient or 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). This 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 Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. As mentioned above, the Panel placed glycerin in Category I as an ear wax removal aid. FDA is proposing reclassification of glycerin in Category III for effectiveness. This reclassification is discussed in the agency's response to comment 6 above.

2. In its report and recommended monograph, the Panel often referred to the active ingredient as carbamide peroxide in glycerin with subsequent discussion clarifying that the anhydrous form of glycerin is the vehicle to be used. Glycerin is glycerin U.S.P., which has a moisture content of approximately 5 percent, and anhydrous glycerin is an ingredient that may be prepared by heating glycerin U.S.P. at 150° C for 2 hours to drive off the moisture content (Ref. 1). The agency wishes to clarify that the active ingredient should correctly be referred to as carbamide peroxide formulated in an anhydrous glycerin vehicle.

Reference

(1) Martin, E. W., "Dispensing of Medications," 7th Mack Publishing Co., Easton, PA, p. 284, 1971.

3. The agency is redesignating proposed Subpart D of the monograph as Subpart C and placing the labeling sections under Subpart C.

4. The Panel recommended that the labeling of the product should identify the product as an "earwax softening agent." FDA is proposing that it would be more appropriate to identify the product as an "earwax removal aid" and to allow the phrase "softens and loosens excessive earwax" as another allowable statement in labeling (see comment 13 above).

5. The Panel's definitions of "age (dosage) usage" and "cerumen" have been deleted as unnecessary because these terms are not used in the tentative final monograph, a definition of "anhydrous glycerin" has been proposed, and a definition of "earwax removal aid" has replaced the definition of "earwax softening agent."

6. The Panel recommended the classification of one labeling indication and eight warnings as Category I labeling. To simplify and clarify the labeling, FDA is proposing to modify the Panel's labeling indication and directions for use, delete two warnings and add one, and combine or otherwise modify the other warnings so that the OTC topical otic drug monograph now requires four labeling warnings. In addition, the agency is proposing to use the signal word "warning" instead of the signal word "caution" in labeling. The agency has also expanded the labeling by proposing "Other allowable statements," which may be used in addition to required labeling language. The labeling modifications are discussed in comments 8 through 25 above.

7. In several of its recommended warnings, the Panel used the phrase "consult physician." This phrase has been consistently used in OTC drug labeling as advice to the consumer in case of symptoms that indicate a condition that cannot be self-treated. Believing that the word "doctor" is more commonly used and better understood by consumers, the agency is substituting "doctor" for "physician" in the warnings appearing in the tentative final monograph. These changes are proposed as part of a continuing effort to achieve OTC labeling language that is simple, clear, and accurate, in keeping with § 330.10(a)(4)(v), (21 CFR 330.10(a)(4)(v)), which states in part, "Labeling * * * shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use." If the phrases "consult a doctor" and "unless directed by a doctor" are adopted in the final monograph for topical otic drug products, the agency proposes to use this language in other final monographs and other applicable OTC drug regulations, and will propose amendments to those regulations accordingly. Public comment on the proposed changes in labeling language is invited.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Public Law 96-354). Specifically, it would leave carbamide peroxide, the active ingredient used in currently marketed OTC ear wax removal aid drug products, in Category I; move glycerin, currently not used in any of these products, to Category III; and leave analgesics in Category II. The only reformulation necessary would involve products containing analgesics; however, many of these products have already been reformulated. Necessary relabeling will not result in minimal costs because manufacturers will have 12 months from the date of publication of the final monograph to use existing stocks of labels and print new ones. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC topical otic drug products. 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 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, 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 that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 344

OTC drugs: Topical otic drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982)), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended to add new Part 344 to read as follows:

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

Subpart A—General Provisions

Sec.
344.1 Scope.
344.3 Definitions.

Subpart B—Active Ingredients

344.10 Topical otic active ingredient.

Subpart C—Labeling

344.50 Labeling of topical otic drug products.

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

Subpart A—General Provisions

§ 344.1 Scope.

(a) 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 conditions in this part in addition to each of the general conditions established in § 330.1.

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

§ 344.3 Definitions.

As used in this part:

(a) *Anhydrous glycerin.* An ingredient that may be prepared by heating glycerin U.S.P. at 150° C for 2 hours to drive off the moisture content.

(b) *Earwax removal aid.* A drug used in the external ear canal that aids in the removal of excessive earwax.

Subpart B—Active Ingredients

§ 344.10 Topical otic active ingredient.

The active ingredient of the product consists of carbamide peroxide 6.5 percent forumlated in an anhydrous glycerin vehicle.

Subpart C—Labeling

§ 344.50 Labeling of topical otic 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 "earwax removal aid."

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

(1) "For occasional use as an aid in the removal of excessive earwax."

(2) *Other allowable statements.* In addition to the required information specified in paragraphs (a), (b)(1), (c) and (d) of this section, the labeling of the product may contain any of the following statements provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(i) "Softens and loosens excessive earwax."

(ii) "Aids in the removal of accumulated earwax."

(iii) "Aids in the removal of excessive earwax."

(iv) "Tropical earwax softening and lossening agent."

(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) "Do not use for more than 4 days; if excessive earwax remains after use of this product, consult a doctor."

(4) "Avoid contact with the eyes."

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": "FOR USE IN THE EAR ONLY. Adults and children over 12 years of age: Tilt head sideways and place 5 to 10 drops into ear. Tip of applicator should not enter ear canal. Keep drops in ear for several minutes by keeping head tilted or placing cotton in the ear. Use twice daily for up to 4 days if needed, or as directed by a doctor. Any wax remaining after treatment may be removed by gently flushing the ear with warm water, using a soft rubber bulb ear syringe. Children under 12 years of age: consult a doctor."

Interested persons may, on or before September 7, 1982 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 9, 1982. 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 above office 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 11, 1983, 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 9, 1983. These dates are consistent 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 above office 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 9, 1983. 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.

Dated: May 17, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: June 21, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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