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 887 (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 astringent 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

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