

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 349 and 369

[Docket No. 80N-0145]

Ophthalmic Drug Products for Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) ophthalmic drug products (drug products applied to the eyelid or instilled in the eye), other than antiinfective OTC ophthalmic drug products, are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and new data and information on OTC ophthalmic drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA. Elsewhere in this issue of the *Federal Register*, FDA is reopening the administrative record for OTC ophthalmic drug products to include only those data on antiinfective ingredients that were submitted after the closing of the administrative record. The administrative record will remain open until July 5, 1988, for submission of public comments on that data.

EFFECTIVE DATE: March 6, 1988.

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

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, together 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 display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC ophthalmic drug products was published in the *Federal Register* of June 28, 1983 (48 FR 29788). Interested persons were invited to file by August 29, 1983, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by October 27, 1983. New data could have been submitted until June 28, 1984 and comments on the new data until August 28, 1984.

In considering the antiinfective portion of the ophthalmic monograph, the agency has determined that there are complex scientific issues that need to be resolved before a final determination can be made with respect to ingredients in this class. These issues do not directly relate to the other segments of the ophthalmic monograph. Accordingly, in order to complete the publication of other segments of the ophthalmic final monograph without undue delay, the agency is not including an antiinfective segment in this document. Elsewhere in this issue of the *Federal Register*, FDA is reopening the administrative record for OTC ophthalmic drug products to include only those data on antiinfective ingredients that were submitted after the closing of the administrative record. The administrative record will remain open until July 5, 1988, for submission of public comments on that data. The agency intends to publish its final decision on ophthalmic antiinfectives in a future issue of the *Federal Register*. Final agency action for the other segments of the ophthalmic drug product rulemaking occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC ophthalmic drug products.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is

no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC ophthalmic drug products (48 FR 29788), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the *Federal Register*. Therefore, on or after March 6, 1989, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC ophthalmic drug products, one drug manufacturers' association, eight drug manufacturers, two consumer groups, one professional medical organization, and one consumer submitted comments. A request for an oral hearing before the Commissioner was also received on one issue. Copies of the comments and the hearing request received are on public display in the Dockets Management Branch. Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final monograph, the agency has considered the objections, a request for oral hearing, and changes in the procedural regulations.

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 notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments on OTC 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 drug 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 tentative 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 867 (2d Cir. 1981).

2. Two comments disagreed with the definition of eyewash products proposed in § 349.3(f) and the description of eyewashes proposed in § 349.20 of the tentative final monograph (48 FR 29798). Both comments felt that a statement that these products contain no pharmacologically active ingredients is unnecessary and should be deleted from both the definition and the description of eyewashes. One comment listed the ingredients suggested by the Panel as suitable for buffering or adjusting the pH of ophthalmic solutions (45 FR 30016) and stated that many of these ingredients are pharmacologically active at concentrations higher than the amounts usually present when these ingredients are used as buffers or pH adjusters in eyewash products. The comment contended that manufacturers should not have to be concerned if an ingredient happens to reach a level that is pharmacologically active if no claim for any pharmacologic action is being made for these ingredients. The comment recommended that the

description of eyewashes in § 349.20 be amended to read: "These products may only 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." The comment added that the definition of eyewashes should be consistent with § 349.20 and proposed the following definition: "Eyewash, eye lotion, irrigating solution. A sterile aqueous solution for bathing or mechanically flushing the eye containing tonicity agents to establish isotonicity with tears and agents to establish pH and buffering to achieve the same pH as tears." The second comment asserted that a definition without the phrase "containing no pharmacologically active ingredients" is more appropriate because classes of products should be defined positively, in terms of what those products are or what they contain, rather than what they are not or do not contain. The comment suggested substituting the word "washing" for the term "flushing" for additional clarity.

The agency agrees with the comments that the statement that eyewashes "contain no pharmacologically active ingredients" is unnecessary. As one of the comments noted, this statement may be unclear because many of the ingredients present in low concentrations in eyewashes as buffers or pH adjusters are pharmacologically active at higher concentrations. The agency also agrees that, wherever possible, classes of products should be defined positively by stating what those products contain, rather than what they do not contain. Therefore, in this final monograph, the agency is deleting the words "contain no pharmacologically active ingredients" from the product description for eyewashes in § 349.20 and is revising the statement to read: "These products 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."

In addition, the agency is deleting the words "containing no pharmacologically active ingredients" from the definition for eyewash, eye lotion, and irrigating solution in § 349.3(f). The agency also believes that the word "mechanically" is unnecessary in this definition and thus is revising the definition to read: "A sterile aqueous solution intended for washing, bathing, or flushing the eye."

B. Comments on OTC Ophthalmic Drug Ingredients

3. One comment contended that boric acid meets the definition of an

astrigent and an eyewash as stated in the notice of proposed rulemaking (48 FR 29791): For astringents—"helps to clear mucus from the outer surface of the eye." and For eyewashes—"bathes or mechanically flushes the eye." The comment stated that "some cognizance must be taken of the long history of mishap-free use of mild boric acid solution in eyewashes, etc." The comment maintained that, although boric acid is not bactericidal, it has demonstrated some bacteriostatic properties, is a pharmaceutical necessity as a pH buffer and a preservative, and its "efficacy in ophthalmic preparations is more of an astringency action than a therapeutic action." The comment further noted that ophthalmologists often prescribe mild boric acid solution and that the product is a standard first aid item, which is noncorrosive, nonirritating, and nonmutagenic.

The "definitions" cited by the comment appeared at 48 FR 29791 as "claims based on the Panel's definitions" and are partial excerpts from the definition of each of these ophthalmic drug classes proposed in § 349.3 of the tentative final monograph (48 FR 29797 and 29798). The complete definitions read as follows: "*Astringent*. A locally acting pharmacologic agent which, by precipitating protein, helps to clear mucus from the outer surface of the eye"; and "*Eyewash, eye lotion, irrigating solution*. A sterile aqueous solution containing no pharmacologically active ingredients, intended for bathing or mechanically flushing the eye."

Boric acid was reviewed by the Ophthalmic Panel as an antiinfective ingredient and was found to be safe when used in the amounts contained in OTC ophthalmic drug products; however, the Panel found that there were insufficient data to prove its effectiveness as an ophthalmic antiinfective (45 FR 30029). Although the Ophthalmic Panel did not evaluate boric acid as an ophthalmic astringent, the Advisory Review Panel on OTC Miscellaneous External Drug Products included boric acid in its review of astringent drug products. That Panel did not find any data demonstrating the safety and effectiveness of boric acid when used as an OTC astringent active ingredient and, therefore, classified it as Category II for that purpose. (See the *Federal Register* of September 7, 1982; 47 FR 39426 and 39444.) The comment did not submit any data or cite any references to show that boric acid in an ophthalmic formulation acts as an astringent by precipitating protein. Therefore, because the agency has no

data to establish boric acid as a safe and effective astringent in ophthalmic drug products, it is not including this ingredient as an ophthalmic astringent in this final monograph.

The Ophthalmic Panel found boric acid solutions to be "at best bacteriostatic when in contact with pathogenic bacteria for less than one hour" (45 FR 30029). The Panel stated that studies were needed to establish the usefulness of boric acid in the treatment of eye infections, e.g., the bacteriostatic effects of boric acid must be demonstrated to be sufficiently rapid to be useful in infections of the eye. The Panel acknowledged that boric acid and its sodium salt are used as a buffer system in ophthalmic preparations and that this buffer system is effective and well tolerated in eye drops. The Panel listed boric acid among the buffering agents, but not among the preservative agents, suitable for the formulation of eyewashes and other ophthalmic solutions (45 FR 30016). In the tentative final monograph for OTC ophthalmic drug products, the agency proposed in § 349.20 that eyewash 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.

Boric acid is not being included as an active ingredient in this final monograph. It is considered an inactive ingredient when used as part of a buffering system in ophthalmic drug products. 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 in the amounts administered and do not interfere with the effectiveness of the product or with tests to be performed on the product. Boric acid may be included as a buffering agent in the formulation of OTC ophthalmic drug products provided that it meets the above criteria. (For further discussion of inactive ingredients, see comment 4 below.)

4. Acknowledging that preservative systems were not addressed in the tentative final monograph, one comment submitted, for the record, data to support a sorbic acid/edetate disodium (EDTA) preservative system for ophthalmic solutions. The data consisted of: (1) Summaries of clinical investigations in support of sorbic acid/EDTA as a suitable preservative system for saline and cleaning solutions for contact lenses, (2) a bibliography of articles on sorbic acid from the scientific literature, (3) summaries of animal

testing data, and (4) summaries of laboratory testing data. The comment stated that the Panel concluded in its report that sorbic acid in combination with suitable preservatives might be an effective preservative system (45 FR 30020). The comment pointed out that the sorbic acid/EDTA combination preservative system has been approved as safe and effective in ophthalmic solutions by FDA's Office of Medical Devices and described a variety of currently marketed ophthalmic solutions preserved with sorbic acid/EDTA, such as various wetting, cleaning, and storage solutions for soft (hydrophilic) contact lenses. The comment claimed that a sorbic acid preservative system is less toxic than preservatives such as thimerosal, chlorhexidine, and quaternary ammonium compounds. Although the data submitted were compiled from ophthalmic solutions used with soft (hydrophilic) contact lenses, the comment believed that the sorbic acid/EDTA preservative system has been extensively studied for use in the eye area and that the data support this preservative system in general for OTC ophthalmic drug products.

Sorbic acid and EDTA, used as preservatives, are inactive ingredients. 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. Accordingly, the agency is not reviewing the data submitted by the comment in this rulemaking proceeding.

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. In addition, § 330.1(a) requires that all products covered by an applicable OTC drug monograph be manufactured in compliance with current good manufacturing practices, as established in 21 CFR Parts 210 and 211.

Section 200.50 (21 CFR 200.50) requires all ophthalmic drug products to be sterile. Paragraph (b)(1) states that liquid ophthalmic drug products packaged in multiple-dose containers should: "contain one or more suitable and harmless substances that will inhibit the growth of microorganisms." In conclusion, based on these regulations, the agency evaluates inactive ingredients used as preservatives on an individual basis for

each ophthalmic drug product and does not include such conditions in the applicable OTC drug monograph.

C. Comments on Labeling of OTC Ophthalmic Drug Products

5. Several comments contended that FDA should not prescribe exclusive lists of terms from which indications for use for OTC drugs must be drawn, thereby prohibiting alternative OTC drug labeling terminology to describe such indications which is truthful, not misleading, and intelligible to the consumer. Two comments stated that their views on this subject were presented to FDA in oral and written testimony in connection with the September 29, 1982 agency hearing on the exclusivity policy.

In the *Federal Register* of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph where exact language has been established and identified by quotation marks in an applicable monograph or other regulation, e.g., 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the final rule revising the labeling policy.

6. One comment objected to the agency's proposed substitution of the word "doctor" for "physician" in OTC drug labeling. The comment indicated an essential difference between these terms. The term "physician" means "doctor of medicine," whereas the term "doctor" can refer to any of a broad spectrum of academic disciplines. The comment recommended that the agency specify use of the term "physician," as

opposed to the term "doctor," on OTC drug labels to enhance consumers' awareness of the proper individual they should consult if further medical care is needed. The comment also stated that it seemed contradictory to label OTC drugs with their scientific names (e.g., ophthalmic hypertonicity agent) and, at the same time, be concerned that the common term "physician" would confuse consumers.

In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs, including the one for OTC ophthalmic drug products, 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 any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This final monograph provides that option. (See § 349.50(a).)

7. Expressing concern about the labeling "verbiage" proposed in the tentative final monograph for OTC ophthalmic drug products, one comment maintained that the use of this verbiage on small bottles and cartons will deter consumers from reading the labeling, thus decreasing the chances that consumers will be made aware of important information and warnings. The comment recommended "streamlining" and combining the proposed warning for all ophthalmic drug products in § 349.50(b)(1) with the proposed warnings for ophthalmic demulcent drug products in § 349.60(c)(1) and (2) to read: "Do not touch bottle tip to any surface since this may contaminate solution. Replace cap after using. If irritation persists or increases, discontinue use and consult a physician." The comment also recommended that the proposed warning in § 349.50(b)(1) and the warnings proposed for ophthalmic vasoconstrictor drug products in § 349.75(c)(1) through (4) be combined and revised as follows: "Do not touch bottle tip to any surface since this may contaminate solution. Replace cap after using. If irritation persists for more than 72 hours, discontinue use and consult a physician. If you have glaucoma, do not use except under the supervision of a physician. Overuse of this product may produce increased redness of the eye." The comment contended that these revisions would convey the intended message in a concise manner.

The agency recognizes the need for concise wording in the labeling of ophthalmic drug products that are likely to be marketed in small packages. In the tentative final monograph, the agency revised the Panel's recommended labeling statements to include only essential information. (See comment 18 at 48 FR 29795.) The agency emphasizes that its proposed warnings provide information that is essential for the safe and effective use of OTC ophthalmic drug products by the consumer. The comment's suggested combining and "streamlining" of the warnings for OTC ophthalmic demulcent and vasoconstrictor drug products deletes some of the warnings proposed by the agency. The comment neglected to include the statements about "eye pain," "changes in vision," and "continued redness" in its suggested warning statements. The Panel felt that this type of information was necessary in the labeling for these products (45 FR 30024), and the agency concurs. In the proposed rulemaking for OTC ophthalmic drug products, the agency modified the wording of this information without changing the Panel's intent in order to make the warning more understandable to consumers. (See comment 16 at 48 FR 29794.)

The general term "irritation," suggested by the comment, does not inform the consumer of specific symptoms which may indicate a serious condition requiring medical attention. The comment also suggested deleting the warning "If solution changes color or becomes cloudy, do not use." The agency feels that this statement is necessary because it alerts the consumer against using a possibly defective product. The comment's suggested revision of the warning for ophthalmic demulcent drug products deletes the phrase limiting the OTC use of the product to 72 hours. The agency believes that such a limitation is necessary. (See comment 9 below.) The comment's proposed alternatives do not provide the consumer with all of the essential warning information; therefore, the warnings for ophthalmic demulcents and vasoconstrictors proposed in §§ 349.60(c) and 349.75(c), respectively, are being included in this final monograph without the requested changes.

The agency believes that the warning proposed in § 349.50(b)(1) of the tentative final monograph may be shortened without changing its intent. Although the comment's suggested rewording shortened the warning, it also changed the emphasis of the warning by rearranging it and changed the intent of

the warning by stating that it applies only to solutions, whereas it equally applies to ointments. The agency is revising the warning and including it in § 349.50(c)(1) of the final monograph to read in part as follows: "To avoid contamination, do not touch tip of container to any surface * * *." This wording is also included in a warning in § 349.50(c)(2) to accommodate single-use packages. (See comment 8 below.)

The agency concludes that all of the warnings included in this final monograph are essential to ensure the proper and safe use of OTC ophthalmic drug products by the public. Therefore, all the warnings need to appear on OTC 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. The labeling provisions in Part 201 (e.g., §§ 201.10(i), 201.15, 201.60, 201.61, and 201.62) address various requirements for labeling drugs including drugs packaged in containers too small to accommodate a label with sufficient space to bear all the information required for compliance with various regulations. When an OTC ophthalmic drug product is packaged in a container that is too small or otherwise unable to accommodate a label with sufficient space to bear all of the information required by this final monograph, the required information shall appear elsewhere in the label in accord with the labeling requirements in Part 201. 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.

8. One comment pointed out that the part of the warning proposed in § 349.50(b)(1) that reads "replace cap after using" is inappropriate for ophthalmic drug products which are packaged in single-use containers. The comment suggested that wording such as "Do not reuse—Once opened, discard" be permitted for single-use packages.

The agency agrees that an alternative warning statement is appropriate for single-use ophthalmic drug products. Therefore, in this final monograph, the agency is specifying that the warning in § 349.50(c)(1) applies to multi-use

containers and is including an alternative warning for single-use packages in § 349.50(c)(2) as follows:

For ophthalmic drug products packaged in single-use containers. "To avoid contamination, do not touch tip of container to any surface. Do not reuse. Once opened, discard."

9. One comment recommended deletion of the phrase limiting use to 72 hours from the warning for OTC ophthalmic demulcent drug products proposed in § 349.60(c)(1), which reads: "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." The comment argued that there are no medical reasons for restricting the use of an ophthalmic demulcent product and noted that, currently, ophthalmic demulcent products, particularly those used to relieve dry eye syndrome, are recommended for use as often as necessary. The comment also pointed out that contact lens lubricating solutions, which are used as often as necessary, may contain the same active ingredient as ophthalmic demulcent products (i.e., hydroxypropyl methylcellulose).

In the tentative final monograph, the agency combined and modified two long warning statements recommended by the Panel and proposed the above warning for all OTC ophthalmic drug products except hypertonicity agents and eyewashes. (See comment 16 at 48 FR 29794.) In doing so, the agency retained the Panel's recommendation that consumers should not self-medicate for more than 72 hours without consulting a doctor. This warning was combined with information about discontinuing use and consulting a doctor if the condition worsens or persists during this time, and with information on certain conditions under which use should be discontinued.

The agency also discussed a 72-hour limitation in the tentative final monograph. (See comment 17 at 48 FR 29794.) The agency disagrees with the comment's contention that OTC ophthalmic demulcent drug products may be used as often as necessary and need not carry the warning "if the condition worsens or persists for more than 72 hours, discontinue use." OTC ophthalmic demulcent drug products are used to treat conditions such as minor irritation and dryness of the eye. OTC ophthalmic demulcent drug products are distinguishable from contact lens lubricating solutions, which are not used to relieve disease symptoms. Rather, contact lens lubricating solutions are accessories to a medical device and,

therefore, may be indicated for daily use. The Panel strongly recommended limiting self-medication with OTC ophthalmic drug products to 72 hours because the symptoms treated may indicate a serious condition requiring treatment by a physician. The Panel specifically addressed the treatment of dry eye with OTC ophthalmic demulcent products and recommended that long-term use be allowed only under the direction of a physician (45 FR 30008). The Panel stated that while "these products are intended to serve as tear substitutes and are used on an ongoing basis, safeguards against the unsupervised use of tear substitute preparations for long periods must be established through proper labeling to warn consumers that professional consultation should be sought if symptoms persist for more than 72 hours." The agency agrees with the Panel's recommendation and is including a 72-hour time limit in the warnings for OTC ophthalmic demulcent drug products in this final monograph.

10. Several comments objected to FDA's requirement that data be submitted to support use of the term "tired eyes" in the labeling of OTC ophthalmic drug products. (See comment 10 at 48 FR 29792.) Two of the comments contended that the agency's use of informal rulemaking to declare that certain words are false or misleading is unauthorized by statute and improper "irrespective of whether such data will be made available" to show that consumers equate "tired eyes" with symptoms of minor irritation and redness in the eyes. One of these comments maintained that the term "tired eyes" should be allowed to continue in use until evidence is produced to show that consumers are being deceived or misled by it.

Another comment contended that the term "tired eyes" should be allowed as an indication for eyewashes and for ophthalmic vasoconstrictor drug products, and an additional comment proposed that the term "tired eyes" should be allowed as an indication for ophthalmic demulcent drug products as well as for ophthalmic vasoconstrictor drug products. The comment submitted a report summarizing two marketing research surveys of users of eye drops to support its request (Ref. 1). The first survey had two parts. In one part, consumers chose their own words to describe their reasons for using eye drops. In the second part, the same consumers rated the importance of 58 product features or benefits enumerated by the market research firm. In the second study, the subjects were given cards, each stating a product feature or

benefit, and were asked to rate the importance of each feature or benefit in choosing an eye drop product. The comment contended that the results of the studies make it apparent that users of eye drops "express" the feeling of eye discomfort with the term "tired eyes."

The agency has previously addressed the legality of the OTC drug review procedures. (See comment 1 above.) The classification of a labeling claim and the requirement for data to support the general recognition of that labeling claim in an OTC drug monograph are consistent with the OTC drug review procedures.

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 that phrasing that promises benefits from using OTC ophthalmic drug products for such a condition is unproven and thus unacceptable. It recommended a Category II classification for the "tired eyes" claim in the advance notice of proposed rulemaking. Two comments to the advance notice of proposed rulemaking requested that the claim "tired eyes" be removed from Category II. Both comments claimed that the term "tired eyes" as used by consumers describes the appearance of minor irritation and redness in the eyes. One of the comments added that such use has been shown through market research. In the tentative final monograph (48 FR 29792), the agency pointed out that neither comment had submitted data showing that "tired eyes" is a condition which benefits from the use of OTC ophthalmic drug products and agreed with the Panel that product claims for benefits to "tired eyes" are scientifically unfounded. However, in order to provide the comments an opportunity to support their claims, the agency reclassified the term from Category II to Category III and stated that if adequate data were submitted to show that consumers equate "tired eyes" with minor irritation and redness in the eyes, i.e., conditions that benefit from the use of OTC ophthalmic drug products, the agency would consider reclassifying the term to Category I.

In order to establish a Category I indication for an OTC drug product, data are necessary to show that a consumer with a well-defined and clearly-understood condition receives therapeutic benefits from the use of the product. The market research surveys submitted in support of "tired eyes" as a Category I indication were not designed to provide such data. Although the

surveys show that the term "tired eyes" in the labeling of ophthalmic drug products is familiar to consumers, they provide no data demonstrating that consumers equate "tired eyes" with minor irritation or redness in the eyes, two conditions which have been shown to benefit from the use of OTC ophthalmic drug products. Therefore, the agency is not including "tired eyes" as an indication for any of the ophthalmic drug classes in this final monograph.

However, since publication of the tentative final monograph, the agency has revised its labeling policy for OTC drug products. (See comment 5 above.) FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action. Truthful and nonmisleading terms that provide additional information about an OTC drug product but are not directly related to its safe and effective use are considered outside the scope of the OTC drug review and may appear elsewhere in the labeling, separate from the monograph approved statements. Because the submitted surveys demonstrate that consumers are familiar with the term "tired eyes" in the labeling of OTC ophthalmic drug products, the agency considers "relief of tired eyes" acceptable additional information but not an indication for the labeling of an OTC ophthalmic drug product.

As discussed in comment 16 below, the agency is concerned about the danger of overuse or unnecessary use of OTC ophthalmic vasoconstrictor drug products and wants to assure that a vasoconstrictor is only used for one specific symptom: redness due to minor eye irritations. Neither the submitted surveys nor any other information submitted to the agency provide data showing that the term "tired eyes" means redness to consumers. The agency believes that the term "tired eyes" might encourage consumers to use a vasoconstrictor unnecessarily for the relief of symptoms other than redness of the eye due to minor eye irritations. For this reason, the agency concludes that "tired eyes" may not be used on any

part of the labeling of OTC ophthalmic vasoconstrictor drug products.

Although "tired eyes" is considered outside the scope of the review for some OTC ophthalmic drug products, it will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. In addition, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. Such terms may be included elsewhere in the labeling.

Reference

(1) Comment No. C00992, Docket No. 80N-0145, Dockets Management Branch.

11. Several comments requested that the terms "cooling" or "cools," "soothing" or "soothes," "refreshing" or "refreshes," and "comforting" be allowed as indications for ophthalmic demulcent and vasoconstrictor drug products. In support of its request, one comment submitted a report summarizing two market research surveys on consumer terminology among eye drop users (Ref. 1). The comment stated that the "study indicates that when eye drop users were asked to give their reasons for using eye drops, a substantial number of the users responded that they sought to 'soothe,' 'cool,' or make their eyes feel 'comfortable,'" and that, furthermore, "when a group of users was asked to select the degree of importance of 49 product features or benefits, 79 percent of the users responded that the 'soothing' effect of eye drops was, at least, 'very important.'" Another comment requested that product attributes such as "cooling," "soothing," or "refreshing" be included in a section on other allowable statements for OTC eyewash products in the ophthalmic final monograph. The comment stated that these terms reflect the neutral, isotonic attributes of eyewashes.

The agency has reviewed the market research report and finds that the two studies indicate that many users want the "soothing" and "cooling" they get from eyedrops, but the studies do not support the request that terms such as "comforting," "cooling," "soothing," and "refreshing" should be permitted as indications for ophthalmic demulcent and vasoconstrictor drug products. Because the participants were asked to select terms from a list of "features and benefits" enumerated by the marketing research firm instead of using their own

words, the "features and benefits" sections of the surveys are not very useful for assessing consumer terminology. Also, the data were not summarized separately for vasoconstrictor and demulcent users; thus, the responses of the different groups of users cannot be assessed.

The "reasons for using eye drops" section of the first survey is more useful for assessing consumer terminology because consumers use their own words to express their reasons for using eye drops; about half of the responses stated that eye drops were used to "soothe," to "cool," or for "tiredness." However, the terms "soothe/cool/tiredness" were grouped together in the survey's summary, as were the responses from the users of vasoconstrictor and demulcent eye drops. Although the summary indicates that many users want the "soothing" and "cooling" they get with eye drops, there is no way to assess the response rate for the separate terms nor to assess how the different groups of eye drop users responded to the question of why they used eye drops.

The agency recognizes that terms such as "soothing," "cooling," "refreshing," and "comforting" reflect formulation attributes of some products, but does not agree that the terms are appropriate indications for OTC ophthalmic drug products. The Panel stated in its report that indications for the use of ophthalmic preparations "should be simply and clearly stated, should provide the user with enough information for effective and safe use of the preparation, and should include the statement that the preparation is for the temporary relief of symptoms applicable to the ingredients it contains" (45 FR 30023). In addition, the Panel addressed the term "soothing" as a product attribute and defined product attributes as terms that describe certain physical and chemical qualities of OTC ophthalmic drug products (45 FR 30024). However, the Panel emphasized, and the agency agrees, that these terms are not indications for use, but merely factual statements related to product performance.

The agency has no objection to the use of terms, such as "soothing," "cooling," "refreshing," or "comforting," that describe certain physical and chemical qualities of a drug, as long as these terms are appropriate for the product and do not imply that any therapeutic effect might occur, are true and not misleading, and are distinctly separated from labeling indications. For example, the terms "soothing" or "comforting" may be appropriate for

ophthalmic emollient and demulcent drug products because they describe physical and chemical qualities of these drugs. However, terms such as "soothing" or "comforting" are not appropriate for ophthalmic vasoconstrictor drug products because these terms do not describe physical or chemical qualities of these drugs. Terms describing a product's characteristics (e.g., color, odor, flavor, and feel) appear in the labeling for the consumer's information. The agency concludes that it is not necessary to include terms such as these in the final monograph for OTC ophthalmic drug products.

Reference

(1) "Marketing Research Among Eye Drop Users Concerning Consumer Terminology," Comment No. C00992, Docket No. 80N-0145, Dockets Management Branch.

12. One comment objected to the tentative final monograph limiting the statement of identity of OTC ophthalmic drug products to only one or two terms in most cases and urged the agency to allow manufacturers alternative ways of describing the statement of identity as provided in existing agency regulations. The comment cited 21 CFR 201.61 as requiring the label to include the established name of the drug, if any, followed by an accurate statement of the general pharmacological category(ies) of the drug.

Two comments contended that either the term "eye drops" or the term "decongestant eye drops" should be allowed as a statement of identity for ophthalmic vasoconstrictor drug products. Both comments argued that consumers have used hundreds of millions of these products for many years under the term "eye drops" and that changing this term now may lead to consumer confusion. One comment felt that the term "decongestant eye drops" is well understood by consumers and that the agency's proposed term "eye redness reliever" might actually confuse consumers. The comment stated that the term "eye redness reliever" appears to be an incomplete reference to the decongestant action of vasoconstrictor ophthalmic products because that term does not refer to the drug's principal action of relieving minor eye irritation and accompanying symptoms, such as redness, itching, stinging, etc. The second comment urged that for combination ophthalmic drug products that have no established name, any reasonable statement of general pharmacologic action or principal intended action such as "eye drops for the relief of eye irritation and redness" be allowed in the statement of identity.

Wherever possible, the agency prefers to use the general pharmacologic category as the statement of identity for OTC drug products; however, where this is not appropriate, the principal intended action is used. The term "eye drops" by itself does not inform the consumer of the pharmacologic category or the principal intended action of a drug product.

As explained in the tentative final monograph for OTC ophthalmic drug products, the agency believes that the term "decongestant" is not readily understood by consumers as it applies to the eye (48 FR 29792). Vasoconstrictor ingredients are used in nasal decongestant drug products as well as in ophthalmic drug products. The decongestant action of vasoconstrictor ingredients in nasal drug products refers to the shrinking of nasal mucosa in the treatment of mucosal congestion accompanying hay fever, allergic rhinitis, sinusitis, and other respiratory conditions (Ref. 1). The action of these same vasoconstrictor ingredients when topically applied to the eye refers to the constriction of blood vessels resulting in the whitening of the conjunctiva by reducing redness (Ref. 2). The agency believes that consumers more commonly equate decongestant action with relief from the nasal stuffiness and general irritation related to respiratory conditions than with the relief of redness of the eyes. Thus, the agency considers that "decongestant eye drops" is a poorly understood phrase, and that "eye redness reliever" better describes in layman's terms the principal action of an OTC ophthalmic vasoconstrictor and is readily understood by consumers. Furthermore, the term "eye redness reliever" is currently used in the labeling of OTC ophthalmic vasoconstrictor drug products.

The agency believes that, contrary to the comment's assertion, the term "eye redness reliever" is a complete and accurate description of the principal action of an OTC ophthalmic vasoconstrictor ingredient, which is used to relieve redness in the eye and not for any other symptom. In its report, the Panel recommended that vasoconstrictor ingredients be used only if redness is present along with minor irritation of the eye. For the symptomatic relief of itching, tearing, and smarting, the Panel recommended eye washes, astringents, demulcents, or emollients (45 FR 30009). (See also comment 15 below.)

The agency disagrees with the suggestion by one of the comments that any reasonable statement of general pharmacologic action would suffice as a

statement of identity for combination products with no established name. For OTC combination ophthalmic drug products, the agency requires that the statement of identity include the statement of identity for each of the active ingredients as set forth in the final monograph. This approach is consistent with that used for all other types of OTC combination drug products. (See also comment 13 below.)

The agency recognizes that OTC ophthalmic vasoconstrictor products have been marketed for years as "eye drops" and does not oppose the inclusion of this term in the statement of identity in addition to the required pharmacological category for each class of ophthalmic drug product. In this final monograph, the agency is modifying, where appropriate, the statement of identity for OTC ophthalmic drug products to allow for a choice of a term describing the appropriate dosage form of the product, i.e., "drop," "lotion," or "ointment," as well as to allow for a choice between the terms "ophthalmic" and "eye." For example, the statement of identity for ophthalmic vasoconstrictor drug products in § 349.75(a) will read: "The labeling of the product contains the established name of the drug(s), if any, and identifies the product as a 'redness reliever' or a 'vasoconstrictor (redness reliever)' (select one of the following: 'eye' or 'ophthalmic') (insert dosage form, e.g., drops)."

References

(1) Weiner, N., "Norepinephrine, Epinephrine, and the Sympathomimetic Amines," in "The Pharmacological Basis of Therapeutics," 6th Ed., Edited by A.G. Gilman, L.S. Goodman, and A. Gilman, MacMillan Publishing Co., Inc., New York, p. 168, 1980.

(2) Newell, F.W., "Ophthalmology: Principles and Concepts," 5th Ed., The C.V. Mosby Co., St. Louis, p. 149, 1982.

13. One comment objected to the tentative final monograph limiting the statement of identity of OTC ophthalmic drug products to only one or two terms in most cases and urged the agency to allow manufacturers alternative ways of describing the statement of identity as provided in existing agency regulations. The comment cited 21 CFR 201.61 as requiring that if the drug is a combination which has no established name, the statement of identity may be a prominent and conspicuous statement of the general pharmacological action(s) in terms which are meaningful to laymen.

The comment objected to the agency's proposal that the statement of identity for eyewashes contain the established

name of all the components identified in § 349.20, all of which are inactive ingredients by FDA's definition. The comment asserted that the agency's explanation for this action, i.e., conformation to the requirements of section 502(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(e)), is unfounded on two counts: (1) Section 502 applies to drugs and devices, and an eyewash is neither a drug nor a device; and (2) section 502(e) does not empower the agency to require that inactive ingredients be listed on the label of OTC eyewashes. The comment urged that the requirement be deleted from the statement of identity for eyewashes.

In the notice of proposed rulemaking, the agency explained that eyewash products are considered drugs rather than devices (48 FR 29789). The act defines a drug as, in part, an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man * * *," (21 U.S.C. 321(g)). The Advisory Review Panel on OTC Ophthalmic Drug Products discussed the conditions that should be treated with eyewashes. These conditions include inflammation and irritation of the eye caused by loose foreign material, airborne pollutants and allergens, or by chlorinated water (45 FR 30010 and 30047). Eyewashes are used to dilute or remove the offending irritant from the eye. In addition, the solutions are used for eye irrigation following diagnostic procedures and for postoperative irrigation (45 FR 30047).

In the tentative final monograph, the agency concurred with the Panel's consideration of eyewashes as drug products and stated that these products are properly regulated as drugs under the act (48 FR 29789). Consistent with the determination that these products are drugs, the agency stated in the proposed rule that the identity statement of these products should conform to section 502(e) of the act (48 FR 29796). Section 502(e) requires the established name of each active ingredient to appear in the labeling for products fabricated from two or more ingredients. Even though the agency stated in § 349.20 that eyewashes contain no pharmacologically active ingredients, it considered each ingredient of the eyewash product to have an active role in the proper functioning of the product. Thus, the agency felt it would be consistent with the labeling for all other OTC drug products to have the established name of all of the components of this particular product appear in the statement of identity section of the labeling.

The agency has reconsidered this proposed requirement. FDA regulations dealing with the statement of identity (21 CFR 201.61(b)) provide that the requirement for a statement of identity for an OTC drug that is a mixture and that has no established name "shall be deemed to be satisfied by a prominent and conspicuous statement of the general pharmacological action(s) of the mixture or of its principal intended action(s) in terms that are meaningful to the layman." The agency has determined that this section of the regulations is applicable to eyewash products and that the description of the principal intended action, i.e., "eyewash," "eye lotion," or "eye irrigating solution," will be sufficiently meaningful to the consumer to satisfy the statement of identity requirements.

Nevertheless, the agency believes that inactive ingredients should be listed in OTC drug product labeling in order to alert consumers with known allergies or intolerances to the presence of these ingredients. The Proprietary Association (PA), which submitted this comment objecting to the component listing requirement for eyewashes, recently announced that its member companies will voluntarily list inactive ingredients in the labeling of OTC drug products under guidelines established by the association (Ref. 1). The agency commends this voluntary action and notes that the action further makes the proposed agency requirement unnecessary. The agency is therefore not including the phrase "contains the established name of all components identified in § 349.20 and" in the statement of identity for eyewashes. The statement of identity (§ 349.78(a) of this final monograph) will read as follows: (a) *Statement of identity.* The labeling of the product identifies the product with one or more of the following terms: "eyewash," "eye lotion," or "eye irrigating solution."

Reference

(1) "Proprietary Association Adopts Voluntary Disclosure of Inactive Ingredients," News Release, The Proprietary Association, Washington, DC, May 14, 1984, copy included in OTC Volume 100FM.

14. Expressing concern about the labeling "verbiage" proposed in the tentative final monograph for OTC ophthalmic drug products, one comment maintained that the combination of this verbiage and small bottles and cartons will deter consumers from reading the labeling, thus decreasing the chances that consumers will be made aware of important information and warnings. The comment recommended revising the indications for ophthalmic demulcent

drug products proposed in § 349.60(b) (1) through (4) to read: "To temporarily relieve burning and discomfort due to dryness of the eyes and minor eye irritation. Also, to protect against further irritation." The comment also recommended that the indication proposed for ophthalmic vasoconstrictor drug products in § 349.75(b) be revised to read as follows: "To remove redness and help relieve minor eye irritation." The comment contended that these revisions would convey the same message in a concise manner.

The agency recognizes the need for concise wording in the labeling of ophthalmic drug products that are likely to be marketed in small packages. (See comment 18 at 48 FR 29795.) For this reason, the agency proposed four concise indication statements that could be used for OTC ophthalmic demulcent drug products. The indication proposed by the comment is not more concise than any one of the agency's proposed indications; rather, it is an attempt to combine all four indications into a single statement. The agency emphasizes that manufacturers need not place all of the indications on the labeling of their products, but may choose one or more of the indications that they wish to use. In addition, the agency has determined that if a manufacturer wishes to use more than one of the indications for an ophthalmic demulcent drug product, the indications may be combined to eliminate duplicate words and phrases as long as the resulting indication is clear and not misleading. The agency is revising the final monograph to allow this to be done. (This provision to combine indications to eliminate duplicative words or phrases is being made for the indications for all OTC ophthalmic drug products in § 349.50(b) of the final monograph.) Therefore, the agency sees no need to revise the wording of the indications for OTC ophthalmic demulcent drug products in § 349.60(b) (1) through (4) as proposed by the comment.

The indication proposed by the agency for ophthalmic vasoconstrictor drug products clearly describes the condition for which such ingredients should be used. The revision suggested by the comment is only slightly shorter but it conveys a different message. The agency's proposed indication states that the product is for relief of redness of the eye due to minor eye irritations, whereas the comment's proposed indication substitutes "and" for "due to" and thus indicates that vasoconstrictor drug products relieve minor eye irritations. (For further discussion of the indications for OTC ophthalmic

vasoconstrictor drug products, see comment 15 below.) The agency believes the indication proposed in the tentative final monograph for ophthalmic vasoconstrictor drug products can be further shortened by changing "For the relief of" to "Relieves" as follows: "Relieves redness of the eye due to minor eye irritations" while still maintaining the meaning of the indication. This shortened indication is included in this final monograph.

15. Two comments requested additional indications for ophthalmic vasoconstrictor drug products and proposed the following statements: "For the relief of minor eye irritation"; "For the relief of minor eye irritation and accompanying symptoms such as (optional, any or all of the following: redness, itching (or itchiness), burning, stinging, or soreness)"; and "For the relief of minor eye irritation due to (select any or all of the following: sun, wind, dust, smoke, contact lenses, plant allergies, colds, strain)."

One comment contended that these statements are truthful and not misleading claims for ophthalmic vasoconstrictor drug products. The other comment offered "Removes redness" as a fourth additional indication and stated that all four indications include terms that consumers commonly associate with OTC ophthalmic vasoconstrictor drug products.

In its discussion of indications for the use of OTC ophthalmic preparations, the Panel stated, in part, that the indications section "should include the statement that the preparation is for the temporary relief of symptoms applicable to the ingredients it contains" (45 FR 30023). The Panel also stated that itching, tearing, smarting, and burning may be relieved by eyewashes, astringents, demulcents, and emollients, and that redness is a symptom of irritation which can be relieved by a vasoconstrictor (45 FR 30009). The action of a vasoconstrictor when applied to the surface of the eye is described in the literature as blanching, bleaching, and whitening of reddened conjunctiva (Refs. 1 and 2). The mechanism by which this occurs is discussed in comment 12 above. Thus, the agency believes that an OTC ophthalmic vasoconstrictor ingredient is indicated for only one specific symptom, i.e., relief of redness in the eye.

The agency finds the first three indications suggested by the comment unsuitable for OTC ophthalmic vasoconstrictor drug products, because they incorrectly emphasize that the product is "for the relief of minor eye irritation," whereas the ophthalmic vasoconstrictor active ingredient is only

being used to relieve one symptom of minor eye irritation, that of redness. In its general discussion of ocular vasoconstrictors, the Panel stated that redness resulting from minor ocular irritation may be relieved by aqueous eye drops containing low concentrations of an ocular vasoconstrictor, which functions by constricting blood vessels underlying the surface of the eye that have dilated in response to noxious or irritating agents (45 FR 30033). The indications suggested by the comment emphasize that the product is for the relief of minor eye irritation; however, the agency concludes that such emphasis is inappropriate because the product is only to be used on an OTC basis for relief of the redness resulting from a minor eye irritation. The agency also believes that it is unnecessary to list possible causes of irritation in the indications statement for vasoconstrictors and other classes of ophthalmic drug products. Such lists would detract attention from the indicated symptom and would make the indications longer than necessary for safe and effective use of the product. However, the agency recognizes that the causes for the minor eye irritation resulting in redness of the eyes could be included elsewhere in the labeling as long as they are true and not misleading. The agency does not recognize colds, allergies, or strain as minor irritations which result in redness, but agrees with the Panel that dust and smoke are noxious or irritating agents which could cause redness. The Panel also listed gases, other airborne pollutants as well as smoke, and chlorinated water during swimming as possible causes for redness of the eye that could be relieved with an OTC drug product (45 FR 30010). The Panel recognized exposure to sun or wind as a cause of dryness in the eye treatable with OTC demulcent and emollient ingredients (45 FR 30023), but did not recognize such exposure as a cause of redness. The agency also believes that exposure to sun and wind has a drying effect on the eye which should be treated with OTC demulcent or emollient ingredients, but not with vasoconstrictor ingredients. A combination product containing a demulcent and a vasoconstrictor ingredient (as provided in § 349.30(c)) would be appropriate OTC treatment of irritated eyes which are both dry and red as a result of exposure to sun and wind.

The fourth suggested indication "Removes redness" is almost identical to a phrase in the statement of identity for ophthalmic vasoconstrictor ingredients proposed in § 349.75(a) which states, in part, "eye redness

reliever." However, "removes redness" alone is not an appropriate indication for an OTC vasoconstrictor product because it does not include the information that, in order for eye redness to be treated OTC, the redness must be the result of minor irritation. The Panel enumerated serious conditions, such as an embedded foreign body, uveitis, narrow angle glaucoma, or a flash burn, which exhibit redness as a symptom, but which are not amenable to OTC treatment (45 FR 30010 and 30011). The agency believes that OTC treatment of such conditions could lead to serious complications.

The agency is concerned about overuse or unnecessary use of OTC ophthalmic vasoconstrictor ingredients. The Panel strongly recommended against too-frequent or prolonged use of these ingredients, citing the dangers in delaying treatment of serious conditions as well as the risk of adverse side effects, such as excessive cell loss, prolonged constriction of conjunctival blood vessels followed by dilation of these blood vessels or rebound hyperemia, and subjective effects of ocular stinging and burning. (See comment 16 below and 45 FR 30033.) The Panel also pointed out that these ingredients, at higher concentrations, cause dilation of the pupil (mydriasis) and that, even at the low concentrations specified for OTC use, these ingredients may, occasionally, trigger mydriasis, especially in subjects who wear contact lenses, whose cornea is abraded, or who have lightly colored irises (Refs. 3 and 4). This dilation of the pupil may in turn precipitate an attack of narrow-angle glaucoma in a susceptible user (Ref. 5).

Because ophthalmic vasoconstrictors as OTC ingredients are only necessary for the relief of redness in the eye due to minor irritation and because there are risks inherent in the too-frequent or prolonged use of these ingredients, the agency concludes that the single indication for OTC ophthalmic vasoconstrictor ingredients is appropriate. Therefore, the agency is not including the comments' recommended indications in this final monograph. The indication for ophthalmic vasoconstrictor drug products proposed in the tentative final monograph, i.e., "For the relief of redness of the eye due to minor eye irritations," has been shortened to read "Relieves redness of the eye due to minor eye irritations." (See comment 14 above.) This shortened indication for OTC ophthalmic vasoconstrictor drug ingredients is included in § 349.75(b) in the final monograph.

References

- (1) Newell, F.W., "Ophthalmology: Principles and Concepts," 5th Ed., C.V. Mosby Co., St. Louis, p.149, 1982.
- (2) Havener, W.H., "Ocular Pharmacology," 3d Ed., C.V. Mosby Co., St. Louis, p. 221, 1974.
- (3) Sugar, H.S., "The Glaucomas," in "Modern Ophthalmology, Topical Aspects," 2d Ed., Edited by A. Sorsby, J.B. Lippincott, Philadelphia, p. 612, 1972.
- (4) Obianwu, H.O., and M.J. Rand, "The Relationship Between the Mydriatic Action of Ephedrine and the Colour of the Iris," *British Journal of Ophthalmology*, 49:264-270, 1965.
- (5) Weiss, D.I., and R.N. Shaffer, "Mydriatic Effects of One-Eighth Per Cent Phenylephrine: A Potential Cause of Angle-Closure Glaucoma," *Archives of Ophthalmology*, 68:727-729, 1962.
16. One comment objected to the agency's proposed warning (in § 349.75(c)(3)) against rebound hyperemia for ophthalmic vasoconstrictor drug products containing tetrahydrozoline hydrochloride. The comment argued that this warning is not supported by the evidence contained in the record. The comment contended that it is not valid for the agency to cite the Panel's advice that excessive use of these products might produce rebound hyperemia as a reason to require the warning for tetrahydrozoline when several controlled studies referred to in the Panel's report found no rebound hyperemia from the use of tetrahydrozoline hydrochloride (Refs. 1 through 4). The comment added that rebound hyperemia caused by excessive use of nasal products containing naphazoline hydrochloride has no application to tetrahydrozoline hydrochloride. Furthermore, the comment argued that the 157 tetrahydrozoline adverse reaction reports to FDA during the years 1969 to 1982 (Ref. 5) do not establish a single case of rebound hyperemia and attest to a remarkable record of safety for the more than 250 million bottles of ophthalmic tetrahydrozoline hydrochloride used by consumers in that period. The comment agreed that a warning against overuse is appropriate for vasoconstrictors that have been shown to produce rebound hyperemia, but that the warning is not justified for tetrahydrozoline hydrochloride.
- In the tentative final monograph, the agency concluded that the labeling of all ophthalmic vasoconstrictor drug products should contain a warning against excessive use and proposed the following: "Overuse of this product may produce increased redness of the eye." The agency stated that the Panel had recommended this warning even after the Panel noted that the studies cited by the comment had not reported rebound

hyperemia, that the 157 adverse reaction reports cited by the agency were not reviewed by the Panel, and that these adverse reactions were all reported after completion of the four controlled studies in which rebound hyperemia was not reported.

An updated adverse reaction report on tetrahydrozoline hydrochloride covering the years 1969 to 1984 lists approximately 280 adverse reactions from the OTC use of this drug (Ref. 6); more than 90 of the adverse reactions are reported as "conjunctivitis," and 45 of the total are reported as "no drug effect" (Ref. 6). The term "rebound hyperemia" is not an option in the agency's computer system for recording adverse reactions, and consumers are generally unaware of the meaning of the term; however, among the phrases used by consumers to describe the tetrahydrozoline hydrochloride side effect which is listed by the agency in the adverse reaction report as "conjunctivitis" are "eyes turn redder," "eyes are redder than before," "eyes get blood red," and eyes "turn bloodshot" (Ref. 6). "Does not get red out," "failed to clear redness," and "eyes still red" are some of the phrases used by consumers to describe the tetrahydrozoline hydrochloride side effect which is recorded by the agency in the computer information on tetrahydrozoline hydrochloride adverse reaction report as "no drug effect" (Ref. 5). Because both "conjunctivitis" and "no drug effect" are identified by consumers as "redness of the eye," the agency believes that these reactions could be cases of rebound hyperemia. The agency believes that consumers need to be alerted that overuse of these products may produce increased redness of the eye. Therefore, the agency is including in this final monograph the warning "Overuse of this product may produce increased redness of the eye" for all ophthalmic drug products containing a vasoconstrictor.

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) Adverse Reaction Information on Tetrahydrozoline in OTC Ophthalmic Drug Products Retrieved from the Drug Experience Information System, January 1969 to December 1982, OTC Volume 100TFM, Docket No. 80N-0145, Dockets Management Branch.

(6) Adverse Reaction Information on Tetrahydrozoline Hydrochloride in OTC Ophthalmic Drug Products Retrieved from the Drug Experience Information System, January 1969 to May 1984, OTC Volume 100FM, Docket No. 80N-0145, Dockets Management Branch.

17. One comment objected to "the implicit prohibition" of the phrase "tear substitute" on the label of eyewash products. The comment stated that rigorous interpretation of the agency's ruling is that an ophthalmic product must contain a demulcent in order to be labeled as a tear substitute. The comment added that the agency requires that eyewashes, with no demulcent, must be equivalent to human tears in pH, tonicity, viscosity, absence of active ingredients, etc. The comment pointed out that, in the response to comment 3 in the notice of proposed rulemaking, the agency stated that "eyewash products be similar to tears . . ." (48 FR 29790). The comment requested that the labeling of all eyewash products which conform in composition and physical properties to the requirements of the final rule for ophthalmic drug products be permitted to include the phrase "tear substitute" at the manufacturer's discretion.

The Panel defined the term "tear replacement, tear substitute" as "a preparation intended to counteract dryness in the eye; often used for the relief of symptoms in 'dry eye' in which production volume or quality of tears is inadequate" (45 FR 30007). The agency recognizes that OTC ophthalmic preparations labeled as "artificial tears" contain ophthalmic demulcents. Ophthalmic demulcents provide a mechanical means for lubricating and protecting mucous membranes or abraded surfaces by mimicking the action of mucin, which is the natural demulcent in tears.

Eyewashes (eye lotions, irrigating solutions) are OTC ophthalmic solutions intended for flushing or irrigating the eye to remove loose foreign material, air pollutants, or chlorinated water (48 FR 29799). The agency believes that it would be inappropriate to label these products as "tear substitutes" when their intended use is to bathe or flush the eye to remove a foreign substance. Eyewashes contain no pharmacologically active ingredients, but should be formulated to 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 (48 FR 29798). Because an eyewash is intended to be used in the eyes, it should be physiologically compatible with tears; however, unlike an OTC ophthalmic demulcent, an eyewash is not intended to treat dry eyes or to be used as a tear substitute. Therefore, for the reasons stated above, the agency disagrees with the comment and is not accepting the comment's recommendation to permit the use of the term "tear substitute" on the label of OTC eyewashes.

18. Referring to the agency's discussion in the tentative final monograph (see comment 11 at 48 FR 29792) that adverse environmental conditions, such as smog, foreign material, and airborne pollutants can cause symptoms of irritation, discomfort, burning, stinging, smarting, and itching of the eye, and that if the eye is not damaged by such debris, the relief of these symptoms occurs with the removal of the irritating substance with an eyewash, one comment stated that the labeling indications for eyewashes in proposed § 349.78(b) "should reflect the symptomatic relief which FDA states is obtained by the use of an eyewash." The comment stated that claims should be allowed to convey this information to the consumer and requested that the following 10 indications for eyewashes be added to § 349.78:

(1) "Aids in the relief of irritation, discomfort, burning, stinging, smarting and itching due to foreign material, air pollutants such as pollen or smog and/or due to swimming in chlorinated water."

(2) "Aids in the relief of irritation (discomfort) due to the presence of foreign material such as dust or an eyelash in the eye."

(3) "Aids in the relief of burning, itching and stinging of the eyes due to the presence of air pollutants such as smog."

(4) "Aids in the relief of burning, itching and stinging of the eye due to swimming in chlorinated water."

(5) "Aids in the relief of itching of the eyes due to the presence of pollen."

(6) "Bathes (washes) the eye aiding in the relief of irritation due to foreign material."

(7) "Bathes (washes) the eye aiding in the relief of irritation due to smog and other air pollutants."

(8) "Bathes (washes) the eye aiding in the relief of burning and/or itching due to swimming in chlorinated water."

(9) "Bathes (washes) the eye providing cooling, refreshing relief from irritation of the eye due to the presence of foreign material such as air pollutants."

(10) "Bathes (washes) the eye providing cooling, refreshing relief from burning and/or stinging of the eyes due to contact with chlorinated water while swimming."

A second comment questioned whether "flushing" and "irrigating" are the most meaningful terms that could be used in proposed § 349.78(b) to describe to consumers the cleansing function of an eyewash. The comment stated that consumers may associate the word "flushing" with a toilet and "irrigation" with a ditch. The comment urged that proposed § 349.78(b) be expanded to include the following terms: "cleansing," "washing," "bathing," "flooding," and "immersing."

The agency agrees with the comments that the indications for eyewashes could be expanded to include some of the information contained at 48 FR 29792 and to use alternate terms to describe the cleansing function of an eyewash. Ocular irritation, discomfort, burning, stinging, smarting, and itching are symptoms that can be relieved with an eyewash. The symptoms are caused by loose foreign materials, air pollutants, or chlorinated water in the eye. Air pollutants can also be further identified as pollen or smog. The agency believes that the intent of the comment's 10 suggested indications can be more simply achieved by combining them into one indication which includes many of the terms recommended by the comment.

The agency further believes that the terms "cleansing," "washing," and "bathing" may be used to convey the same message as "flushing" or "irrigating," but that the terms "flooding" and "immersing" are not as clear and are not meaningful when used in conjunction with the eye. For example, to immerse an eye could be misinterpreted as meaning to completely submerge it, and flooding is not normally associated with a cleansing action or the removal of irritants accomplished by using an OTC eyewash drug product.

In conclusion, the agency is revising § 349.78(b) in this final monograph by including a second indication that reads as follows:

"For" (select one of the following: "flushing," "irrigating," "cleansing," "washing," or "bathing") "the eye to help relieve" (select one or more of the following: "irritation," "discomfort," "burning," "stinging," "smarting," or "itching") "by removing" (select one or more of the following: "loose foreign material," "air pollutants (smog or pollen)," or "chlorinated water").

19. Noting that the tentative final monograph for OTC ophthalmic drug

products did not provide a section for "Other Allowable Statements," one comment requested that such a section be included in the final monograph for OTC ophthalmic drug products. The comment cited the tentative final monograph for OTC oral mucosal injury drug products (48 FR 33984) as providing two other allowable statements for oral wound cleansers: "assists in the removal of foreign material from minor oral wounds" and "physically removes debris from minor oral wounds" and stated that, since an eyewash functions in a similar manner, the following "Other Allowable Statements" would be appropriate and should be included in the monograph:

(1) "Assists in the removal of foreign material from the eye";

(2) "Physically removes debris (foreign material) from the eye"; and

(3) "Bathes the eye, removing debris."

Under the current policy regarding the exclusivity of labeling terms, the agency will not include a section entitled "Other Allowable Statements" in final monographs for OTC drug products. (See the *Federal Register* of May 1, 1986 (51 FR 16258).)

20. Two comments urged elimination of the proposed warning for eyewashes in § 349.78(c)(2), which reads, "Not for use in open wounds in or near the eyes. Consult a doctor." (See 48 FR 29799.) Acknowledging that open wounds in or near the eye can be very serious and that professional medical attention should be sought as soon as possible, one comment nevertheless maintained that flushing a wound with a sterile liquid to remove debris and avoid infection is an appropriate action in an emergency situation where medical attention is not immediately available. Stating that it did not object to the portion of the warning requiring a physician's care, the comment proposed the following warning: "Obtain immediate medical treatment for all open wounds in or near the eyes," and concluded that such a warning would not preclude flushing a wound with a sterile eyewash.

The second comment contended that the warning in § 349.78(c)(1) which reads, "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," adequately directs consumers to see a physician when appropriate. The comment concluded that eyewashes should not be singled out to carry the warning in § 349.78(c)(2), especially when washing a wound in or near the eyes with an eyewash is beneficial until the consumer can see a physician.

The agency agrees with the comments that washing an open wound in or near the eyes with an OTC eyewash should not be specifically prohibited in the labeling of that drug product. However, the seriousness of open wounds in or near the eyes should be emphasized in the labeling of OTC eyewash drug products. Consumers also should be urged to seek professional treatment as soon as possible. Such warnings are appropriate on OTC eyewash products because a consumer will more likely use an OTC eyewash, if available, to clean such a wound than any of the other classes of OTC ophthalmic drug products. The agency does not believe that the general warning in § 349.78(c)(1) is adequate to encourage consumers to seek professional treatment for an open wound in or near the eyes. Therefore, a separate warning is needed for OTC eyewashes.

The agency concludes that the alternate warning suggested by one of the comments is sufficient to alert the consumer to seek professional treatment for open wounds in or near the eyes and that a warning prohibiting use of an eyewash for such cleansing purposes is not required. Therefore, the agency is not including the warning proposed in § 349.78(c)(2) of the tentative final monograph but is replacing it with the following warning: "Obtain immediate medical treatment for all open wounds in or near the eyes."

D. Comments on Testing Guidelines for OTC Ophthalmic Drug Products

21. Two comments disagreed with the agency's position on the Draize rabbit eye irritation test for evaluating the safety of ophthalmic drug products, as set forth in the notice of proposed rulemaking at 48 FR 29795. One comment contended that the Draize test only identifies grossly irritating substances, may be inaccurate because of the differences between rabbit and human eyes, and functions solely in a pass/fail capacity for nearly all compounds. According to a comment, in vitro methods and refined animal techniques offer the possibility of assaying parameters more relevant to eye irritation while causing less pain to animals. The comment advocated two approaches: (1) The refinement of current procedures for the short term, and (2) the eventual replacement of rabbits with a suitable alternative. The short-term refinements suggested by the comment were from the Inter-agency Regulatory Liaison Group publication "Recommended Guidelines for Acute Eye Irritation Testing," which states that:

1. Known corrosive substances should be assumed to be irritants and not be tested.

2. Dermal irritancy tests should precede eye tests. Severe dermal responses need not be subjected to eye irritancy tests.

3. The number of rabbits used in Draize tests should be substantially reduced.

The comment argued that, as a minimum requirement, FDA should adopt and clearly state the short-term refinements listed above in order to minimize the number of animals exposed to irritants. The comment submitted a review of some methods which show potential for replacing rabbit eyes as testing vehicles and included a description of an alternative to the Draize test which utilizes the chorioallantoic membrane of the chick embryo to assay irritation. The comment urged that the agency acknowledge that alternatives which are at least equivalent to the Draize test are available.

The other comment argued that the agency failed to specify the circumstances in which in vitro data on eye irritation would be accepted and stated that "the FDA Notice of Proposed Rulemaking discourages the notion that current efforts to develop alternatives will ever lead to new testing acceptable to your agency." The comment suggested that "whole eye" testing need not be confined to the Draize test and that cell and tissue culture methods will ultimately provide data which will overcome the difficulties of interspecies transposition and provide testing which is adequately protective as well as more elegant and more humane. This comment recommended that the agency establish study groups and research communication centers to encourage research on in vitro alternatives to the Draize test. The comment requested an oral hearing on these objections and comments.

The agency recognizes the limitations of the Draize test and has discussed these limitations in the notice of proposed rulemaking for OTC ophthalmic drug products (48 FR 29795); however, this test is, at present, the most reliable method for determining the potential harmfulness, or safety, of a product instilled in the eye. The agency is actively considering alternatives to the rabbit eye irritation test and to other animal protocols and is aware of the methods mentioned in the comments. Among the assays which show promise of replacing the Draize rabbit eye irritation test are cell culture methods using corneal epithelial, stromal, and

endothelial cell lines. In addition, in vitro cell culture research using a protozoan species as a model for identifying potential ocular irritants and a tissue culture method utilizing excised cornea from animal or eyebank eyes are being investigated (Ref. 1). Four toxicology laboratories are involved in testing a battery of sensitive in vitro assays reported to be useful in ranking chemicals as mild to severe irritants in the rabbit eye. The assay, described by one comment, which utilizes the chorioallantoic membrane of the chick embryo offers a test system which more closely resembles the complexities of an in vivo assay. Because it is a living tissue, the membrane is rich in blood vessels and responds accordingly to chemical irritants. The developer of this method is looking for collaborators in other laboratories to validate his assay (Ref. 2). However, these assays need further development and have not yet been developed to the point where they can replace the Draize test. The investigators pursuing these alternatives are working on establishing parameters for toxicity assessment so that the most irritating chemicals will be screened by these tests without the need of having them instilled into a rabbit eye. Complete validation of an assay requires that it be tested on a wide spectrum of compounds, in many different laboratories. In vitro findings must be related to in vivo data and the results must indicate that the assay is predictable, reliable, and reproducible (Ref. 2). None of these methods has, as yet, been accepted as a replacement for the Draize rabbit eye irritation test; however, the agency encourages the utilization of in vitro testing to prescreen obviously irritating chemicals and minimize the number of animals used in testing.

The agency's primary mission is consumer protection. In carrying out this mission, the agency must recommend testing procedures which have been demonstrated to be universally recognized as valid for detecting any ocular irritancy of an ophthalmic drug product prior to human use. The agency regrets the necessity of animals being used for toxicological testing and has taken steps to promote humane treatment of these animals as well as to minimize the number of animals used for testing and research. In the Federal Register of January 22, 1981, the agency committed itself to use the Inter-agency Regulatory Liaison Group guidelines for acute eye irritation testing. (See 46 FR 7077.) In November 1983, FDA sponsored a public workshop on acute toxicity studies, inviting representatives

from FDA, other government agencies, and industry. A report of the workshop was issued in February 1984 (Ref. 3).

At that workshop, the agency announced its intention to form a committee to review the care and handling of animals used in testing. As a result of the workshop, the Steering Committee on Animal Welfare Issues was formed in January 1984 and was charged with addressing a number of specific issues, such as:

1. Are mechanisms in place to ensure continuing compliance with the Animal Welfare Act and with the highest standards of animal care?

2. Are FDA procedures so ordered as to obtain the maximum amount of useful scientific information while utilizing the fewest number of animals?

3. Is FDA making the maximum use of and encouraging the continued development of reliable in vitro alternatives to in vivo methodologies?

All of the agency Centers and the Office of the Commissioner were represented on the Steering Committee, which presented a final report on animal welfare issues to the Commissioner on August 15, 1984 (Ref. 1). The report indicated that all of the Centers in the agency have practices and procedures for assuring humane care and treatment of animals. In particular, two facilities are accredited by the American Association for Accreditation of Laboratory Animal Care, the highest formal accreditation, and the others have self-assessment procedures that meet or exceed Public Health Service standards. The report also lists many instances where in vitro testing has eliminated the need for animal testing in agency guidelines for industry toxicity studies. Based on the Committee's recommendation, the Commissioner established an agency-wide Animal Research Council to function as a resource to the various Centers and the Commissioner, and as a means of communication and coordination for the agency.

As discussed above, the agency is addressing the concerns for which the comment requested an oral hearing. Therefore, the Commissioner concludes that a hearing on this issue is not warranted.

References

(1) Agency Steering Committee On Animal Welfare Issues, Food and Drug Administration, "Final Report to the Commissioner," August 15, 1984, Docket No. 84N-0299, Dockets Management Branch.

(2) Dagani, R., "In Vitro Methods May Offer Alternatives to Animal Testing," *Chemical and Engineering News*, p. 28, November 12, 1984.

(3) Office of Science Coordination, Food and Drug Administration, "Final Report on Acute Studies Workshop," February 23, 1984, OTC Volume 100FM, Docket No. 80N-0145, Dockets Management Branch.

II. Summary of Significant Changes

1. The agency is clarifying the definition of an OTC ophthalmic drug product in § 349.3(a) to reflect that some products are applied to the eyelid rather than instilled in the eye.

2. The agency is not including the words "contain no pharmacologically active ingredients" in proposed § 349.20 in this final monograph and is revising the description for eyewashes to read: "These products 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." The agency is also not including the words "containing no pharmacologically active ingredients" in the definition for eyewash, eye lotion, and irrigating solution in § 349.3(f). (See comment 2 above.)

3. To eliminate duplicate words for any product with more than one indication, the agency has added the following in § 349.50(b): "Indications applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable." (See comment 14 above.) Accordingly, proposed § 349.50(b) has been redesignated § 349.50(c) in this final monograph.

4. The agency is shortening and modifying the warning proposed in § 349.50(b)(1) of the tentative final monograph (redesignated as § 349.50(c)(1)) to apply to ophthalmic drug products packaged in multi-use containers. The warning now reads: "To avoid contamination, do not touch tip of container to any surface. Replace cap after using." The agency is also including a new warning in § 349.50(c)(2), which applies to ophthalmic drug products packaged in single-use containers, as follows: "To avoid contamination, do not touch tip of container to any surface. Do not reuse. Once opened, discard." (See comments 7 and 8 above.) Accordingly, the warning proposed in § 349.50(b)(2) of the tentative final monograph has been redesignated § 349.50(c)(3).

5. Section 502(e)(i) of the act (21 U.S.C. 352(e)(1)) provides that the label must bear the established name and quantity or proportion of mercury or any derivative or preparation of such substance whether active or inactive. In order that all requirements for OTC ophthalmic drug products containing

mercury can be found in one location, the agency is incorporating this statutory requirement for labeling the quantity of the mercury-containing ingredient into § 349.50(c)(3).

6. Because submitted market research studies do not establish that consumers equate the term "tired eyes" with symptoms of minor irritation and redness in the eyes, the agency is not including "tired eyes" as an indication for any of the ophthalmic drug classes in this final monograph. However, the agency concludes that the term "relief of tired eyes" is acceptable additional information that may appear elsewhere in the labeling, separate from monograph approved statements, of any OTC ophthalmic drug product except OTC ophthalmic vasoconstrictors. (See comment 10 above.)

7. The agency is providing manufacturers the option of selecting the term "eye" or "ophthalmic" as well as a term describing the dosage form of the product in the statement of identity for ophthalmic astringent drug products in § 349.55(a), ophthalmic demulcent drug products in § 349.60(a), ophthalmic emollient drug products in § 349.65(a), ophthalmic hypertonicity drug products in § 349.70(a), and ophthalmic vasoconstrictor drug products in § 349.75(a). (See comment 12 above.)

8. The agency is clarifying § 349.14 by adding concentration limits for each of the approved ophthalmic emollient active ingredients. The concentrations are based on information from several sources. The Panel stated that lanolin materials by themselves are not suitable for direct application to tissues and are usually incorporated at a concentration of 1 to 10 percent in oleaginous ointment bases (45 FR 30045). The concentration of mineral oil was included in a submission to the Panel (Ref. 1) and in the Physicians' Desk Reference for Ophthalmology (Ref. 2). The agency is applying the same concentration for light mineral oil as an emollient because of its similarity to mineral oil. The concentration of white wax was reported in the Panel's discussion (45 FR 30045) and in Remington's Pharmaceutical Sciences (Ref. 3). The Panel considered both white wax and paraffin as agents for increasing the consistency of ointment products and not for use alone as emollients (45 FR 30046). The agency agrees and is also applying the same principles for yellow wax because of its similarity to white wax. The Panel stated that white petrolatum and white ointment can be used alone as ocular emollients (45 FR 30045) and the Physicians' Desk Reference for Ophthalmology identifies

two presently marketed emollient products consisting of 100 percent white petrolatum (Refs. 4 and 5).

In order to address any product that was not reviewed by the Panel and that contains concentrations of emollients other than those included in the monograph, the agency requests manufacturers to submit the formulations in a petition to amend the monograph before the effective date of the final monograph. The agency will consider amending the monograph accordingly.

References

- (1) OTC Volume 100041.
- (2) "Physicians' Desk Reference for Ophthalmology," 15th Ed., Medical Economics Company, Oradell, NJ, p. 97, 1987.
- (3) "Remington's Pharmaceutical Sciences," 17th Ed., edited by A.R. Gennaro, et al., Mack Publishing Co., Easton, PA, pp. 1302-1303, 1985.
- (4) "Physicians' Desk Reference for Ophthalmology," 13th Ed., Medical Economics Company, Oradell, NJ, p. 108, 1985.
- (5) "Physician's Desk Reference for Ophthalmology," 15th Ed., Medical Economics Company, Oradell, NJ, p. 148, 1987.

9. The agency has determined that the term "nonionic lanolin derivatives" is not descriptive enough to be included in an OTC drug final monograph. Although this term was proposed in the tentative final monograph, the agency subsequently contacted the manufacturer of a product containing nonionic lanolin derivatives several times requesting information on the chemical nature and composition of this ingredient so that it could be properly defined and characterized (Ref. 1). For an ingredient or mixture to be included in an OTC drug final monograph, it is necessary to have publicly available chemical information that can be used by other manufacturers to identify the ingredient should they desire to use it in their products. Because the agency has not received any detailed chemical description of nonionic lanolin derivatives, § 349.14(a)(3), which referred to nonionic lanolin derivatives in the tentative final monograph, is not being included in this final monograph.

Reference

- (1) Memoranda of Telephone Conversations between J. Cobb, FDA, and P. Nowacki, Allergan Pharmaceuticals, dated March 28, 1985; July 24, 1985; July 31, 1985; August 30, 1985; and May 7, 1986 in OTC Volume 100FM, Docket No. 80N-0145, Dockets Management Branch.

10. The agency is shortening the indication for ophthalmic vasoconstrictors proposed in § 349.75(b)

to read "Relieves redness of the eye due to minor eye irritations." (See comment 14 above.)

11. The agency is not including the proposed phrase "contains the established name of all components identified in § 349.20" in the statement of identity for eyewashes in § 349.78(a). The agency has determined that the description of the principal intended action, i.e., "eyewash," "eye lotion," or "eye irrigating solution" satisfies the statement of identity requirements for eyewashes. (See comment 13 above.)

12. In order to permit alternate terms to describe the cleansing function of an eyewash, the agency is expanding the indications for eyewashes proposed in § 349.78(b). (See comment 18 above.)

13. The agency is replacing the warning proposed in § 349.78(c)(2) ("Not for use in open wounds in or near the eyes. Consult a doctor.") with the following warning: "Obtain immediate medical treatment for all open wounds in or near the eyes." (See comment 20 above.)

14. The agency is including a section on the labeling of ophthalmic combination drug products in § 349.79.

III. The Agency's Final Conclusions on OTC Ophthalmic Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC ophthalmic drug products are generally recognized as safe and effective and not misbranded. The agency has determined the following ingredients to be a monograph condition for their respective ophthalmic drug class:

Ophthalmic drug class	Ingredient
Astringent.....	Zinc sulfate (0.25%)
Demulcent.....	Carboxymethylcellulose sodium (0.2 to 2.5%)
	Dextran 70 (0.1% when used with another polymeric demulcent agent included in the monograph)
	Gelatin (0.01%)
	Glycerin (0.2 to 1%)
	Hydroxyethyl cellulose (0.2 to 2.5%)
	Hydroxypropyl methylcellulose (0.2 to 2.5%)
	Methylcellulose (0.2 to 2.5%)
	Polyethylene glycol 300 (0.2 to 1%)
	Polyethylene glycol 400 (0.2 to 1%)
	Polysorbate 80 (0.2 to 1%)
	Polyvinyl alcohol (0.1 to 4%)
	Povidone (0.1 to 2%)
	Propylene glycol (0.2 to 1%)

Ophthalmic drug class	Ingredient
Emollient.....	Anhydrous lanolin (1 to 10 percent in combination with one or more oleaginous emollient agents included in the monograph)
	Lanolin (1 to 10 percent in combination with one or more oleaginous emollient agents included in the monograph)
	Light mineral oil (up to 50 percent in combination with one or more other emollient agents included in the monograph)
	Mineral oil (up to 50 percent in combination with one or more other emollient agents included in the monograph)
	Paraffin (up to 5 percent in combination with one or more other emollient agents included in the monograph)
	Petrolatum (up to 100 percent)
	White ointment (up to 100 percent)
	White petrolatum (up to 100 percent)
	White wax (up to 5 percent in combination with one or more other emollient agents included in the monograph)
	Yellow wax (up to 5 percent in combination with one or more other emollient agents included in the monograph)
Eyewash.....	Water, tonicity agent(s), pH and buffering agent(s), and a preservative
Hypertonicity agent.	Sodium chloride (2 to 5%)
Vasoconstrictor.....	Ephedrine hydrochloride (0.123%)
	Naphazoline hydrochloride (0.01 to 0.03%)
	Phenylephrine hydrochloride (0.08 to 0.2%)
	Tetrahydrozoline hydrochloride (0.01 to 0.05%)

With the exception of ophthalmic antiinfective drug products, all other ingredients are considered nonmonograph ingredients and any drug product marketed for use as an OTC ophthalmic drug product that is not in conformance with the monograph (21 CFR Part 349) may be considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved NDA.

The agency has examined the economic consequences of this final rule 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 final 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 final rule will not have a significant economic impact on a substantial number of small entities.

The agency is withdrawing a portion of § 369.20 under the entry "OPHTHALMIC PREPARATIONS" because aspects of this entry are superseded by the requirements of the final monograph for OTC ophthalmic drug products (Part 349).

List of Subjects

21 CFR Part 349

Labeling, Over-the-counter drugs, Ophthalmic drug products.

21 CFR Part 369

OTC drugs, Warning and caution statements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. By adding a new Part 349 consisting of §§ 349.1-349.80, to read as follows:

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

Subpart A—General Provisions

Sec.

349.1 Scope.

349.3 Definitions.

Subpart B—Active Ingredients

349.10 Ophthalmic astringent.

349.12 Ophthalmic demulcents.

349.14 Ophthalmic emollients.

349.16 Ophthalmic hypertonicity agent.

349.18 Ophthalmic vasoconstrictors.

349.20 Eyewashes.

349.30 Permitted combinations of active ingredients.

Subpart C—Labeling

349.50 Labeling of ophthalmic drug products.

349.55 Labeling of ophthalmic astringent drug products.

349.60 Labeling of ophthalmic demulcent drug products.

349.65 Labeling of ophthalmic emollient drug products.

349.70 Labeling of ophthalmic hypertonicity drug products.

349.75 Labeling of ophthalmic vasoconstrictor drug products.

349.78 Labeling of eyewash drug products.

349.79 Labeling of permitted combinations of active ingredients.

349.80 Professional 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); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

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 the eyelid or instilled in the eye.

(b) *Astringent.* A locally acting pharmacologic agent which, by precipitating 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 intended for washing, bathing, or 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 constriction of conjunctival blood vessels.

Subpart B—Active Ingredients

§ 349.10 Ophthalmic astringent.

The active 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) Carboxymethylcellulose sodium, 0.2 to 2.5 percent.

(2) Hydroxyethyl cellulose, 0.2 to 2.5 percent.

(3) Hydroxypropyl methylcellulose, 0.2 to 2.5 percent.

(4) Methylcellulose, 0.2 to 2.5 percent.

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

(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, 1 to 10 percent in combination with one or more oleaginous emollient agents included in the monograph.

(2) Lanolin, 1 to 10 percent in combination with one or more oleaginous emollient agents included in the monograph.

(b) Oleaginous ingredients:

(1) Light mineral oil, up to 50 percent in combination with one or more other emollient agents included in the monograph.

(2) Mineral oil, up to 50 percent in combination with one or more other emollient agents included in the monograph.

(3) Paraffin, up to 5 percent in combination with one or more other emollient agents included in the monograph.

(4) Petrolatum, up to 100 percent.

(5) White ointment, up to 100 percent.

(6) White petrolatum, up to 100 percent.

(7) White wax, up to 5 percent in combination with one or more other emollient agents included in the monograph.

(8) Yellow wax, up to 5 percent in combination with one or more other emollient agents included in the monograph.

§ 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 ingredient of the product consists of one of the following, within the established concentration 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 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.

The following combinations are permitted provided each active ingredient is present within the established concentration, and the product is labeled in accordance with § 349.79.

(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 combined 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 this 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 this part.

(b) Where applicable, indications in this part applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this part, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(1) *For ophthalmic drug products packaged in multi-use containers.* "To avoid contamination, do not touch tip of container to any surface. Replace cap after using."

(2) *For ophthalmic drug products packaged in single-use containers.* "To avoid contamination, do not touch tip of container to any surface. Do not reuse. Once opened, discard."

(3) *For ophthalmic drug products containing mercury compounds used as a preservative.* "This product contains (name and quantity of mercury-containing ingredient) as a preservative. Do not use this product if you are sensitive to" (select one of the following: "mercury" or "(insert 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, if any, and identifies

the product as an "astringent" (select one of the following: "eye" or "ophthalmic") "(insert dosage form, e.g., drops)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," 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 a "lubricant" or "demulcent (lubricant)" (select one of the following: "eye" or "ophthalmic") "(insert dosage form, e.g., drops)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," 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 a "lubricant" or "emollient (lubricant)" (select one of the following: "eye" or "ophthalmic") "(insert dosage form, e.g., ointment)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," 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 § 349.14: "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 a "hypertonicity" (select one of the following: "eye" or "ophthalmic") "(insert dosage form, e.g., drops)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following phrase: "For the temporary relief of corneal edema."

(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 § 349.16:

(1) "Do not use this product except under the advice and supervision 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."

(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 a "redness reliever" or "vasoconstrictor (redness reliever)" (select one of the following: "eye" or "ophthalmic") "(insert dosage form, e.g., drops)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following phrase: "Relieves 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 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 states, under the heading "Indications," one of the following phrases:

(1) "For" (select one of the following: "flushing," "irrigating," "cleansing," "washing," or "bathing") "the eye to remove" (select one or more of the following: "loose foreign material," "air pollutants (smog or pollen)," or "chlorinated water").

(2) "For" (select one of the following: "flushing," "irrigating," "cleansing," "washing," or "bathing") "the eye to help relieve" (select one or more of the following: "irritation," "discomfort," "burning," "stinging," "smarting," or "itching") "by removing" (select one or more of the following: "loose foreign material," "air pollutants (smog or pollen)," 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, consult a doctor."

(2) "Obtain immediate medical treatment for all open wounds in or near the eyes."

(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.

§ 349.79 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each

ingredient in the combination, as established in the statement of identity sections of this part. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of this part.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of this part.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of this part.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of

this part. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

§ 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).

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

2. The authority citation for 21 CFR Part 369 continues to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050-1052 as amended, 1055-1056 as

amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

§ 369.20 [Amended]

3. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended under the entry for "OPHTHALMIC PREPARATIONS," to read as follows:

* * * * *

OPHTHALMIC PREPARATIONS. (See also § 200.50 of this chapter.)

Boric acid offered for use in the preparation of ophthalmic solutions should bear the statement: Prepare solution by boiling in water. Store in a sterile container. Prepare sufficient for one day's use and discard unused portion.

* * * * *

Dated: November 16, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 88-4585 Filed 3-3-88; 8:45 am]

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