DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 349

[Docket No. 80N-0145]

Ophthalmic 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 or proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) ophthalmic drug products (drug products applied to or instilled in the eye) 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 Ophthalmic 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 August 29, 1983. New data by June 28, 1984. Comments on the new data by August 28, 1983. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Comments on the agency's economic impact determination by October 27, 1983.

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, National Center for Drugs and Biologics (HFN-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 6, 1980 (45 FR 30002) 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 ophthalmic drug products, togeather with the recommendations of the Advisory Review Panel on OTC Ophthalmic 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 August 4, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by September 3, 1980.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, one drug manufacturers' association, five drug manufacturers, and many individual consumers submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on May 6, 1980 (45 FR 30002), 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) to establish Part 349 (21 CFR Part 349), FDA states for the first time its position on the establishment of a monograph for OTC ophthalmic 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 ophthalmic drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC ophthalmic 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.

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

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Category 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 ophthalmic drug products (published in the **Federal Register** of May 6, 1980 (45 FR 30002)),

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 have their products 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.

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 April 26, 1973 (38 FR 10306) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

The Agency's Tentative Conclusions on the Comments

A. General Comments on Ophthalmic Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC rulemaking proceedings.

The agency addressed this issue in paragraphs 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 tenative final monograph for antacid drug products, published in the **Federal Register** of November 12, 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) and *National Association 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 eyewash products be regulated as ophthalmic devices and not as OTC drug products. The comment noted that § 349.3(g) of the Panel's recommended monograph states that eyewashes, eye lotions, and irrigating solutions contain no active ingredients and are intended for bathing or mechanically flushing the eye. The comment stated that this definition corresponds to the definition of the term "device" contained in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(h)). The comment stated that, as defined in the act, the primary difference between devices and "drugs" is that devices do not achieve any of their principal intended purposes through chemical or metabolic action.

The act defines a device, in part, as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, or accessory, which is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and which does not achieve any of its principal intended purposes through chemical action within or on the body and which is not dependent upon being metabolized to achieve any of its principal intended purposes (21 U.S.C. 321(h)). The act defines a drug, in part, as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, but does not include devices or their components, parts, or accessories (21 U.S.C. 321(g)).

Although the act states that a "device" may not achieve any of its principal intended purposes through chemical action or by being metabolized, it does not state that a "drug" must function through chemical or metabolic action. In fact, many classes of drugs achieve their intended purposes without exerting a chemical action or by being metabolized. Examples, include some sunscreens, some dandruff preparations, and various laxative preparations such as mineral oil and psyllium. Some ophthalmic drug products achieve their intended purpose as a result of their physical composition rather than any chemical action, for example, demulcents and emollients. The Panel described a rational physical composition for an OTC eyewash preparation as consisting of water, sodium chloride and other tonicity agents to establish isotonicity with tears, agents for establishing pH and buffering to achieve the same pH as tears, and a suitable preservative agent (45 FR 30046). The Panel concluded that a solution of this general composition can be safely and effectively used as a drug product for flushing the eye to remove irritating substances or foreign material. An eyewash is intended for in vivo use—instillation in the eye. It is not an instrument, apparatus, implement, machine, contrivance, implant, or in vitro reagent, nor is it similar or related to those products that are listed in the "device" definition. The agency accepts the Panel's consideration of eyewashes, eye lotions, and irrigating solutions as ophthalmic drug products even though they contain no pharmacologically active ingredients and believes that they are properly regulated as drugs under the act. This position is consistent with recent action by the agency in reclassifying a hydroxpropyl cellulose ophthalmic insert from a medical device approved for marketing to an approved new drug. (See the **Federal Register** of October 15, 1982; 47 FR 46139.)

B. Comments on Specific Ophthalmic Active Ingredients

3. One comment questioned the exclusion of demulcents from eyewash products in § 349.22 of the Panel's monograph. The comment stated that

demulcents are described in the Panel's report as safe and effective additives without restriction and, therefore, should not be excluded from the list of ingredients approved for use in eyewash and tear-substitute products.

The agency notes that the Panel excluded the use of demulcents in eyewashes but not in tear-substitute products. The Panel described ophthalmic demulcents as ingredients for use "as tear substitutes and viscosity agents" to be applied topically to the eye to protect and lubricate mucous membrane surfaces and relieve dryness and irritation. The primary function of a demulcent is to act as an ophthalmic lubricant to coat the surface of tissues and protect the underlying cells from external stimuli. On the other hand, the primary function of an eyewash is to wash, bathe, irrigate, or mechanically flush foreign bodies, pollen, and noxious chemicals from the eye. An eyewash is used to dilute or remove irritants, not to lubricate or coat irritated surfaces.

The Panel determined that an eyewash should be neutral and comfortable to the eye, and should not contain active ingredients, such as vasoconstrictors, anti-infectives, astringents, etc. (45 FR 30046). An eyewash should have a physiological composition similar to tears, which are the first line of defense for the conjunctiva and cornea. Whenever foreign material is present, the output of tears greatly increases as a means of flushing out or diluting the irritant. Because the intended action of eyewash products is similar to that of tears, the Panel recommended that eyewash products be similar to tears, i.e., isotonic, neutral aqueous solutions which contain no active ingredients. The Panel felt there is no apparent practical benefit in combining an eyewash with an active ingredient such as a demulcent. If needed, a separated ophthalmic demulcent drug product might be effectively used following the use of an eyewash. The agency concurs with the Panel and is not including any active ingredient for use in eyewash products.

4. One comment opposed the removal of currently available mild anesthetics and anti-infectives from OTC eye medications. The comment claimed that this action will increase the cost of eye medication and inconvenience the patient because the availability of OTC ophthalmic medication to nonmedical eye practitioners (optometrists) would be further restricted. As an example of increased cost, the comment stated that without an ophthalmic anesthetic, rural optometrists would no longer be able to use Goldmann tonometry for measuring intra-ocular pressure and would have to purchase expensive equipment for air tonometry. The increased costs would then be passed on to the consumer.

The Panel concluded that ophthalmic anesthetics should only be used under the direction and supervision of a physician because these ingredients can mask the symptoms of serious eye disorders that require professional attention. Also, the misuse or abuse of ophthalmic anesthetics by consumers could lead to serious eye damage, e.g., corneal ulcerations with scarring and permanent visual loss. The Panel documented cases of severe corneal damage as a result of the use of ophthalmic anesthetics, as well as allergic reactions to these drugs (45 FR 30026). The Panel, however, did not intend to limit the use of these drugs by other professionals, such as optometrists. The Panel recognized that ophthalmic anesthetics are very important and necessary when used by ophthalmologists and optometrists for certain ophthalmic procedures. Such procedures as tonometry and gonioscopy require the proper use of an ophthalmic anesthetic by a well-trained professional. Dispensing authority regarding the availability of ophthalmic anesthetics to optometrists is a State-level issue and will not be addressed by the agency in this rulemaking. The agency accepts the Panel's recommendations and is not proposing to classify any ophthalmic anesthetic ingredient in Category I in this tentative final monograph.

In reviewing ophthalmic anti-infectives, the Panel recognized that there are many ophthalmic infections such as blepharitis, conjunctivitis, and hordeolum (stye) that may not require immediate attention by a doctor because these conditions are normally self-limiting and adverse effects are rare. The Panel determined that at the present time there are no anti-infective ingredients that can be generally recognized as safe and effective for OTC ophthalmic use. The Panel reviewed boric acid, mild silver protein, yellow mercuric oxide, and sulfacetamide sodium as anti-infective ingredients. Boric acid and mild silver protein were placed in Category III because there are insufficient data available to determine their effectiveness as ophthalmic anti-infective ingredients. Yellow mercuric oxide was placed in Category III because data are lacking to show that it is safe and effective. Sulfacetamide sodium, currently marketed as a prescription drug, was placed in Category II for OTC use because it produces a high incidence of sensitization and severe irritation to the eye. In the preamble to the Panel's report the agency stated that it is concerned that, because the symptoms of minor and serious infections are often similar, there may be potential for serious harm to the eye if professional treatment is delayed. The agency made an initial determination that the benefits to be derived from the use of these drugs OTC do not outweigh the risks and proposed to classify ophthalmic anti-infectives in Category II (45 FR 30002). The agency invited specific comment on this proposal and received only the comment described above, which provided no data to support the continued availability of currently available OTC ophthalmic anti-infective drug products The agency reaffirms its position and proposes to classify all ophthalmic anti-infectives in Category II in this tentative final monograph.

5. One comment objected to the Panel's listing of camphor as a "nonessential" ingredient and its decision to exclude it from eyewash drug products (45 FR 30021). The comment claimed that camphor in sufficiently dilute concentration (less than 0.05 percent weight/weight) is both safe and effective in achieving and maintaining product sterility. The comment further stated that camphor has been used in its eyewash/tear substitute products for many years and these products have shown excellent antibacterial properties, i.e., microbial growth is prevented even in the absence of heat sterilization during the manufacturing process. The comment claimed that an independent testing laboratory observed that products containing camphor have excellent antibacterial properties; however, no data were submitted to support this claim.

The Panel did not include camphor in its discussion of preservative agents. It recommended empirical preservative effectiveness tests, such as the official United States Pharmacopeia (U.S.P.) antimicrobial preservative effectiveness test, and stressed the importance of demonstrating that the preservative selected for a formulation will be effective until its expiration date (45 FR 30016). The comment did not submit any data on the antimicrobial testing performed on its products nor state if camphor or the drug products were tested using the protocol established by the U.S.P. or similar protocols.

The OTC drug review is an active, not an inactive, ingredient review. The OTC panels occasionally made recommendations with respect to

inactive ingredients; however, these recommendations were made for public awareness and were not intended to be included in the OTC drug monographs. Inactive ingredients, although not included in OTC drug monographs, must meet the requirements of § 330.1(e) (21 CFR 330.1(e)) that they be suitable ingredients that are safe and do not interfere with the effectiveness of the product or with tests to be performed on the product. Thus, camphor may be included as an inactive ingredient in OTC ophthalmic drug products provided that it meets the above critertia.

6. One comment submitted data on polyethylene glycol 6000 and requested that it be classified as a Category I ophthalmic demulcent. The data consisted of animal safety studies with polyethylene glycol 6000 as a single active ingredient in a saline vehicle and in an artificial tear formulation, and two human effectiveness studies with finished combination products containing polyethylene glycol 6000 as one of the active ingredients (Ref. 1).

The agency has reviewed the data and concludes that they do not justify placing polythylene glycol 6000 in Category I. The data from the animal safety studies adequately established the ocular safety of polyethylene glycol 6000. However, no data were submitted to demonstrate the effectiveness of polyethylene glycol 6000 when used alone as an ophthalmic demulcent. Only human effectiveness studies involving finished combination products which contained polyethylene glycol 6000 as one of the active ingredients were reported. These studies were not designed to show the effectiveness of polyethylene glycol 6000 as a single active ingredient or to demonstrate its contribution to the effectiveness of the finished combination products. Additional data are needed to demonstrate that polyethylene glycol 6000 alone is an effective OTC ophthalmic demulcent.

Based on the data reviewed, the agency is proposing to classify polyethylene glycol 6000 in Category III as an ophthalmic demulcent in this tentative final monograph. The agency's detailed comments and evaluation on the data are on file in the Dockets Management Branch (Ref. 2).

References

(1) Comment No. C00378, Docket No. 80N-0145, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to J. D. Mutch, Cooper Laboratories, Inc., coded LET002, Docket No. 80N-0145, Dockets Management Branch.

C. Comments on Labeling of Ophthalmic Drug Products

7. Two comments contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims. The comments stated that limiting the indications to the exact terminology of the monograph is overly restrictive because the Panel itself had used alternate terminology throughout the report in discussing the indications for these products.

During the course 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 specified time periods or through petitions to amend monographs under § 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 conducted an open public forum on September 29, 1982 at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was 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). The agency's decision on this issue will be announced in the **Federal Register** following conclusion of its review of the material presented at the hearing.

8. One comment cited excerpts from the Panel's definitions for the various pharmacologic classes of ophthalmic active ingredients and stated that those statements were as truthful as the indications recommended by the Panel and should be allowed in the claims for these products. For example, the comment stated that the following claims based on the Panel's definitions are as truthful as the Panel's proposed labeling:

a. For anti-infectives—"destroys or limits the multiplication of microorganisms."

b. For astringents—"helps to clear mucus from the outer surface of the eye."

c. For demulcents—"protects and lubricates mucous membrane surfaces and relieves dryness and irritation."

d. For emollients—"protects or softens tissues, prevents dryness and cracking."

e. For eyewashes—"bathes or mechanically flushes the eye."

f. For hypertonicity agents—"draws water from the body tissues and fluids" or "draws water out of the cornea."

g. For vasoconstrictors—"causes transient constriction of conjunctival blood vessels."

The Panel's recommended indications address symptoms that consumers can recognize and advise consumers under what conditions they should use an ophthalmic drug product. The Panel's definitions, however, were not intended to address symptons or state when the product should be used. For example, the comment's "truthful claim" for a vasconstrictor, "causes transient constriction of conjunctival blood vessels," does not indicate to consumers under what conditions the product should be used, nor does it indicate the symptoms that need to be recognized and relieved. On the other hand, the Panel's recommended indication informs consumers that the product will "relieve redness of the eye due to minor eye irritations. " The Panel's definitions generally state the action of the ingredient and cannot be equated with indication statements that should inform consumers what symptoms the product relieves.

The agency believes that conversion of the comments's "truthful claims" into indication statements that are simple and clearly stated would in general result in indication that are very similar to those already recommended by the Panel. For example, the claim quoted by the comment for a demulcent, "protects and lubricates mucous membrane surfaces and relieves dryness and irritation," could easily be revised into one of the Panel's three recommended

indications which inform consumers that a demulcent product will "relieve dryness of the eye." The example offered by the comment for eyewash products, "bathes or mechanically flushes the eye," is similar to the following indication recommended by the Panel, "for flushing or irrigating the eye to remove loose foreign material, or chlorinated water."

It is the agency's intention that the labeling of OTC drug products be as simple, truthful, and informative as possible. Simply because words or phrases are found in the definition of a pharmacological class of an OTC drug product does not necessarily mean that those words or phrases are appropriate for inclusion under indications for use on the labeling for that product. The information needs to be in language that provides consumers adequate guidance for the effective and safe use of the product.

9. There comments contended that some of the descriptive terms used in the statements of identity recommended by the Panel are too specific and not easily understood by consumers. The comments stated that alternate terms that are more meaningful to the consumer should be permitted. The terms "decongestant eye drops" and "redness remover" were suggested as preferable to "ophthalmic vasoconstrictor." The term "eye lubricant" was recommended in place of the term "demulcent" in § 349.60(a) to communicate better to the consumer that the primary function of the product is the lubrication of the eye and relief of dryness. Other terms suggested were "soothing" for "demulcent," and "softening" or "relaxing" for emollient.

The agency agrees with the comments and believes that some of the statements of identify recommended by the Panel, although scientifically correct, may not be easily understood by the average consumer needing an OTC ophthalmic drug product. Therefore, the agency is proposing alternate descriptive terms that might be more meaningful to the consumer for the statements of identity required in the labeling of drug products containing ophthalmic vasoconstrictors, demulcents, and emollients. The agency believes that the term "eye lubricant" would convey to a consumer the purpose of the drug product more clearly than "demulcent" or "emollient", and "eye redness reliever" is more meaningful than "ophthalmic vasoconstrictor." The agency feels that "eye redness reliever" more accurately describes the action of an ophthalmic vasoconstrictor than "redness remover," the term suggested by the comment. In addition, "relief of redness" is currently used in labeling of ophthalmic drug products containing vasoconstrictors and, therefore, should be easily understood by the consumer. These optional terms are being proposed in the tentative final monograph. However, terms such as "soothing," "softening," and "relaxing" are not appropriate language for use in statements of identity for ophthalmic drug products because they are ambiguous and not very informative. Also, the term "decongestant eye drop" will not be included because the term "decongestant" is not readily understood by consumers with respect to the eye.

10. Two comments requested that the claim "tired eyes" be deleted from the category II labeling section of the Panel's report (45 FR 30023, 30024, and 30035). Both comments claimed that the term as used by consumers describes the ordinary appearance of minor irritation and redness in the eyes. One comment added that such use of this term has been shown by contact with consumers through market research and other communications. The other comment stated that, after the use of an ophthalmic vasoconstrictor, consumers believe that their eyes feel and look refreshed.

The agency believes that the comments' arguments supporting the use of the term "tired eyes" may have merit. However, neither comment submitted any data to demonstrate that consumers define "tired eyes" as minor irritation and redness in the eyes, conditions for which an OTC ophthalmic drug can be used. The Panel felt that the term "tired eyes" implies fatigue as a result of normal visual activities such as reading, watching television, or doing close work (45 FR 30023 and 30024) and stated that product claims "for improvement of tired eyes" are scientifically unfounded and misleading to the consumer (45 FR 30035). The agency will consider reclassification of the term "tired eyes" to Category I if adequate data are presented to show that consumers equate "tired eyes" with symptoms of minor irritation and redness in the eyes. The agency is reclassifying this term from Category II to Category III in this tentative final monograph.

11. One comment suggested expanding the indication for ophthalmic demulcents in § 349.60(b)(2), which reads "for the temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun," to include other similar and common environmental factors that adversely affect the eye, e.g., "smog or poor air quality."

The recommended indication for ophthalmic demulcents in § 349.60(b) are based on their lubricating properties which provide relief from minor irritations and dryness of the eye. Smog and haze contain very fine, widely dispersed particles which can be very irritating to the eye, but do not have a drying effect on the eyes similar to that resulting from prolonged exposure to the wind or sun. Thus, a demulcent may not be the OTC ophthalmic product of choice when dealing with exposure to smog. An eyewash, which is intended for removing irritants such as foreign bodies, pollen, and noxious chemicals from the eye, would be more effective. In its general discussion of eye washes, the Panel describes exposure of the eye to adverse environmental conditions, such as smog, and the symptoms of irritation which can develop (45 FR 30046 and 30047). Foreign material in the eyes can result in a foreign body sensation, inflammation, swelling, tearing, uncontrolled blinking of the eyelids, or symptoms of irritation, discomfort, burning, stinging, smarting, and itching. When such symptoms occur, foreign material may be present in an undissolved form, such as dust or an eyelash; as suspended particulate material in tears, such as pollen or smog; or as noxious materials, such as airborne pollutant gases and chemicals, dissolved in tears. Provided the eye is not damaged by such debris, the relief of symptoms occurs with removal of the irritating substance. This removal can be more easily accomplished with an eyewash than with a demulcent, and the Panel's recommended indication for eyewashes in § 349.80(b) includes air pollutants as an example of substances eyewashes may be used to remove. Therefore, the agency is not proposing to include "smog or air quality" in the indications for ophthalmic demulcents. The agency invites further comment on this issue.

12. Two comments opposed the warning recommended by the Panel in § 349.75(c)(1)(iv) for ophthalmic vasoconstrictors. The warning states: "Overuse of this product may produce increased redness of the eye." Both comments stated that there is no evidence in the record to prove that overuse of an ophthalmic vasoconstrictor will produce increased redness of the eye, know as rebound hyperemia. One comment cited several controlled studies in which rebound vasodilation (rebound hyperemia) did not occur in subjects using an ophthalmic product containing

tetrahydrozoline hydrochloride (Refs. 1 through 4). The comment urged that the warning be applicable only to vasoconstrictors for which there is evidence that rebound hyperemia occurs and that it not be required for tetrahydrozoline hydorchloride.

The Panel strongly recommended against too-frequent or prolonged use of ophthalmic vasoconstrictors, pointing out that excessive use might produce hyperemia, among other adverse side effects (45 FR 30033). Rebound hyperemia in the eye results from a prolonged constriction of the conjunctival blood vessels followed by dilation of those blood vessels. The Panel stated that on encountering the symptoms of rebound hyperemia, a consumer could be led to believe that more of the product is needed, when actually discontinuing use of the vasoconstrictor is necessary to relieve the condition.

The Panel noted that rebound hyperemia has not been reported from the use of ophthalmic products containing naphazoline hydrochloride or tetrahydrozoline hydrochloride. however, rebound congestion from excesive use of nasal products containing naphazoline hydrochloride has been documented (Refs 5, 6, and 7). In addition, an agency review of adverse reaction reports submitted to FDA since 1969 for OTC ophthalmic drug products containing tetrahydrozoline hydrochloride shows 43 cases in which the products failed to clear the redness and soothe the eyes (listed as "lack of drug effect" by the agency) (Ref. 8). Some of these may well be cases of rebound hyperemia. In all, 157 cases of adverse reactions, including 46 cases of conjunctivitis and 17 cases of eye pain, were reported for ophthalmic drug products containing tetrahydrozoline hydrochloride. These adverse reactions were all reported after completion of the four controlled studies cited by the comment in which rebound hyperemia was not reported (Refs. 1 through 4).

The Panel proposed that the labeling of all ophthalmic vasoconstrictor drug products contain a warning against excessive use. The agency concurs with the Panel's recommendation and is proposing in the tentative final monograph the Panel's suggested warning "Overuse of this product may produce increased redness of the eye" for all ophthalmic drug products containing a vasoconstrictior.

References

(1) Grossman, E. E., and R. H. Lehman, "Ophthalmic Use of Tyzine: A Clinical Study of this New Vasoconstrictor," *American Journal of Ophthalmology*, 42:121–123, 1956.

(2) Menger, H. C., "New Ophthalmic Decongestant, Tetrahydrozoline Hydrochloride: Clinical Use in 1,156 Patients with Conjunctival Irritation," *Journal of the American Medical Association*, 170:178–179, 1959.

(3) "Ophthalmic Use of Tetrahydrozoline Hydrochloride (Visine)," *Journal of the American Medical Association*, 173:677, 1960.

(4) Stokes, J. J., "Clinical Evaluation of Tetrahydrozoline Ophthalmic Solution," *Journal of the Medical Association of Georgia*, 47:540–541, 1958.

(5) Schiller, J. W., "Deleterious Effects of Privine Hydrochloride," Letter to the Editor, *New England Journal of Medicine*, 232:333, 1945.

(6) Thomas, J. W., and U. Fabiano, "Privine sensitivity: A Report of Eight Cases," *Southern Medical Journal*, 39:658–664, 1946.

(7) Feinberg, S.M., and S. Friedlaender, "Nasal Congestion from Frequent Use of Privine Hydrochloride," *Journal of the American Medical Association*, 128:1095–1096, 1945.

(8) Department of Health and Human Services, Food and Drug Administration, Adverse Reaction Summary Listings, pertinent pages for 1969–82, OTC Volume 100TFM.

13. One comment requested that the Panel's recommended warning against the use of mercury-containing OTC ophthalmic drug products by persons sensitive to mercury (45 FR 30024) include the name of the particular mercury-containing compound used in an OTC ophthalmic drug product, lieu of a reference to the element involved, mercury. The comment claimed that persons sensitve to chemicals are more likely to be aware of the name of a particular chemical substance, e.g., thimerosal, rather than the name of the element it contains, e.g., mercury.

At present there are no Category I ophthalmic active ingredients that contain mercury. However, the agency is aware that mercury compounds, such as thimerosal, are used as preservatives in OTC ophthalmic drug products. The Panel recognized that allergic reactions may result from mercurial preservatives being present in OTC ophthalmic drug products and recommended this mercury warning for each therapeutic class of ophthalmic drugs reviewed. The agency concurs with the Panel that this warning is appropriate. A similar situation is the agency's regulation concerning sensitivity to the color additive FD&C yellow No. 5. In § 201.20 (21 CFR 201.20), the agency requires that all OTC and prescription drug products containing this agent declare its presence in labeling, using the names FD&C yellow No. 5 and tartrazine.

The agency believes that the warning recommended by the Panel, "Do not use this product if you are sensitive to mercury," is clear and more likely to be understood by consumers than a warning listing only the name of a mercury-containing compound. The agency does not expect people with this sensitivity to know the name of every chemical formulation which contains mercury, some of which are not obvious, e.g., thimerosal. However, the agency has no objection to a manufacturer including the name of the mercury-containing compound in the warning statement. The agency also believes that it should be clear that mercury is present in the product as a preservative, not a an active ingredient. Therefore, in this tentative final monograph the agency is proposing the following warning: "This product contains (name of mercury-containing ingredient) as a preservative. Do not use this product if you are are sensitive to" (select one of the following): "mercury" or "(name of mercury-containing ingredient) or any other ingredient containing mercury."

14. One comment recommended elimination of the warning "Not for use in open wounds" for eyewash products in § 349.80(c) (1) (ii) of the recommended monograph. The comment stated that many eyewash products are excellent for flushing foreign substances from open wounds in or near the eyes and may be used effectively for this purpose.

In reviewing the Panel's report, the agency finds that the Panel actually recommended that the above warning read "Not for use in eyes with open wounds," (45 FR 30047) rather than "not for use in open wounds" as stated in the monograph. Open wounds in or near the eyes can be serious. The agency believes that such wounds should not be self-treated with an eyewash, but that a doctor should be consulted. Therefore, the agency is proposing to expand the warning in the tentative final monograph to read "Not for use in open wounds in or near the eyes. Consult a doctor."

15. One comment contended that the warning for eyewash products in § 349.80 (c) (1) (v) of the Panel's monograph "If solution changes color or becomes cloudy, do not use," is superflous and unnecessary. The comment stated that eyewash products are subject to the requirements for stability testing and expiration dating in 21 CFR 211.137 and 211.166 and are presumed to be safe and effective at least until the expiration date. Therefore, the comment considered addtitional warnings involving product deterioration to be unnecessary.

The agency disagrees that this warning is unnecessary. The Panel discussed the formulation of OTC ophthalmic drug products with regard to

the physiology and sensitivity of the eye and recommended that all ophthalmic solutions should be isotonic and buffered; clear and free from foreign particles, fibers, and filaments; and formulated with preservatives to prevent microbial contaminations (45 FR 30014). A solution that has changed color or has become cloudy, for whatever reason, has likely undergone a physical or chemical change and could be unsafe to use in an already irritated eye. The recommended warning would alert the consumer against using a defective product that could possible be harmful and is therefore being proposed is this tentative final monograph.

16. One comment recommended rewording the warning statement for eyewashes in § 349.80(c)(1)(iv) of the Panel's recommended monograph: "If you experience severe pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once." The comment stated that the warning bears little relevance to the use or misuse of eyewash products and offered as a substitute, "If changes to vision or unusual pain in or near the eyes occur, consult a physician."

The Panel discussed ophthalmic disorders and symptoms that may be treated with ophthalmic drug products. The Panel stated that there are very few disorders of the eye that are amenable to treatment with OTC ophthalmic preparations and that OTC ophthalmic ingredients generally relieve symptoms of eye disorders, but do not have any truly curative effect (45 FR 30008–30012). The Panel cautioned that one of the major problems with the OTC use of ophthalmic medications is that their use is generally based on trail and error. Use of an inappropriate drug can lead to exacerbation of symptoms or worsening of the disorder itself through improper treatment. To prevent mistreatment of a serious eye disorder requiring professional treatment, the Panel recommended that the labeling of all OTC ophthalmic products include the warning statement in § 349.80(c)(1)(iv).

The agency believes that the warning could be modified, without changing the Panel's intent, to make it more understandable to consumers. First, the warning should describe symptoms in terms that mention the eye. Symptoms such as severe pain and headache are very general, and consumers may experience them in various conditions not necessarily related to the use of ophthalmic drug products. Also, the term "sudden appearance of floating spots" is vague, and most consumers would not understand this part of the recommended warning. The term "eye pain," implying all types of eye pain, would be more helpful to consumers than the phrase recommended by the Panel, "pain on exposure to light." The agency has added the symptom of persistent eye irritation to the warning because the Panel stated that persistent irritation often occurs with conditions of the eye such as conjunctivitis, keratitis; and blepharitis that require professional attention. Determination of "acute redness of the eyes" requires a subjective judgement on the part of the consumer concerning the degree of redness. It would be confusing to consumers to include "acute redness of the eyes" as a warning for these or other ophthalmic drug products. It would be more appropriate for the consumer to determine whether redness persists and is unrelieved after treatment with an OTC ophthalmic drug product.

The agency is proposing to modify the Panel's recommended warning for eyewash products in § 349.80(c)(1)(iv) and combine it with the recommended warning for eyewash products in § 349.80(c)(1)(i). The resulting warning as proposed in the tentative final monograph reads as follows: "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists, consult a doctor." Further, the agency is proposing that this warning statement be used for all OTC ophthalmic drug products. Therefore, for hypertonicity agents, the agency is proposing to modify and combine § 349.70(c)(1)(i) and § 349.70(c)(1(ii) to read as follows: "Do not use this product except under the advice and supervison of a doctor. If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists, consult a doctor." For all other OTC ophthalmic drug products the agency is proposing that the first and second sentences under "Warnings" should be combined to read as follows: "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor." (See comment 17 below.)

17. Three comments objected to the Panel's warning, "Do not use this product for more than 72 hours except under the advice and supervision of a physician * * *." Two of the comments were opposed because the warning creates a new, "across-the-board," maximum time limit which prohibits the use of OTC ophthalmic drug products except eyewashes and hypertonicity agents beyond that time limit except under the advice and supervision of a doctor. The comments acknowledged that a warning should tell the consumer to discontinue use of the product if relief has not been obtained after a reasonable period of time, contended that the recommended warning does not convey the Panel's intended meaning, and suggested the following warning: "If relief is not obtained within 72 hours or if symptoms persist or worsen, discontinue use of this product and consult a physician." The third comment stated that limiting the use of a product to 72 hours provides little assurance that a serious undiagnosed ophthalmic disorder will be treated promptly, and suggested that the warning "If symptoms worsen or persist, the medication should be discontinued and a physician should be consulted at once" would be adequate.

The comments cited examples in which the environment or work situation may cause chronic minor irritations from foreign materials and allergens that would require use of an OTC ophthalmic drug product for longer than 72 hours but would not require a visit to a doctor. Examples included minor eye irritations due to airborne dust, smoke, smog, or pollen on consecutive days, or swimming daily in a highly chlorinated pool.

At several places in its discussion of "Disorders of the Eye That May Be Treated With Ophthalmic Drug Products" (45 FR 30008, 30009, 30010, and 30012), the Panel stated that use of a product should be discontinued and professional advice sought if symptoms worsen or persist for more than 72 hours. In the section on "Labeling of OTC Ophthalmic Drug Products; Warnings" (45 FR 30024), the Panel stated that "The labeling of these preparations should warn the consumer of serious symptoms which indicate disorders requiring immediate professional attention and alert him or her to seek professional advice if less serious symptoms do not respond within a reasonable period of time or worsen in reaction to an OTC medication." These statements indicate that the Panel believed it is acceptable for the consumer to continue the use of an OTC ophthalmic drug product for more than 72 hours without professional consultation if symptoms are relieved and do not persist or worsen.

The agency concurs with the comments and believes that the Panel intended that an OTC ophthalmic drug product should be discontinued and professional advice sought if symptoms

worsen or persist for more than 72 hours. This intent can be addressed by expanding the warning discussed in comment 16 above to read: "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor." Therefore, the agency is proposing to include this warning in the tentative final monograph as a labeling requirement for all OTC ophthalmic drug products except hypertonicity agents and eyewashes.

18. One comment was concerned about the length of the Panel's recommended label statements, especially the indications and warnings for demulcents and vasoconstrictors in §§ 349.60 and 349.75. The comment stated that the recommended labeling is too long to best inform the consumer, would exceed available bottle space, or would require the reduction of print size to an illegible size typeface. The comment added that printing some of this information on a carton or a package insert would not help because usually these are not kept by consumers and, therefore, the information is not available when needed. The comment recommended that warnings and indication statements be assigned priorities, with only the most essential required on small containers.

The indications section for ophthalmic demulcents at § 349.60(b) offers four short statements, any one of which will satisfy the indications requirement. The statements are similar in content and vary slightly in length. A company may select which of these statements it wishes to use on its product. The indication for ophthalmic vasoconstrictors is a single short statement describing the condition for which these ingredients should be used. This statement is not unduly long and is absolutely necessary for the consumer's understanding of the product's function.

The required warning statements for drug products containing ophthalmic demulcents and vasoconstrictors are more numerous and longer, but just as essential. These statements alert the consumer to any serious problems that may arise while using the product. If there is no improvement after using the product or the condition worsens, the consumer needs the information provided. It is at this time that the warnings may be the most important statements on the label. In recommending general warnings for OTC ophthalmic drug products, the Panel considered the consequences of self-medication of serious eye disorders and wanted to warn the consumer of serious symptoms which indicate disorders requiring immediate professional attention (45 FR 30024). In addition, the Panel recommended specific warnings for certain ingredients, e.g., mercury, found in some ophthalmic drug products.

In reviewing the Panel's recommended indications and warnings for OTC ophthalmic drug products, the agency has shortened and consolidated some of these statements. (See comments 16 and 17 above.) Because only one indication statement is necessary, there is no need to set priorities as suggested by the comment. All of the warnings proposed in this tentative final monograph are essential to assure proper and safe use of OTC ophthalmic drug products by the public and, therefore, all need to appear on ophthalmic drug products regardless of the size of the container. In those instances where an OTC ophthalmic drug product is packaged in a container that is too small to include all the required labeling, the product can be enclosed in a carton or be accompanied by a package insert that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label.

D. Comments on Testing Guidelines for Ophthalmic Drug Products

19. Many comments opposed the Panel's recommendation that the Draize rabbit eye irritation test be used to evaluate the safety of OTC ophthalmic drug products. Most of the comments argued that it is cruel and inhumane to subject rabbits to this procedure. In addition, many comments questioned the reliability of the test and recommended that more research should be conducted to find a suitable alternative to the Draize test. Many comments recommended that techniques involving cell or tissue cultures be developed.

The agency shares the concern expressed by the comments regarding the welfare of laboratory animals used for toxicological testing. In accordance with the requirements of the Laboratory Animal Welfare Act of 1967, as amended, the agency is giving constant attention to the use of animals to ensure that they are being treated in conformity with this act.

The agency also agrees that, within the limits of scientific and economic capability, research should be directed toward finding better and more humane methods for testing the safety, or harmfulness, of products. Tissue and cell culture techniques are very useful for studying the action of chemicals when scientists wish to answer questions specifically directed to certain cells of an organ. However, the results of a tissue or cell culture test alone cannot be the basis for deciding on the safety of a substance, at least not at this time. The eye is a complex biological system, and the effect of a chemical on a specific cell or tissue in culture may differ significantly from the effect experienced in the entire system. Animal testing, therefore, remains unavoidable at present. Some testing may be performed in humans. The agency does not believe, however, that anyone would accept the testing of potentially harmful substances in humans prior to some initial animal testing that could reasonably assure absence of injury.

It is somewhat difficult to extrapolate from rabbit test data to human experience and predict precisely the severity of an adverse reaction that may occur in a consumer, if an improperly tested, corrosive product were instilled into the eye. Nevertheless, the rabbit eye irritation test is currently the most reliable method to determine the harmfulness, or safety, of a substance introduced into the eye. For determining adverse reactions in the eye, cell or tissue culture techniques may be viewed more as scientific concepts than safety tests. At this time FDA believes that many years of further research will be required before these techniques will be useful as predictive tests.

As noted in part II. paragraph A.2. below, the Panel's testing guidelines are considered recommendations to the agency, and manufacturers are not restricted to these guidelines in testing Category II or Category III conditions.

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 has made the following changes in the categorization of ophthalmic active ingredients proposed by the Panel. The agency is proposing to place all currently marketed OTC ocular anti-infectives in Category II instead of

Category III as recommended by the Panel. In addition, the agency proposes to place polyethylene glycol 6000, which was not reviewed by the Panel, in Category III as an ocular demulcent. As a convenience to the reader, the following list is included as a summary of the categorization of ophthalmic active ingredients proposed by the Panel and the agency.

Ophthalmic active ingredients	Panel	Agency
1. Ophthalmic anesthetics:		
Antipyrine	II	II.
Piperocaine hydrochloride	II	II.
2. Ophthalmic anti-infectives:		
Boric acid	III	II.
Mild silver protein	III	II.
Sulfacetamide sodium	II	II.
Yellow mercuric oxide	III	II.
3. Ophthalmic astringents:		
Infusion of rose petals	III	III.
Zinc sulfate	I	I.
4. Ophthalmic demulcents:		
Carboxymethylcellulose sodium.	I	I.
Dextran 70	I	I.
Gelatin	I	I.
Glycerin	I	I.
Hydroxyethylcellulose	I	I.
Hydroxypropyl methylcellulose.	I	I.
Methylcellulose	I	I.
Polyethylene glycol 300	I	I.
Polyethylene glycol 400	I	I.
Polyethylene glycol 6000	Not reviewed	III.
Polysorbate 80	I	I.
Polyvinyl alcohol	I	I.
Povidone	I	I.
Propylene glycol	I	I.
5. Ophthalmic emollients:		
Anhydrous lanolin	I	I.
Lanolin	I	I.
Light mineral oil	I	I.
Mineral oil	I	I.
Nonionic lanolin derivatives.	I	I.
Paraffin	I	I.
Petrolatum	Not reviewed	I.
White ointment	I	I.
White petrolatum	I	I.
White wax	I	I.
Yellow wax	Not reviewed	I.
6. Ophthalmic hypertonicity agent:		
Sodium chloride (2–5%)	I	I.
7. Ophthalmic vasoconstrictors:		
Ephedrine hydrochloride	I	I.
Naphazoline hydrochloride.	I	I.
Phenylephrine hydrochloride:		
(a) (0.08–0.27%)	I	I.
(b) (less than 0.08%)	III	III.
Tetrahydrozoline hydrochloride.	I	I.
8. Eyewashes:		
No pharmacologically active ingredients.	I	I.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for ophthalmic drug products (45 FR 30032, 30035, and 30038). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. The agency's position concerning the Draize Test, described by the Panel at 45 FR 30022, is discussed in comment 19 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any ophthalmic 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

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 by the agency follows.

1. The agency is proposing that all OTC ophthalmic anti-infective drug products be classified in Category II. (See comment 4 above.)

2. The agency reviewed data on polyethylene glycol 6000, which was not evaluated by the Panel, and is classifying this ingredient as a Category III ophthalmic demulcent drug product in this tentative final monograph. (See comment 6 above.)

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

4. Although the use of white petrolatum or white wax, in lieu of petrolatum or yellow wax, results in a more aesthetically pleasing ophthalmic ointment, the use of either white petrolatum or white wax is not medically mandated. However, on its own initiative, the agency is proposing to expand the list of ophthalmic emollient active ingredients in § 349.14(b) to include petrolatum and yellow wax as well as white petrolatum, white wax, and other ingredients.

5. The Panel recommended the use of the phrase "eye lotion" as one of the acceptable statements of identity in § 349.80 for eyewash drug products. The phrase "eye lotion" is also an acceptable term for cosmetic eye makeup preparations (21 CFR 720.4(c)(3)(iv)). The agency does not believe that consumer confusion will occur from the use of this phrase on both eyewash drug products and eye makeup preparations and has proposed this phrase as a statement of identity for eyewash drug products in this tentative final monograph. (See § 349.78(a)). The agency invites further comment on this issue.

6. In this tentative final monograph, the agency is proposing to revise the statement of identity for OTC eyewash products (§ 349.78(a)) to require a listing of any ingredients identified in § 349.20. Although these drug products contain no pharmacologically active ingredients, the identity statement of the drug product must conform to the requirements of section 502(e) of the act (21 U.S.C. 352(e)).

7. The agency is revising the wording of the statement of identity for three ophthalmic drug classes. The phrase "eye lubricant or ophthalmic demulcent (eye lubricant)" will replace "ophthalmic demulcent" in § 349.60(a). The phrase "eye lubricant or ophthalmic emollient (eye lubricant)" will replace "ophthalmic emollient" in § 349.65(a). The agency is also proposing to substitute "eye redness reliever or ophthalmic vasoconstrictor (eye redness reliever)" for "ophthalmic vasoconstrictor" in § 349.75(a). (See comment 9 above.)

8. The agency is proposing to expand the warning for eyewash products in § 349.80(c)(1)(ii) of the advance notice of proposed rulemaking (redesignated § 349.78(c)(1)(ii) in the proposed rule), "Not for use in open wounds," to read as follows: "Not for use in open wounds in or near the eyes. Consult a doctor." (See comment 14 above.)

9. The agency is incorporating the Panel's recommended warning in § 349.80(c)(3) ("Rinse cup with clean water immediately before and after each use, and avoid contamination of rim and inside surfaces of cup.") into the directions in § 349.78(d)(1) of this tentative final monograph. The agency is also revising all the "Directions" paragraphs in this tentative final monograph to conform with the format of other recently published tentative final monographs.

10. The agency is proposing a warning for ophthalmic drug products containing mercury used as a preservative, to read "This product contains (name of mercury-containing ingredient) as a preservative. Do not use this product if you are sensitive to" (select one of the following): "mercury" or "(name of mercury-containing ingredient) or any other ingredient containing mercury." (See comment 13 above.) The agency is also proposing a new section (§ 349.50) entitled "Labeling of ophthalmic drug products," in which labeling, such as the mercury warning, that is required for all OTC ophthalmic drug products will be placed.

11. The agency is proposing to combine and revise some of the warnings recommended by the Panel for ophthalmic drug products. (See comments 16 and 17 above.)

12. The agency is reclassifying the term "tired eyes" from Category II to Category III in this tenative final monograph. The agency will consider reclassification of this term to Category I in the final monograph if adequate data are presented to show that consumers equate "tired eyes" with symptoms of minor irritation and redness in the eyes. (See comment 10 above.)

13. As implied in the Panel's discussion of ophthalmic demulcents and emollients at 45 FR 30014, the indications for these ingredients are the same. The agency believes that the same indication statements should be allowed for both and, therefore, is proposing to include the following indication in § 349.65(b) for drug products containing ophthalmic emollients: "For the temporary relief of burning and irritation due to dryness of the eye."

14. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor". This tentative final monograph proposes that option.

15. To eliminate inconsistencies and duplication, the agency is proposing to revoke the existing warning and caution statements for OTC ophthalmic drug products included in 21 CFR 369.20 when the final monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC ophthalmic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC ophthalmic drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC ophthalmic 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 ophthalmic 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 ophthalmic 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 carefully considered the potential environmental effects of the proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact and the evidence supporting this finding, contained in an environmental assessment (under 21 CFR 25.31, proposed in the **Federal Register** of December 11, 1979; 44 FR 71742), may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 349

OTC drugs, Ophthalmic 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 by adding new Part 349, to read as follows:

PART 349—OPHTHALMIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

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

§ 349.1 Scope.

(a) An over-the-counter ophthalmic 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 and 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.

§ 349.3 Definitions.

As used in this part:

(a) *Ophthalmic drug product.* A drug product, which should be sterile in

accordance with § 200.50, to be applied to or instilled in the eye.

(b) *Astringent.* A locally acting pharmacologic agent which, by preciptating protein, helps to clear mucus from the outer surface of the eye.

(c) *Buffering agent.* A substance which stabilizes the pH of solutions against changes produced by introduction of acids or bases from such sources as drugs, body fluids, tears, etc.

(d) *Demulcent.* An agent, usually a water-soluble polymer, which is applied topically to the eye to protect and lubricate mucous membrane surfaces and relieve dryness and irritation.

(e) *Emollient.* An agent, usually a fat or oil, which is applied locally to eyelids to protect or soften tissues and to prevent drying and cracking.

(f) *Eyewash, eye lotion, irrigating solution.* A sterile aqueous solution containing no pharmacologicaly active ingredients, intended for bathing or mechanically flushing the eye.

(g) *Hypertonicity agent.* An agent which exerts an osmotic gradient greater than that present in body tissues and fluids, so that water is drawn from the body tissues and fluids across semipermeable membranes. Applied topically to the eye, a hypertonicity agent creates an osmotic gradient which draws water out of the cornea.

(h) *Isotonicity.* A state or quality in which the osmotic pressure in two fluids is equal.

(i) *Vasoconstrictor.* A pharmacologic agent which, when applied topically to the mucous membranes of the eye, causes transient construction of conjunctival blood vessels.

Subpart B—Active Ingredients

§ 349.10 Ophthalmic astringent.

The activce ingredient and its concentration in the product is as follows: Zinc sulfate 0.25 percent.

§ 349.12 Ophthalmic demulcents.

The active ingredients of the product consist of any of the following, within the established concentrations for each ingredient:

(a) Cellulose derivatives:

(1) Hydroxyethylcellulose, 0.2 to 2.5 percent.

(2) Hydroxypropyl methylcellulose, 0.2 to 2.5 percent.

(3) Methylcellulose, 0.2 to 2.5 percent.

(4) Sodium carboxymethylcellulose, 0.2 to 2.5 percent.

(b) Dextran 70, 0.1 percent when used with another approved polymeric demulcent agent.

(c) Gelatin, 0.01 percent.

(d) Polyols, liquid:

(1) Glycerin, 0.2 to 1 percent.

(2) Polyethylene glycol 300, 0.2 to 1 percent.

(3) Polyethylene glycol 400, 0.2 to 1 percent.

(4) Polysorbate 80, 0.2 to 1 percent.

(5) Propylene glycol, 0.2 to 1 percent.

(e) Polyvinyl alcohol, 0.1 to 4 percent.

(f) Povidone, 0.1 to 2 percent.

§ 349.14 Ophthalmic emollients.

The active ingredients of the product consist of any of the following:

(a) Lanolin preparations:

(1) Anhydrous lanolin.

(2) Lanolin.

(3) Nonionic lanolin derivatives.

(b) oleaginous ingredients:

(1) Light mineral oil.

(2) Mineral oil.

(3) Paraffin.

(4) Petrolatum.

(5) White ointment.

(6) White petrolatum.

(7) White wax.

(8) Yellow wax.

§ 349.16 Ophthalmic Hypertonicity agent.

The active ingredient and its concentration in the product is as follows: Sodium Chloride 2 to 5 percent.

§ 349.18 Ophthalmic vasoconstrictors.

The active ingredients of the product consist of any of the following, within the established concentrations for each ingredient:

(a) Ephedrine hydrochloride, 0.123 percent.

(b) Naphazoline hydrochloride, 0.01 to 0.03 percent.

(c) Phenylephrine hydrochloride, 0.08 to 0.2 percent.

(d) Tetrahydrozoline hydrochloride, 0.01 to 0.05 percent.

§ 349.20 Eyewashes.

These products contain no pharmacologically active ingredients, but contain water, tonicity agents to establish isotonicity with tears, agents for establishing pH and buffering to achieve the same pH as tears, and a suitable preservative agent.

§ 349.30 Permitted combinations of active ingredients.

(a) Any single ophthalmic astringent active ingredient identified in § 349.10 may be combined with any single ophthalmic vasoconstrictor active ingredient identified in § 349.18.

(b) Any two or three ophthalmic demulcent active ingredients identified in § 349.12 may be combined.

(c) Any single ophthalmic demulcent active ingredient identified in § 349.12 or any ophthalmic demulcent combination identified in paragraph (b) of this section may be conbined with any single ophthalmic vasoconstrictor identified in § 349.18.

(d) Any single ophthalmic astringent active ingredient identified in § 349.10 may be combined with any single ophthalmic vasoconstrictor active ingredient identified in § 349.18 and any single ophthalmic demulcent identified in § 349.12 or ophthalmic demulcent combination identified in paragraph (b) of the section.

(e) Any two or more emollient active ingredients identified in § 349.14 may be combined as necessary to give the product proper consistency for application to the eye.

Subpart C—Labeling

§ 349.50 Labeling of ophthalmic drug products.

(a) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in §§ 349.55, 349.60, 349.65, 349.70, 349.75, and 349.78.

(b) the labeling of the product contains the follow warnings, under the heading "Warnings":

(1) "To avoid contamination of this product, do not touch tip of container to any other surface. Replace cap after using."

(2) For ophthalmic drug products containing mercury compounds used as a preservative: "This product contains (name of mercury-containing ingredient) as a preservative. Do not use this product if you are sensitive to" (Select one of the following): "mercury" or "(name of mercury-containing ingredient) or any other ingredient containing mercury."

§ 349.55 Labeling of ophthalmic astringent drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug(s), if any, and identifies the product as an "ophthalmic astringent."

(b) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the following phrase: "For the temporary relief of discomfort from minor eye irritations."

(c) *Warnings.* In addition to the warnings in § 349.50, the labeling of the product contains the following warnings under the heading "Warnings" for products containing any ingredient identified in § 349.10:

(1) "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor."

(2) "If solution changes color or becomes cloudy, do not use."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": Instill 1 to 2 drops in the affected eye(s) up to four times daily.

§ 349.60 Labeling of ophthalmic demulcent drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug(s), if any, and identifies the product as an "eye lubricant" or an "ophthalmic demulcent (eye lubricant)."

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

(1) "For the temporary relief of burning and irritation due to dryness of the eye."

(2) "For the temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun."

(3) "For use as a protectant against further irritation or to relieve dryness of the eye."

(4) "For use as a lubricant to prevent further irritation or to relieve dryness of the eye."

(c) *Warnings.* In addition to the warnings in § 349.50, the labeling of the product contains the following warnings under the heading "Warnings" for products containing any ingredient identified in § 349.12:

(1) "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor."

(2) "If solution changes color or becomes cloudy, do not use."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": Instill 1 or 2 drops in the affected eye(s) as needed.

§ 349.65 Labeling of ophthalmic emollient drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug(s), if any, and identifies the product as an "eye lubricant" or an "ophthalmic emollient (eye lubricant)."

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

(1) "For the temporary relief of burning and irritation due to dryness of the eye."

(2) "For the temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun."

(3) "For use as a protectant against further irritation or to relieve dryness of the eye."

(4) "For use as a lubricant to prevent further irritation or to relieve dryness of the eye."

(c) *Warnings.* In addition to the warnings in § 349.50, the labeling of the product contains the following warning under the heading "Warnings" for products containing any ingredient identified in § 349.14: "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": Pull down the lower lid of the affected eye and apply a small amount (one-fourth inch) of ointment to the inside of the eyelid.

§ 349.70 Labeling of ophthalmic hypertonicity 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 "ophthalmic hypertonicity agent."

(b) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the following phrase: "For the temporary relief of corneal edema."

(c) *Warnings.* In addition to the warning in § 349.50, the labeling of the product contains the following warnings under the heading "Warning" for products containing any ingredient identified in § 349.16:

(1) "Do not use this product except under the advice and supervision of a doctor. If you experience eye pain, changes in vision, contained redness or irritation of the eye, or if the condition worsens or persists, consult a doctor."

(2) "This product may cause temporary burning and irritation on being instilled into the eye."

(3) "If solution changes color or becomes cloudy, do not use."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": Instill 1 or 2 drops in the affected eye(s) every 3 or 4 hours, or as directed by a doctor.

§ 349.75 Labeling of ophthalmic vasoconstrictor drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug(s), if any, and identifies the product as an "eye redness reliever" or an "ophthalmic vasoconstrictor (eye redness reliever)".

(b) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the following phrase: "For the relief of redness of the eye due to minor eye irritations."

(c) *Warnings.* In addition to the warnings in § 349.50, the labeling of the product contains the following warnings under the heading "Warnings" for products containing any ingredient identified in § 349.18:

(1) "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor."

(2) "If you have glaucoma, do not use this product except under the advice and supervision of a doctor."

(3) "Overuse of this product may produce increased redness of the eye."

(4) "If solution changes color or becomes cloudy, do not use."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": Instill 1 to 2 drops in the affected eye(s) up to four times daily.

§ 349.78 Labeling of eyewash drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of all components identified in § 349.20 and identifies the product with one or more of the following terms: "eyewash," "eye lotion," or "eye irrigating solution."

(b) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the following phrase: "For flushing or irrigating the eye to remove loose foreign material, air pollutants, or chlorinated water."

(c) *Warnings.* In addition to the warnings in § 349.50, the labeling of the product contains the following warnings under the heading "Warnings" for all eyewash products:

(1) "If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists, a consult a doctor."

(2) "Not for use in open wounds in or near the eyes. Consult a doctor."

(3) "If solution changes color or becomes cloudy, do not use."

(d) *Directions.* The labeling of the product contains the following

information under the heading "Directions":

(1) *For eyewash products intended for use with an eyecup.* "Rinse cup with clean water immediately before each use. Avoid contamination of rim and inside surfaces of cup. Fill cup half full and apply the cup to the affected eye, pressing tightly to prevent the escape of the liquid, and tilt the head backward. Open eyelids wide and rotate eyeball to ensure thorough bathing with the wash or lotion. Rinse cup with clean water after each use."

(2) *For eyewash products intended for use with a nozzle applicator.* "Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle."

§ 349.80 Professional labeling.

The labeling of any OTC ophthalmic demulcent drug product provided to health professionals (but not to the general public) may contain instructions for the use of these products in professional eye examinations (i.e. gonioscopy, electroretinography).

Interested persons may, on or before August 29, 1983 submit to the Docket 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 October 27, 1983. 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 documents and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before June 28, 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 August 28, 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 office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 28, 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: June 6, 1983.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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