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Part II

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Food and Drug Administration

Ophthalmic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph, Proposed Rulemaking

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

21 CFR Part 349

[Docket No. 80N-0145]

Ophthalmic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) ophthalmic drug products (products for use in the eye) are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendation of the Advisory Review Panel on OTC Ophthalmic Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by August 4, 1980; reply comments by September 3, 1980.

ADDRESSES: Written comment to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), the FDA received on March 10, 1979, a report of the Advisory Review Panel on OTC Ophthalmic Drug Products. Under §330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner of Food and Drugs is issuing: (1) A proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC ophthalmic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of the FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendation. This document represents the best sceintific judgment of the Panel members but does not necessarily reflect the agency position on any particular matter contained in it.

The agency recognizes that the Panel reviewed inactive ingredients contained in OTC ophthalmic drug products and made recommendations concering whether certain inactive ingredients were suitable for inclusion in these drug products. Because the eye is a particularly sensitive organ, the Panel considered it important to review both active and inactive ingredients in making a determination of safety and effectiveness.

The OTC drug review is limited to a review of active ingredients. Accordingly except for those cases in which a Panel has recommended specific final formulations, only active ingredients have been included in a monograph. Therefore, the Panel's recommendations concerning inactive ingredients have not been included in the monograph. However, the agency recognizes the Panel's concerns and invites specific comment on Part II. E. of the Panel's report (Formulation of OTC Ophthalmic Drug Products). After review of the comments submitted, the agency will address the inactive ingredient issue in the publication of the tentative final monograph and will make an initial determination at that time whether any or all of the Panel's recommendations concerning inactive ingredients should be included in the final monograph.

The Panel concluded that ocular anti-infectives could be generally recognized as safe and effective (Category I) "for the treatment of minor external infections of the eye," such as blepharitis, conjunctivities, and hordeolum (stye), because such infections are usually not serious and would not require attention by a physician. However, the Panel did not classify any ocular anti-infective active ingredients in Category I but did classify three ocular anti-infective active ingredients in Category III for reasons of safety and/or effectiveness. The Panel stated that the symptoms of minor infections amenable to OTC treatment are often similar to serious disorders that are not amenable to OTC treatment. The agency is concerned that, because the symptoms of minor and serious infections are often similar, there may be potential for serious harm to the eye if professional treatment is delayed. The agency has, therefore, made an initial determination that the benefits to be derived from the use of these drugs do not outweigh the risks, and it proposes to classify ocular anti-infectives in Category II in the tentative final monograph. The agency invites specific comments on this proposal.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the Panel and FDA have held as confidential all information concerning OTC ophthalmic drug products submitted for consideration by the Advisory Review Panel. All this information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after June 5, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

Based upon the conclusions and recommendations of the Panel, FDA proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (Category I), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph because the available data are insufficient (Category III) to classify such conditions either Category I or Category II will be the subject of a later notice. The status of Category III conditions after publication of a final order is the subject of the recent decision in *Culter* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). In that case, the court held that "FDA may not lawfully maintain Category III in any form in which drugs with Category III

conditions * * * are exempted from enforcement action." The agency is presently studying the effect of this decision on the OTC drug review procedures. Accordingly, although this document retains the concept of Category III in its original form, the agency's response to the court's decision may result in substantial changes in the regulatory treatment of Category III conditions.

In the **Federal Register** of January 5, 1972 (37 FR 85), the Commissioner announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. In the **Federal Register** of May 11, 1972 (37 FR 9464), the Commissioner published the final regulations providing for the OTC drug review under § 330.10 which were made effective immediately. Pursuant to these regulations, the Commissioner issued in the **Federal Register** of April 26, 1973 (38 FR 10306) a request for data and information on all active ingredients utilized in OTC ophthalmic drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report pursuant to § 330.10(a)(1) on the safety, effectiveness, and labeling of those products:

Philip Paul Ellis, M.D., Chairman; Joann Caccavale, R.Ph.; Donald E. Cadwallader, Ph.D.; Calvin Hanna, Ph.D.; William H. Havener, M.D.; James F. Koetting, O.D., Ph.D.; and Pearl Alexandrina Watson, M.D.

The Panel was first convened on September 10, 1973, in an organizational meeting. Working meetings were held on October 26 and 27, December 11 and 12, 1973; February 15 and 16, April 9 and 10, June 4 and 5, September 27 and 28, December 6 and 7, 1974; February 7 and 8, May 9 and 10, September 12 and 13 and October 24 and 25, December 12 and 13, 1975; February 12 and 14, April 9 and 10, June 25 and 26, October 15 and 16, December 3 and 4, 1976; February 4 and 5, March 25 and 26, June 3 and 4, September 16 and 17, 1977; February 3 and 4, April 7 and 8, June 2 and 3, September 15 and 16, December 15 and 16, 1978; and March 9 and 10, 1979. The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA–305), Food and Drug Administration (address above).

Three nonvoting liaison representatives served on the Panel. Stanley Kaplan, O.D., nominated by an ad hoc group of consumer organizations, served as the consumer liaison. William E. O'Malley, M.D., Ph.D., served as the industry liaison until April 1974 and was followed by Hugh A. Miller, M.D. Both were nominated by the Proprietary Association.

The following employees of FDA served with the Panel: Richard D. North, M.D., as Executive Secretary until April 1974, followed by K. C. Pani, M.D., until December 1975, followed by A. F. Scafadi, M.D.; John T. McElroy, J.D., as Panel Administrator; Lloyd G. Scott, R.Ph., as Drug Information Analyst until October 1973, followed by Thomas H. Gingrich, R.Ph., until September 1975, followed by Timothy T. Clark, R.Ph., until February 1978, followed by Donald Johnson, R.Ph., until February 1978, followed by Charma Konnor, R.Ph., until August 1978, followed by Chester G. Trybus.

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

Samuel B. Aronson, M.D.; Robert H. Becker; Vivian Boniuk, M.D.; Eugene A. Conrad, Ph.D.; Woody Davis, M.D.; Stuart Eriksen, Ph.D.; Miles Galin, M.D.; Harry W. Gordon, Ph.D.; Maurice Gordon; G. Peter Halberg, M.D.; Nancy C. Hall, Ph.D; Donald L. MacKeen, Ph.D.; Robert W. Morgan, M.D.; Russell E. Phares, Ph.D.; R. D. Poe, Ph.D.; Maurice Poster, O.D.; Paul Roberts, M.D.; Dennis Shepard, M.D.; Murry J. Sibley, Ph.D.; and Charles Tracy, M.D.

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

The Panel thoroughly reviewed the literature and data submissions, listened to additional testimony from interested persons, and considered all pertinent data and information submitted through March 10, 1979, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC ophthalmic drug products are set out in three categories:

Category I. Conditions under which OTC ophthalmic drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC ophthalmic drug products are not generally recognized as safe and effective or are misbranded.

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

I. Submission of Data and Information

Pursuant to the notice published in the **Federal Register** of April 26, 1973 (38 FR 10306) requesting the submission of data and information on OTC ophthalmic drugs, the following firms made submissions related to the indicated products:

A. Submissions By Firms

Firms	Marketed products
Abbott Laboratories, North Chicago, IL 60064	Clear Eyes, Lensine, Lensine Extra-Strength Cleaner for Contact Lenses, Murine.
Alcon Laboratories, Inc., Fort Worth, TX 76101	Alcon Contact Lens Wetting Solution, Contique Artificial Tears, Contique Contact Lens Wetting Solution, Contique Cleaning Plus Soaking Solution for Hard Contact Lenses, Contique Contact Lens Clean-Tabs, Contique Contact Lens Cleaning Solution, Contique Contact Lens Soakirig Tabs, Contique Contact Lens Soaking Solution, Contique Dual Wet Solution for Hard Contact Lenses, Estivin Ophthalmic Solution, Eye-Stream, Isopto-Frin Eye Drops, Isopto-Tears Lubricant Eye Drops (Isopto-Plain), Lens-Mate, Naphcon Decongestant Eye Drops, Op-Thal-Zin Astringent Eye Drops, Tears Naturale Solution, Ultra Tears Lubricant Eye Drops (Isopto-Alkaline), Zincfrin Eye Drops.
Allergan Pharmaceuticals, Irvine, CA 92664	Blink-N-Clean Contact Lens Solution, Lacri-Lube S.O.P., Lacril Artificial Tears, Liquifilm Contact Lens Wetting Solution, Liquifilm Tears Ocular Lubricant, Prefrin Liquifilm Eye Drops, Prefrin Z-Liquifilm Ophthalmic Solution, Pre-Sert, Total—the All-In-One Contact Lens Solution.
Barnes-Hind Pharmaceuticals, Inc, Sunnyvale, CA 94086.	Degest.
Burton, Parsons and Co., Inc., Washington, DC 20027.	Adsorbonac 2 percent, Adsorbonac 5 percent, Soothe.
Commerce Drug Co., Inc., Farmingdale, NY 11735	Ocu-Bath, Ocu-Drop, Ocu-Tact, Stye.
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927.	Argyrol S.S. 10 percent, Argyrol S.S. 20 percent, Goniosol, M-Z, Phenylzin, Tear-Efrin, Tearisol.
Flow Pharmaceuticals, Inc., Palo Alto, CA 94303	aqua-FLOW, Clerz, Comfy, d-FILM, duo-FLOW, hy-FLOW, Trilisol.
Julius Schmid, Inc., New York, NY 10019	Eye-Gene, Eye-Gene Eye Drops, Eye-Genic Eye Mist.
Norcliff-Thayer, Inc. (Formerly Mitchum Thayer), Tuckahoe, NY 10707.	Mitchum's Eye Drops (Formerly Duo-Eye Drops).
Norwich Pharmacal Co., Norwich, NY 13815	Ocusol Eye Drops, Ocusol Eye Lotion.
Pfizer, Inc., New York, NY 10017	Visine Eye Drops.
Riker Laboratories, Inc., Northridge, CA 91324	Bro-Lac, Op-Isophrin, Wet-Tone.
Sherman Laboratories, Inc., Metairie, LA 70005	Aqueo-Rinses, Dual-Clean, Pena-Vel, Stay-Brite, Stay-Wet, Velva-Kleen.
Softcon Products, Morris Plains, NJ 07950 (Formerly Professional Pharmacal Co., San Antonio, TX 78296).	Bufopto Zinc Sulfate ¼ percent, Efricel ⅛ percent, Methulose, Neozin Ophthalmc Solution, Visculose ½ percent, Visculose 1 percent.
SSS Co., Atlanta GA 30302	20/20 Eye Drops.
Wyeth Laboratories, Inc., Philadelphia, PA 19101	Collyrium with Ephedrine Soothing Eye Drops, Collyrium Soothing Eye Lotion.

In addition, the following firms or groups provided related information:

Firms	Submissions
Alcon Laboratories, Inc., Fort Worth, TX 76101	General guidelines applicable to the evaluation of lens care products; Comments, recommendations, and additional data on cleaning and wetting agents; Additional information on benzalkonium chloride; Collaborative study report on the effect of serum on the preservative effectiveness of hard contact lens solutions.
Allergan Pharmaceuticals, Irvine, CA 92664	Effectiveness data on polyvinyl alcohol as a wetting agent; Methodology for development and testing of safe and effective hard contact lens care products; Safety and effectiveness data on polyetheylene glycol 300, polyoxyl-40-stearate, and polysorbate-80 for use in hard contact lens cleaning products; Comments on warnings and labeling; Additional information on preservative information; Data on "Draize" testing.
Burton Parsons and Co., Inc., Washington, DC 20027.	Background information on lens cleaning solution.
Commerce Drug Co., Inc., Farmingdale, NY 11735	Additional data on mercuric oxide ophthalmic ointment.
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927.	Additional information on PEG; Additional information on mild silver protein; Additional information on flexibility of osmolarity range and PEG.
Ketchum Labs, Inc., Amityville, NY 11701	Comments on preservative test guidelines.
Norcliff Thayer, Inc., Tuckahoe, NY 10707	Safety protocol for 0.05% naphazoline.
Proprietary Association, Washington, DC 20006	Method of testing safety and effectiveness of lens cleaning solutions.
Schering Corp., Bloomfield, NJ 07003	Data on sulfacetamide sodium; Data on use of parabens as preservatives.
K. C. Tsou, Ph.D., University of Pennsylvania, Philadelphia, PA 19174.	Cytochemical methods for detection of corneal damage.
Warner-Chilcott Laboratories Morris Plains, NJ 07950.	In vitro procedure for evaluation of soft contact lens cleaners.

On May 28, 1976, the Medical Device Amendments of 1976 became law. This legislation amends the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 201 et seq.) and provides new authority to assure the safety and effectiveness of medical devices. Several products previously regulated as drugs that were under review by the Panel came within the definition of a medical device under these amendments. The Commissioner reviewed the products previously regarded as drugs and concluded in the **Federal Register** of December 16, 1977 (42 FR 63472) that the following product categories fall within the definition of a medical device: Ophthalmic lens cleaning (sterilizing) solutions and wetting agents for hard contact lenses.

In a notice published in the **Federal Register** of March 6, 1979 (44 FR 12270), FDA announced that it had transferred the responsibility for regulating OTC ophthalmic devices from the agency's Bureau of Drugs to its Bureau of Medical Devices. In addition, the notice announced that the Advisory Review Panel on OTC Ophthalmic Drug Products had summarized its findings and recommended that the Commisioner transfer to the Bureau of Medical Devices that portion of its report concerning products now regulated as medical devices, together with the data and information on those products submitted in response to the call for data notice (38 FR 10306).

It is possible that certain submissions fall within the purview of both the Bureau of Drugs and the Bureau of Medical Devices, depending on the claims associated with the product.

The following is a list of submissions, originally submitted to the Advisory Review Panel on OTC Ophthalmic Drug Products, that have been forwarded to the Bureau of Medical Devices:

Firms	Submissions
Abbott Laboratories, North Chicago, IL 60064	Lensine, Lensine Extra Strength Cleaner for Contact Lenses.
Alcon Laboratories, Inc., Fort Worth, TX 76101	Alcon Lens Wetting Solution, Contique Contact Lens Wetting Solution, Contique Cleaning Plus Soaking Solution for Hard Contact Lenses, Contique Contact Lens Clean-Tabs, Contique Contact Lens Cleaning Solution, Contique Contact Lens Soak-Tabs, Contique Contact Lens Soaking Solution, Contique Dual Wet Solution for Hard Contact Lenses, Total—the All-In-One Contact Lens Solution; Effectiveness data on polyvinyl alcohol as a wetting agent, Methodology for development and testing of safe and effective hard contact lens care products, Safety and effectiveness data on polyethylene glycol 300, polyoxyl-40-stearate, and polysorbate-80 for use in hard contact lens cleaning products; Comments on warnings and labeling, Additional information on preservative information.
Burton Parsons & Co., Inc., Washington, DC 20027.	Background information on lens cleaning solution.
Commerce Drug Co., Ind., Farmingdale, NY 11735.	Ocu-Tact.
Flow Pharmaceuticals, Inc., Palo Alto, CA 94303	Clerz, d-FILM, duo-FLOW, hy-FLOW, Trilisol.
Ketchum Labs, Inc., Amityville, NY 11701	Comments on preservative test guidelines.
The Proprietary Association, Washington, DC 20006.	Method for testing safety and effectiveness of lens cleaning solutions.
Riker Laboratories, Inc., Northridge, CA 91324	Wet Tone.
Sherman Laboratories, Inc., Metairie, LA 70005	Dual-Clean, Pena-Vel, Stay-Brite, Stay-Wet.
Warner-Chilcott Laboratories Morris Plains, NJ 07940.	Information on use of soft contact lens cleaners.

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel:*

Acetic acid
Alkyl dimethyl benzyl ammonium chloride
Antipyrine
Aromatics
Benzalkonium chloride
Benzethonium chloride
Berberine acid sulfate
Berberine hydrochloride
Berberine sulphate
Borax
Boric acid
Calcium chloride
Calcium disodium edetate
Camphor
Camphor water
Chlorobutanol
Chlorobutanol (chloral derivative)
Cod liver oil
Dextrose
Disodium edetate
Disodium edetate (EDTA)
Disodium ethylene diamine tetraacetate
Disodium ethylenediamine tetraacetate
Distilled extract of witch hazel
EDTA
Ephedrine
Ephedrine hydrochloride
Extract of witch hazel
Gelatin
Gelatin A
Glycerin
Hydrastine hydrochloride
Hydroxypropyl methylcellulose
Infusion of rose petals
Magnesium chloride
Methylcellulose
Methylparaben
Mild silver protein
Mineral oil
Naphazoline hydrochloride
Nonionic lanolin derivatives
Peppermint water
Phenylephrine hydrochloride
Phenylmercuric nitrate
Piperocaine hydrochloride
Polyethylene glycol 300
Polysorbate 80
Polyvinyl alcohol
Polyvinyl pyrrolidone
Polyvinylpyrrolidone
Potassium bicarbonate
Potassium carbonate
Potassium chloride
Propylparaben
Purified water
Rose and camphor water
Sodium acetate
Sodium bisulfite
Sodium borate
Sodium carbonate
Sodium carboxymethyl cellulose
Sodium chloride
Sodium citrate
Sodium edetate
Sodium ethylmercurithiosalicylate
Sodium hydroxide
Sodium propionate
Sorbic acid
Tetrahydrozoline hydrochloride
Thimerosal
Water soluble polymeric system
Water-soluble polymers
White petrolatum
Yellow mercuric oxide
Zinc sulfate (zinc sulphate)

2. *Ingredients reviewed by the Panel in addition to the submitted data.*

The Panel reviewed the following ingredients in addition to those contained in marketed products submitted to the Panel:

Anhydrous lanolin
Cetylpyridinium chloride
Chlorhexidine gluconate
Chlorhexidine hydrochloride
Dextran 70
Hydrochloric acid
Hydroxyethylcellulose
Lanolin
Light mineral oil
Oil of peppermint
Oil of rose geranium
Paraffin
Peppermint Oil
Phenylethyl alcohol
Phenylmercuric acetate
Phosphoric acid
Polyethylene glycol 400
Potassium borate
Potassium citrate
Potassium phosphates:
  Dibasic potassium phosphate
  Monobasic potassium phosphate
  Tribasic potassium phosphate
Propylene glycol
Rose geranium oil (African)
Rose water
Sodium benzoate
Sodium bicarbonate
Sodium biphosphate
Sodium metabisulfite
Sodium phosphate
Sodium sulfacetamide
Sodium thiosulfate
Thiourea
Tri-sodium edetate (monohydrate)
White ointment
White wax
Witch hazel water

C. Classification of Ingredients

1. *Active ingredients.* In order to simplify the review of OTC ophthalmic drug products, the Panel has classified the various active ingredients into seven different pharmacologic groups. The Panel has used this pharmacologic group classification throughout the document. A discussion on the pharmacology of these groups is included below. (See part II. paragraph C. below—Pharmacology of OTC Ocular Ingredients.)

Ocular Anesthetics

Antipyrine
Piperocaine hydrochloride

Ocular Anti-Infectives

Boric acid
Mild silver protein
Sulfacetamide sodium
Yellow mercuric oxide

Ocular Vasoconstrictors

Sympathomimetic amines:
  Ephedrine hydrochloride (ephedrine)
  Naphazoline hydrochloride
  Phenylephrine hydrochloride
  Tetrahydrozoline hydrochloride

Ocular Astringents

Infusion of rose petals
Zinc sulfate (zinc sulphate)

Ocular Hypertonicity Agent

Sodium chloride

Ocular Demulcents

Cellulose derivatives:
  Carboxymethylcellulose sodium (sodium carboxymethylcellulose)
  Hydroxyethylcellulose
  Hydroxypropyl methylcellulose
  Methylcellulose
Dextran 70
Geltain
Polyols, liquid:
  Glycerin
  Polyethylene glycol 300
  Polyethylene glycol 400
  Polysorbate 80
  Propylene glycol
Polyvinyl alcohol
Povidone (polyvinyl pyrrolidone, polyvinylpyrrolidone)

Ocular Emollients

Lanolin preparations:
  Anhydrous lanolin
  Lanolin
  Nonionic lanolin derivatives (petrolatum and lanolin alcohol)
Oleaginous ingredients:
  Light mineral oil
  Mineral oil
  Paraffin
  White ointment
  White petrolatum
  White wax

2. *Inactive ingredients.* The Panel reviewed all inactive ingredients and has further classified them as to their suitability for inclusion in OTC ophthalmic preparations. (See part II. paragraph E. below—Formulation of OTC Ophthalmic Drug Products.) The Panel recognizes that some of the ingredients in the inactive list below are also included in the list of active ingredients above. These ingredients, which the Panel has classified as active demulcents and emollients, traditionally have been considered inactive because they are included in ophthalmic preparations as formulation agents, i.e., ointment bases and viscosity agents. However, the Panel believes that these same ingredients can also function as therapeutically active ingredients at the same concentrations commonly used as formulation aids. Both ocular demulcents and ocular emollients can relieve the discomfort occurring from exposure, dryness, and minor irritations, and can protect the eye from further

irritation. Ocular demulcent preparations can also relieve the burning and irritation caused by dry eye and are often used as tear replacements. Therefore, the Panel concludes that these ingredients will be considered as inactive only when used in OTC ophthalmic products as formulation agents and when no labeling claims are made for them. However, if a product makes demulcent or emollient claims for these ingredients as discussed in the labeling section included later in this document, the ingredients will be considered active. (See part II. paragraph G. below—Labeling of OTC Ophthalmic Drug Products.)

The following is a list of inactive ingredients that were submitted to the Panel:

Acetic acid
Aromatic preservative ophthalmic (aromatics)
Benzalkonium chloride (alkyldimethylbenzylammonium chloride)
Benzethonium chloride
Berberine preparations:
  Berberine bisulfite (berberine acid sulfate)
  Berberine hydrochloride
  Berberine sulfate (berberine sulphate)
Boric acid
Calcium chloride
Camphor preparations:
  Camphor
  Camphor water
Cellulose derivatives:
  Carboxymethylcellulose sodium (sodium carboxymethylcellulose)
  Hydroxyethylcellulose
  Hydroxypropyl methylcellulose
  Methylcellulose
Cetylpyridinium chloride
Chlorhexidine gluconate
Chlorhexidine hydrochloride
Chlorobutanol (chlorobutanol, chloral derivative)
Cod liver oil
Dextran 70
Dextrose
Edetic acid preparations:
  Edetate calcium disodium (calcium disodium edetate)
  Edetate disodium (disodium edetate, ETA, disodium ethylene diamine tetraacetate, disodium ethylenediamine tetraacetate)
  Edetate sodium (sodium edetate)
  Edetate trisodium (tri-sodium edetate (monohydrate))
  Edetic acid (EDTA)
Gelatin
Geranium oil, Algerian (oil of rose geranium; rose geranium oil, African)
Hydrastine hydrochloride
Hydrochloric acid
Lanolin preparations:
  Anhydrous lanolin
  Lanolin
  Petrolatum and lanolin alcohol (nonionic lanolin derivatives)
Magnesium chloride
Oleaginous ingredients:
  Light mineral oil
  Mineral oil
  Paraffin
  White ointment
  White petrolatum
  White wax
Parabens:
  Methylparaben
  Propylparaben
Peppermint preparations:
  Peppermint oil (oil of peppermint)
  Peppermint water
Phenylethyl alcohol
Phenylmercuric acetate
Phenylmercuric nitrate
Phosphoric acid
Polyols, liquid:
  Glycerin
  Polyethlene glycol 300
  Polyethylene glycol 400
  Polysorbate 80
  Propylene glycol
Polyvinyl alcohol
Potassium bicarbonate
Potassium tetraborate (potassium borate)
Potassium carbonate
Potassium chloride
Potassium citrate
Potassium phosphates:
  Dibasic potassium phosphate
  Monobasic potassium phosphate
  Tribasic potassium phosphate
Povidone (polyvinyl pyrrolidone, polyvinylpyrrolidone)
Propylene glycol
Purified water
Rose and camphor water
Sodium acetate
Sodium benzoate
Sodium bicarbonate
Sodium biphosphate
Sodium bisulfite
Sodium borate (borax)
Sodium carbonate
Sodium chloride
Sodium citrate
Sodium hydroxide
Sodium metabisulfite
Sodium phosphate
Sodium propionate
Sodium thiosulfate
Sorbic acid
Stronger rose water (rose water)
Thimerosal (sodium ethylmercurithiosalicylate)
Thiourea
Water soluble polymeric system
Water-soluble polymers
Witch hazel water (distilled extract of witch hazel, extract of witch hazel)

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of April 26, 1973 (38 FR 10306). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after June 5, 1980, in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions

The Panel adopted the following definitions related to use of OTC ophthalmic products:

1. *Adjuvant.* Any component added to a drug product to facilitate, modify, increase, or enhance the action or the effectiveness of the principal ingredient(s).

2. *Anti-infective.* A therapeutic agent which destroys or limits the multiplication of micro-organisms.

3. *Antioxidant.* A substance which reduces the determination of a product resulting from interaction of a drug with oxygen.

4. *Astringent.* A locally acting pharmacologic agent which, by precipitating protein, helps to clear mucus from the outer surface of the eye.

5. *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.

6. *Decongestant.* An agent that reduces swelling and redness of the mucous membranes of the eye.

7. *Demulcent.* An agent, usually a water-soluble polymer, that coats mucous membrane surfaces.

8. *Emollient.* An agent, usually a fat or oil, which is applied locally to eye lids to protect or soften tissues and to prevent drying and cracking.

9. *Eye wash, eye lotion, irrigating solution.* A sterile aqueous solution containing no active ingredients, intended for bathing or mechanically flushing the eye.

10. *Hypertonicity agent.* A drug 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 hgypertonicity agent creates an osmotic gradient which draws water out of the cornea.

11. *Ointment adjunct.* A substance used to aid in the formulation of an ointment.

12. *Ointment base.* A semisolid vehicle, to which medicinal substances may be added. It is not usually considered an active ingredient unless used for lubrication or as an emollient.

13. *Ophthalmic ointment.* A sterile semisolid dosge form that may or may not contain an active ingredient for use in the eye.

14. *Ophthamic solution ("eye drops").* A sterile aqueous solution of electrolytes, polymers, drugs, and other substances intended for application into the cul-de-sac, that is, the space between the eyeball and eyelids.

15. *Preservative.* An agent which is added to a product for the purpose of inhibiting the growth of micro-organisms in the product, thereby helping to maintain sterility during use.

16. *Stabilizer.* An agent used to prevent or delay chemical deterioration of a product.

17. *Tear replacement, tear substitute.* 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.

18. *Topical anesthetic agent.* An agent that produces a variable reduction or loss of sensation when applied to surface tissue of the eye.

19. *Vasoconstrictor.* A pharmacologic agent which, when applied topically to the mucous membranes of the eye, causes transient constriction of conjuctival blood vessels.

20. *Viscosity agent.* A water-soluble substance that decreases the fluidity (flow) of an aqueous system; it may mechanically lubricate and protect surfaces of the eye, or prolong the contact of a product on the eye.

B. *Anatomy and Physiology of the Eye*

The Panel includes the following discussion of the anatomy and physiology of the eye as a practical orientation to the uses of OTC opthalmic medications. This discussion is based on a review of several sources (Refs. 1 through 7).

The eye is the organ of sight. The spherical eyeball is suspended in the orbital cavity by muscles and ligaments and cushioned by fat and connective tissue. Blood vessels and nerves are also present in the orbit. The wall of the eyeball, or globe, is composed of three main layers of tissues from outside inward, i.e., the sclera, the uvea, and the retina.

The sclera, or white of the eye, is a tough, fibrous tissue which has very few blood vessels. The sclera surrounds two-thirds of the globe and is continuous with the cornea which covers the remaining third of the eye. The cornea is a clear transparent tissue that covers the front portion of the globe. The normal cornea is devoid of blood vesels but is well supplied with sensitive nerve fibers which makes it one of the most sensitive parts of the body's surface.

The uvea consists of the iris, the ciliary body, and the choroid which are continuous from front to back. These tissues are vascular and contain pigment cells of the eye. The retina is composed mainly of nervous tissue and is a lining for much of the interior surface of the eyeball. Light entering the eye stimulates photoreceptors located in the deep layers of the retina. Electrical-chemical changes occur resulting in nerve stimulation which is conducted to the ganglion cells located in the inner layers of the retina. From here the nerve impulse is transmitted via the nerve fiber layer of the retina, back through the optic nerve and visual pathways in the brain, to the occipital lobes, or posterior portion, of the brain which is the visual center.

The optical apparatus of the eye consists of the cornea and the lens. Layers of clear fluid, known as aqueous humor, and a gel-like material, known as vitreous humor, are between the solid structures. Aqueous humor is located between the cornea and the anterior surface of the lens-iris diaphragm. Vitreous humor is located between the posterior surface of the lens and the inner surface of the retina. The cornea, the lens, and the fluid compartments are avascular and exchanges of substances in these areas take place mainly by diffusion. The iris is a contractile membrane that controls the size of the pupil by dilation or constriction.

The conjunctival membrane covers the outer surface of the white portion of the eye and the inner surfaces of the eyelids. The membrane is loosely attached and permits free movement of the eyeball by the extraocular muscles located in the orbit and attached to the globe. The conjunctiva and the cornea are the most exposed portions of the eyeball.

The eye is mechanically protected by the eyelids and eye lashes. Special nerves and muscles in the eyelids operate the blink reflex. The eyelids also help to provide optimum fluid conditions for the cornea by preventing excessive loss of tear fluid. The eyelids are lubricated and kept moist by the secretions of the lacrimal and sebaceous glands. The inner eyelid surfaces form pocket-like extensions upward and downward; these spaces are called the conjunctival cul-de-sacs.

Tear fluid is produced by the lacrimal, sebaceous, and mucous glands of the eye. Tears are a complex mixture of electrolytes, proteins, carbohydrates, organic acids, mucous, water, oil, and enzymes (lysozyme). The tears are approximately 0.7 percent protein (e.g., mucin, albumin), and their total solids content is about 1.8 percent. The osmotic concentration of the tears is equal to 0.9 percent sodium chloride, and the pH is slightly alkaline. The surface of the eyeball and the cornea are normally moist at all times because of the flow of tears over the surface. The functions of the tears include nutrition, metabolism, secretion, waste-carrying, maintenance of optical clarity, and antibacterial action. Tears flow over the corneal surface, collect in the cul-de-sac, and are drained through openings known as puncta, located in the inner corners of the eyelids. This lacrimal drainage system, consisting of canaliculi, the lacrimal sac, and the naso-lacrimal duct, allows the tears to flow into the nasal cavity. Much of any ophthalmic solution preparation instilled into the cul-de-sac drains into the nasal cavity via the lacrimal drainage system, and the remaining solution is diluted by the continuous replenishment of tears, also termed tear turnover.

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C. Disorders of the Eye That May Be Treated With Ophthalmic Drug Products

1. *Ocular disorders and symptoms amenable to OTC therapy.* There are very few disorders of the eye which are amenable to treatment with OTC ocular preparations. For the most part, OTC ophthalmic ingredients relieve symptoms of eye disorders and do not have any truly curative effect. However, these preparations do appear to have beneficial effect beyond symptomatic relief in some conditions of tear insufficiency and inflammation.

The usual etiologies of disorders for which OTC opthalmic medications can be used are certain physiological changes and irritation resulting from foreign material and allergens.

One of the major problems with the use of OTC opthalmic medications is that the diagnosis of disorders for which such medications can be used is usually a self-diagnosis, generally based on trial and error. A wrong self-diagnosis can lead to exacerbation of symptoms or worsening of the disorder itself through improper treatment. Allergic reactions to OTC ophthalmic ingredients or to preservatives incorporated in their vehicles may occur, also exacerbating symptoms. Untoward ocular or nonocular side effects may occur due to preexisting conditions or other medications being used simultaneously. Therefore, the Panel believes that labeling of OTC ophthalmic preparations (except for hypertonicity and eye wash products) should alert the consumer to the consequences of misdiagnosis by warning that the unsupervised use of these products is limited to 72 hours. The warning should also state that if symptoms worsen or persist the medication should be discontinued and a physician should be consulted at once.

The following are disorders of the eye which OTC ophthalmic drug products can be used to treat:

a. *Tear insufficiency.* Tear insufficiency may produce symptoms of minor eye irritation such as burning, redness, and foreign body sensation. OTC ocular demulcents and emollients are useful to relieve the discomfort and "dry eye" feeling associated with minor eye irritations. The Panel has further discussed eye irritation below. (See part II, paragraph C.1.c. below—Inflammation and irritation of the eye.)

Tear insufficiency also produces a feeling of dryness, burning, foreign body sensation, and signs of irritation, such as chronic redness, and at times punctate epithelial erosions of the cornea and conjuctiva (Ref. 1). Tear insufficiency can result from occlusion of the ducts of the lacrimal gland following such ocular diseases as trachoma, chemical burns, and erythema multiforme, and other conditions such as atrophy of the lacrimal gland. Decreased tear formation may be associated with aging. Tear production is greatly reduced in keratoconjunctivitis sicca and Sjogren's syndrome.

The prognosis and treatment of tear insufficiency disorders depends upon causative factors and the individual case. Professional diagnosis and management are usually indicated, although treatment may involve long-term use of OTC preparations.

Rational formulations of products used to treat tear insufficiency are aqueous solutions containing demulcent agents, tonicity agents, and pH and buffering agents. These ingredients establish the appropriate fluidity, tonicity, and pH of natural tears. There are no prescription products containing ingredients superior in effectiveness to those used in OTC preparations.

The use of OTC products in treating a dry eye without professional diagnosis can permit the exacerbation of an underlying condition through delayed medical attention. Therefore, the Panel concludes that directions suggesting long-term use should be limited to professional labeling and should not be part of OTC labeling. 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 warning that professional consultation should be sought if symptoms persist for more than 72 hours.

(1) *Keratoconjunctivitis sicca.* Keratoconjunctivitis sicca is a disorder of decreased tear secretion. It is characterized by formation of filaments of corneal epithelium and mucus and at times keratinization of the cornea. The latter can result in visual loss. Symptoms include burning, a feeling of fullness, and a gritty foreign body sensation (Ref. 2). Environmental factors, such as heat or wind, which increase the evaporation of tears, exacerbate these symptoms (Ref. 1).

Keratoconjunctivitis sicca can be caused by certain ocular diseases which cause a scarring of the ducts of the lacrimal gland blocking the secretion of fluid, by Sjogren's syndrome, by vitamin A deficiency, and by atrophy of the lacrimal gland (Ref. 2).

Keratoconjunctivitis sicca is amenable to treatment with OTC products that have the wetting, protecting, and lubricating properties of tears (Ref. 3).

Nevertheless, the use of tear substitutes alone in the treatment of keratoconjunctivitis sicca may afford incomplete treatment. In some cases, soft contact lenses used in addition to aqueous tear substitute products may be helpful. Surgery to close the inferior puncta and to lessen drainage of tears or adhesions of the lid margins may be indicated (Ref. 4).

(2) *Sjogren's syndrome.* As noted above, a principal cause of keratoconjunctivitis sicca is Sjogren's syndrome. This is a disorder which occurs primarily in women during the postmenopausal years and is accompanied by xerostomia (dryness of the mouth) and rheumatoid polyarthritis (Refs. 5, 6, and 7). In addition to the other signs and symptoms of a dry eye, chronic conjunctivitis and keratitis are frequently encountered. Additional signs and symptoms of keratoconjunctivitis sicca may be present to a greater of lesser degree (Ref. 5). Sjogren's syndrome may be in auto-immune collagen disease which results in lesions of the lacrimal gland (Refs. 5, 6, and 8). Its course is characterized by minor remissions and exacerbations for the life of the individual (Ref. 9).

In general, management of the disorder includes professional diagnosis and observation, especially in the event that medical or surgical intervention over and above the use of tear substitutes might be indicated. Symptomatic relief, protection, and lubrication of the eye are usually provided by OTC products. Prolonged treatment, however, should be based on professional advice and monitoring.

(3) *Dry eye in the elderly.* Clinical observation and studies of tear production and tear film breakup time indicate that there is a decrease in tear secretion associated with aging. In the elderly, there is an increased incidence of the signs and symptoms of a dry eye which may or not develop into keratoconjunctivitis sicca (Refs. 10 through 13). Tear formation may be sufficient during sleep when closed eyelids prevent tear evaporation, but it is insufficient during the day to moisten the corneal surface properly (Ref. 3).

The disorder may stabilize or become progressively worse. Under professional direction, it is amenable to treatment with OTC tear substitute products (Refs, 3, 14, and 15). Indeed, unless additional treatment such as soft contact lenses or

surgery is indicated (Refs. 1 and 16), OTC tear substitute products provide the most desirable and effective treatment (Refs 1, 15, and 17).

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b. *Corneal edema.* Corneal edema is a disorder in which the water content of the cornea increases, thereby producing swelling and a variable loss of transparency (Ref. 1). In milder corneal edema, symptons are limited to complaints of foggy vision and "halos" around lights. However, blebs (fluid beneath or within the epithelium) may form and cause photophobia and irritation. The blebs may break, giving rise to an excruciating pain resembling foreign body sensation (Ref. 2). Corneal edema may result from several ocular disorders including glaucoma, degeneration of the cells lining the back of the cornea (endothelium), iritis, prolonged contact lens wear, corneal inflammation, and infection (Ref. 3).

In general, the treatment of corneal edema involves management of the underlying primary disorder. Temporary dehydration of the cornea may follow application of hypertonicity agents (Ref. 4). Hypertonicity agents cause water to flow from the cornea into the tear film layer which in turn is drained through the lacrimal drainage system. This results in some dehydration of the cornea. Treatment of underlying causes may be as involved as the use of anti-infectives or surface debridement in cases of bacterial corneal or herpes simplex ulcers. Control of the underlying glaucoma may reduce corneal edema (Refs. 5, 6, and 7). Thus, the treatment of corneal edema is much more complex than the simple temporary dehydration of the cornea and the relief of symptoms of blurred vision. In all cases, professional diagnosis is indicated, even if subsequent treatment should be limited to the application of OTC hypertonic solutions.

The most commonly used hypertonicity agent in OTC products is sodium chloride, either a 2- or 5-percent solution. Although other hypertonicity agents are available, they appear to have no advantages over sodium chloride. Furthermore, use of other hypertonicity agents could be accompanied by irritation or allergic reaction.

Since proper treatment of corneal edema must include management of primary causes, the use of hypertonic solutions by the consumer for blurred vision, irritation, pain, and other symptoms of corneal edema without professional diagnosis and direction could lead to an exacerbation of an underlying disorder. For example, complaints of blurred vision or pain might be indicative of serious ocular disorders, such as glaucoma or corneal ulcer, which would require immediate medical attention.

Labeling of the product must be limited to a simple statement that it is a "hypertonic solution for temporary relief of corneal edema." There should be warnings that the product itself may cause irritation and redness, and that the product should not be used except under the advice and supervision of a physician.

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c. *Inflammation and irritation of the eye*—(1) *General discussion.* The exterior surface of the eye is made up of the thin and transparent cornea and the thin, flexible, mucin-producing conjunctiva which covers the sclera and lines the eyelids. The cornea and cojunctiva are kept moist and lubricated by the tears and mucin (Ref. 1), and the conjunctiva and lid are nourished by underlying blood vessels. The external eye tissues respond to irritants and noxious products in the environment with the prodjction of copious tears. However, when the noxious products are not sufficiently diluted by the tears, the ocular tissues respond by tissue edema (swelling), dilation of the underlying blood vessels (hyperemia or "red eye"), and the migration of white blood cells to the area. Sometimes it takes only minutes for the exterior of the eye to respond violently to noxious agents, and if this response is severe enough the subject should consult a physician for treatment.

Minor reaction of the eye to noxious agents may be recognized as ocular itching, tearing, and smarting, burning sensation. Sometimes this minor ocular irritation can be alleviated by the use of buffered, neutral aqueous eye drops, eye lotions, eye washes, or irrigating solutions. Astringents, demulcents, and emollients may also be used to provide symptomatic relief. If redness is present along with irritation, the condition may be alleviated by using aqueous eye drops containing low concentrations of vasoconstrictors.

The symptoms of conjunctival irritation and inflammation may also result from trauma, severe infection, allergic reaction, or increased intraocular pressure (Refs. 2 and 3). In addition, overuse of ophthalmic

solutions may dilute the tears and mucin, which are the first line of defense of the eye, leading to further inflammation and irritation. Therefore, the Panel recommends that labeling of OTC products used to treat the symptoms of inflammation and irritation should warn the consumer to discontinue use of the products and consult a physician if symptoms persist for more than 72 hours.

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(2) *Specific conditions of inflammation and irritation which are amenable to OTC treatment*—(i) *Presence of loose foreign material in the eye.* Loose foreign material inside the eyelids can cause an ocular infection or inflammation with symptoms of redness, localized swelling, mucus discharge, and tearing. The presence of foreign material in the eye can also result in blepharospasm (uncontrolled blinking and closing of the eyelids); a foreign body sensation; and symptoms of irritation—discomfort, burning, stinging, smarting, and itching. Foreign material may be present in an undissolved form, such as an eyelash or dirt, or it may enter into solution or suspension with the tears.

Provided the eye is not damaged by such debris, the relief of symptoms occurs with removal of the causative substance. Treatment consists of flushing the exposed eye and conjunctival sacs with an irrigating solution (eye wash) to flush away tangible foreign material and substances dissolved or suspended in the tears. A rational formulation for an irrigating solution (eye wash) includes water, tonicity agents to establish isotonicity with tears, agents for establishing pH and buffering to achieve the same pH as tears, and preservatives.

If signs and symptoms do not rapidly disappear following use of an irrigating solution, either ocular damage has occurred, all foreign material has not been removed, or the condition is not due to foreign material. Professional attention is then indicated to determine etiology and introduce appropriate treatment.

Many of the symptoms of irritation, including a foreign body sensation, occur with various disease conditions of the anterior eye, such as conjunctivitis, keratitis, and blepharitis. There is little danger of such disorders becoming exacerbated through use of irrigating solutions alone. However, exacerbation of the undelying condition through delayed professional attention is a distinct possibility. Labeling of irrigating solutions should include the warning that if signs and symptoms continue, professional attention is indicated.

(ii) *Irritation from airborne pollutants and chlorinated water.* Symptoms of irritation can occur as a result of direct stimulation of the eye by gases, smoke, and other airborne pollutants and chlorinated water during swimming. Gases and minute particulate matter enter into solution or suspension with the tears, resulting in a direct irritating effect to the eye and changes in the composition, tonicity, and pH of the tears—all of which can lead to sensations of irritation. Such irritation can result in inflammation and secondary infection of the conjunctiva resulting in a red eye.

Management consists of avoiding the offending allergens and the use of vasoconstrictors, astringents, demulcents, and emollients for symptomatic relief of irritation.

Inasmuch as a multitude of both internal and external diseases of the eye can result in sensations of irritation and signs of inflammation, there exists the distinct possibility that an individual might mistakenly use such products for symptomatic relief of infectious diseases or those of physiological or other origin (e.g., glaucoma). Therefore, labelig must emphasize this concept and warn the user that persisting signs and symptoms require a professional evaluation. If corneal permeability of the eye is sufficiently increased, there is a possibility that mydriasis (dilation of the pupil) could be produced by even low concentrations of vasoconstrictors. Because this mydriasis could percipitate an angle closure glaucoma in susceptible individuals, labeling of OTC ocular vasoconstrictors must also warn the consumer who has been diagnosed as having glaucoma to use these medications only under the advice and supervision of a physician.

(iii) *Allergic conjunctivitis.* Mild allergic conjunctivitis, or inflamation of the conjunctiva, occurs as an immediate type of allergic reaction (Ref. 1).

Edema and congestion are slight. However, the conjunctiva may have a glassy appearance and a slight redness in both its palpebral and bulbar aspects (Refs. 1 and 2). Symptoms of allergic conjunctivitis include itching, burning, photophobia, and watering eyes (Refs. 1, 2, and 3). The condition typically results from exposure to airborne allergens, including pollens, dusts, mold spores, and animal hairs or feathers (Ref. 1). It persists in the presence of the causative allergens and, unless the allergen can be determined and avoid, recurrence is common.

Treatment varies, depending upon the severity of the condition. Topically applied vasoconstrictors and astringents, systemic antihistamines, topical corticosteroids (in more severe cases), and cold compresses may be indicated for treatment. Only in mild cases, in which edema and congestion are slight, is the condition optimally treated with OTC ingredients alone. Such treatment, of course, is primarily for symptomatic relief.

Rational OTC formulations used for allergic conjunctivitis include vasoconstrictors or astringents or a combination of these to reduce the redness, possibly to reduce some swelling, and to precipitate mucus. In mild cases, this is the treatment of choice, whether achieved through self-medication or under professional direction. Demulcents and emollients will aid in relieving discomfort. However, if the signs and symptoms of allergic conjunctivitis are not completely ameliorated through the use of these products, medical consultation is indicated for possible antihistaminic or corticosteroid therapy. Labeling should so warn the consumer.

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2. *Ocular disorders not amendable to OTC therapy*—a. *Embedded foreign body.* A foreign body, such as a particle of metal or airborne debris, especially if embedded in the cornea, may give rise to only minimal signs and symptoms. As is witnessed in the case of wearers' adaptation to contact lenses, the cornea has a remarkable capacity for accepting continued stimulation with an associated decrease in sensation over a period of time. While redness of the eye and sensation of foreign matter in the eye caused by a foreign body may appear to improve with use of an OTC ophthalmic drug product, the foreign body should be removed to prevent further damage to the eye.

b. *Uveitis.* Uveitis includes various conditions of inflammation of the iris, ciliary body, and choroid which have a common blood supply. Types of uveitis

(i.e., iritis, cyclitis, and choroiditis) can be due to numerous causes including trauma (injury), endogenous introduction of inflammatory substances via the circulation (with or without systemic disease), associated intraocular conditions (such as neoplasms), and idiopathic states (Ref. 1).

Although more severe cases of uveitis may be accompanied by abnormalities such as distorted shape of the pupil, pain, photophobia, and decreased vision, the condition can be manifested in early stages simply as a ciliary type of infection (i.e., a redness of the eye primarily encircling the cornea) (Refs. 2 and 3). Such an eye could be considered treatable with an OTC ophthalmic drug product by an uninformed user. All types of uveitis are serious conditions requiring ophthalmologic treatment.

c. *Glaucoma.* Glaucoma is a disease of increased intraocular pressure which can damage the optic nerve and lead to blindness. The aqueous humor (watery fluid within the anterior chamber of the eye) is continually secreted by the ciliary body and circulates through the anterior chamber of the eye, passes through the trabeculum (the meshwork in the far recess of the anterior chamber) into Schlemm's canal, and then into venous channels. In glaucoma, there is an inadequate drainage of aqueous humor, which results in an increased pressure within the eye.

The two primary types of glaucoma are open- and narrow-angle glaucoma. Open-angle glaucoma (chronic glaucoma) has been reported to occur in 1 out of every 40 individuals in the United States over the age of 40 (Ref. 4). Narrow-angle glaucoma, also known as irris block, angle closure, or acute congestive glaucoma, is far less frequently encountered. In chronic glaucoma, the trabeculum is not blocked by the peripheral iris but there is an inadequate drainage of aqueous humor (Ref. 5). In narrow-angle glaucoma, there is a preexisting shallowing of the anterior chamber angle. As a result, the peripheral iris may come in contact with the trabeculum, thereby blocking drainage of aqueous humor (Ref. 6). An attack of narrow-angle glaucoma can be precipitated through dilation of the pupil.

Although chronic glaucoma is characterized by relatively few, if any, symptoms (Ref. 6), in narrow-angle glaucoma the eye may appear red during certain periods of elevated pressure. This could lead a person who is susceptible to narrow-angle glaucoma to seek an OTC remedy such as a vasoconstrictor in an attempt to eliminate redness. Prolonged use of such medications in the presence of glaucoma would result in delayed medical treatment.

Equally important, as indicated above, is dilation of the pupil, which may precipitate attacks of narrow-angle glaucoma (Ref. 6). In acceptable concentrations in eyes with intact corneal epithelium, sympathomimetic drugs used as vasoconstrictors rarely produce mydriasis, or dilated pupil. However, in susceptible persons, use of OTC vasoconstrictors could cause dilation of the pupil and precipitate attacks of narrow-angle glaucoma. Therefore, the Panel recommends the inclusion of a glaucoma warning on OTC ocular vasoconstrictor preparations.

d. *Flash-burns.* Radiation burns from arc welding may occur when the eyes are improperly protected from ultraviolet rays which are readily and largely absorbed by the corneal epithelium. This results in a superficial keratisis (inflammation of the cornea) which may not show gross signs of inflammation, such as a red eye. At times, however, there are associated burns of the face and eyelids (Ref. 7). Three to 6 hours following exposure, symptoms of extreme discomfort are reported, including burning and a sensation of "sand" in the eye (Refs 1, 4, and 8). The condition is entirely self-limiting.

Treatment consists of antibiotics and cycloplegics, patching of the eye, and systemic analgesics (Ref 9). Thus, flash-burns are not amendable to self-medication or treatment with OTC ingredients. The chronic use of topically applied local anesthetics can lead to delayed healing of the cornea and the possibility of corneal ulcer (Ref. 10).

e. *Tear duct infections.* Tear duct infections are quite rare, particularly in adults. Symptoms consist of tearing, mucopurulent discharge, acute swelling, and redness and tenderness over the inner corner of the eye and bridge of the nose. These infections should be treated by an ophthalmologist.

f. *Corneal ulcers.* Infection of the cornea with subsequent ucler formation may follow injury or conjunctivitis, or may be associated with systemic infection. The infections may be either bacterial, viral, or fungal in origin. Corneal ulcers are usually quite painful and often reduce vision. The eye is usually quite red. Corneal ulcers are serious ocular disorders and should be treated promptly by an ophthalmologist.

g. *Professional examination.* There are certain procedures used in professional eye examination which require the use of viscous fluids to separate the examination instruments from the surface of the eye and to establish an ocular seal. Typical formulations include viscosity agents, such as hydroxyethylcellulose, hydroxypropyl methylcellulose, and methylcellulose in aqueous solutions. These ingredients have an OTC use as tear substitute products. However, labeling instructions for professional examination products containing these ingredients will be restricted to professional labeling only, as professional examination is not an OTC indication.

(1) *Gonioscopy.* Gonioscopy is a technique for examining the recesses of the anterior chamber (angle structure) of the eye. It is used for differentiating narrow-angle from wide-angle glaucoma and for detecting foreign bodies, tumors, and debris in the angle. Examination consists of the application to the anesthetized cornea of a diagnostic contact lens containing a viscous fluid on the inner surface of the lens (Ref. 11).

(2) *Electroretinography.* With this technique, retinal function can be evaluated in patients with certain retinal degenerations, choroidemia (progressive atrophy of the choroid and pigment epithelium), circulatory diseases, and opaque media (e.g., cataract). Electroretinography may also be used in infants and children suspected of having decreased vision but who are not old enough for subjective testing. The evaluation of retinal function is accomplished through the recording of electrical potentials from the eye by means of appropriately placed electrodes. The electrode that is placed on the eye itself is placed in juxtaposition to the cornea in a modified haptic contact lens. Viscosity agents are used to establish an ocular seal between the eye and the haptic shell and to protect the cornea from abrasion caused by the electrodes or other parts of the shell (Ref. 12).

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3. *Ocular disorders which might be amenable to OTC therapy.* The Panel believes that certain minor external ocular infections would be amenable to treatment with OTC drug products. However, the Panel recognizes that at the present time there are no anti-infective active ingredients that can be generally recognized as safe and effective. The following are external ocular infections which the Panel believes might be amenable to OTC therapy:

a. *Hordeolum (stye).* Hordeolum is a staphylococcal abscess of the sebaceous glands of the lid margin. Symptoms consist of localized tenderness, redness, and swelling. Occasionally styes point toward the inside of the eyelid (internal stye). Treatment consists of applying warm moist compresses and the instillation of ophthalmic anti-infective preparations several times a day during the acute stages. Recurrences are frequent.

b. *Blepharitis (granulated eyelids).* Blepharitis may be due to seborrhea (dandruff), staphylococcal infections, or to a combination of the two. The symptoms of blepharitis are redness, burning, itching, and crusting of the lid margins. In the staphylococcal type, the scales are dry, and small ulcerative lesions of the skin are observed. In the seborrheic type, the scales are oily, and seborrhea of the scalp is usually present as well. Medical treatment of staphylococcal blepharitis consists of the instillation of an anti-infective ophthalmic ointment into the eye three or four times a day, continued for a week or so after symptoms have disappeared. The treatment of seborrheic blepharitis consists of controlling any existing scalp dandruff, removing scales along the lid margin with a moist cotton applicator, and instilling an anti-infective ophthalmic ointment.

c. *Conjunctivitis ("pink eye").* Conjunctivitis may be due to bacterial infections, viral infections, or allergies. The symptoms of conjunctivitis consist of redness, discharge, and the feeling of sand in the eye. There is no loss of vision, sensitivity to light, or significant pain. Bacterial conjunctivitis may be due to several organisms, the most common pathogens being pneumococcus, *Staphylococcus aureus,* hemophilus, and hemolytic streptococci. Professional care should be sought in order to identify the causative organism. Medical treatment with broad spectrum antibiotics or sulfonamide ophthalmic preparations several times a day usually results in improvement within 48 to 72 hours. Bacterial conjunctivitis is usually a self-limiting disease.

Although the Panel has described professional treatment for hordeolum and blepharitis, self-treatment of hordeolum and blepharitis with OTC ophthalmic products is usually without danger. These disorders may not significantly improve with such self-treatment, but they are usually self-limiting, and serious complications are rare. Treatment with OTC products would not result in significant complications; an allergic reaction may occur rarely.

Conjunctivitis is usually a self-limiting disease; however, self-treament of conjunctivitis carries a greater risk than self-treament of hordeolum and blepharitis. If the conjunctivitis is severe and not responsive to the medication used, secondary corneal infections and ulcerations may occur.

The Panel recognizes the potential risks involved in promoting self-treatment of minor eye infections. If a more serious ocular disorder exists, but is not recognized as being serious and appropriate therapy is delayed, serious ocular problems could result. However, the Panel believes that the general warning statements required on all OTC opthalmic drug products are sufficient to alert consumers to the potential seriousness of ocular problems and to encourage them to seek professional help if the condition worsens or persists for more than 72 hours.

The above discussion was based on a review of several sources (Refs. 1 through 5).

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D. Pharmacology of Ocular Ingredients and their Modes of Action.

To simplify its consideration of OTC ocular ingredients, the Panel classified these ingredients on the basis of principal ocular use. In many cases such classification was also indicative of the mechanism of action of ingredients as well as their ocular use, e.g., ocular vasoconstrictor.

The Panel divided the compounds into the following classifications: Local anesthetics—used to temporarily obtund sensations from the cornea and conjunctiva; anti-infectives—employed to arrest the multiplication of pathogenic micro-organisms to permit bodily defenses to remove the infectious organisms; vasoconstrictor agents—employed to constrict blood vessels of the irritated conjunctiva and in turn reduce ocular irritation; hypertonicity agents—used to induce the flow of water from edematous tissues; astringents—used to reduce ocular irritation due to allergens or physical irritants; demulcents—(water-soluble substances) used to relieve burning and irritation due to dryness of the eye: emollients—(oleaginous substances) used to protect the eyes from irritants or from drying.

All of these ingredients are administered topically to the surface of the eye in an appropriate vehicle, alone or in combination.

1. *Ocular anesthetics.* Anesthetics used in ophthalmic conditions are local anesthetics which produce a transient and reversible loss of sensation in the area where they are applied or injected. These anesthetics may be applied topically to the eye as aqueous solutions or as ointment preparations. So administered, they produce anesthesia of the conjunctiva, scleral surface, and cornea. They do not produce anesthesia to the iris or deeper structures within the eye. Topical anesthetics are used in certain diagnostic procedures such as tonometry (measurement of the intraocular pressure) and gonioscopy (examination of the periphery of the iris and aqueous humor drainage tissues). They are also used to reduce discomfort during minor surgical procedures such as removal of foreign bodies, conjunctival scrapings, and lacrimal canalicular manipulation. Local

anesthetics may be injected in the periocular and adnexal structures. Most ophthalmic surgical procedures can be performed with local anesthetics. The topical anesthetics which have been used in the eye include cocaine, benoxinate, dibucaine hydrochloride, piperocaine, proparacaine hydrochloride, and tetracaine hydrchloride.

The exact pharmacologic mechanisms by which local anesthetics act are not completely understood. For nerve conductivity to occur normally, depolarization of the nerve membrane occurs during which there are changes in sodium and potassium concentrations and changes in electrical potential within and just outside the nerve membrane. Local anesthetics act on the axonal membrane to dampen the height and rate of nerve action potential and to elevate the firing threshold. They slow the speed of impulse conduction and increase the refactory period without greatly changing transmembrane resting potential. Local anesthetics interfere with the process of depolarization (Ref. 1).

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2. *Ocular anti-infectives.* Anti-infectives are chemo-therapeutic agents which destroy or limit the multiplication of micro-organisms. In general, they are drugs which either kill (bactericidal) or inhibit the multiplication (bacteriostatic) of infecting organisms without significantly damaging the host (Refs. 1 and 2). They achieve their effect through disrupting the physical, chemical, or enzymatic processes responsible for cell metabolism, regulation, and multiplication (Ref. 3).

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3. *Ocular vasoconstrictors.* Ocular vasoconstrictors (decongestants) belong to a class of drugs called adrenergic or sympathomimetic amines (Ref. 1). When applied topically to the mucous membranes of the eye they produce transient constriction of small blood vessels. The ocular vasoconstrictors include ephedrine, phenylephrine, naphazoline, and tetrahydrozoline. They are used in OTC products intended to treat irritation and inflammation resulting from irritants and allergens (Refs. 2, 3, and 4).

When vasoconstrictors are used in concentrations higher than are permitted in OTC products, or if there is increased absorption into the eye as a result of prolonged contact lens wear or corneal abrasions, these agents may produce mydriasis (dilation of the pupil) (Refs. 2, 3, and 5). Sympathomimetic amines may lower intraocular pressure (in the eyes with wide open angles); conversely, they are capable of raising intraocular pressure in patients with narrow-angle glaucoma and are contraindicated for this group of patients. If they are sufficiently absorbed into the systemic circulation, toxicities including blood pressure and cardiac irregularities may occur (Refs. 6 and 7).

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4. *Ocular astringents.* In general, astringents are agents which are applied locally to tissue to produce a precipitation of protein. Astringents are used in various dosage forms. For example, astringents are used in the form of a solid styptic pencil to arrest bleeding from small wounds on the surface of the body, or to treat small ulcers of the mucous membranes, by precipitation of protein (Ref. 1). In the concentrations in which astringents are used in OTC ophthalmic preparations, they have little ability to penetrate tissues, and with their actions thus limited these ingredients are safe for use in the eye. Zinc sulfate is the only OTC ingredient classified as a Category I ocular astringent. Zinc sulfate is generally considered to have some mild astringent properties when applied topcially to the eye (Refs. 2, 3, and 4). It is doubtful that a 0.25-percent zinc sulfate solution does more than clear some mucin from the outer surface of the eye and may provide subjective relief from minor eye irritation.

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5. *Ocular hypertonicity agents.* The epithelial cells of the cornea, like all living cells, act as a semipermeable membrane, and, therefore, are subject to the phenomenon of osmosis (Ref. 1). A semipermeable membrane is one which is permeable to water but not to certain dissolved solutes. Osmosis is the movement of water through a semipermeable membrane from a compartment of lower concentration of dissolved particles (molecules or ions) to a compartment of higher concentration of such particles to equalize the number of particles per unit volume (osmotic pressure) in each compartment. A normal body cell, therefore, will either take up water and swell or lose water and shrink, depending upon the concentration of particles per unit volume of its fluid environment (its tonicity). A fluid environment which causes neither swelling nor shrinkage of a cell is isotonic with the cell; a solution that results in a cell's swelling is hypotonic with the cell; and a solution that results in a cell's shrinking is hypertonic with the cell (Ref. 2).

It is generally accepted that tears have a particle content equivalent to a 0.9– to 1.0–percent solution of sodium chloride (Refs. 2, 3, and 4).

In order to remain transparent, the cornea must maintain a relatively deturgescent state of about 75 percent of its weight (Refs. 5 and 6). Both the corneal epithelium and endothelium are involved in the maintenance of this proper water content, and defects or distrubances in these tissues lead to an increase in the water content of the corneal tissues (Refs. 5 through 8). In such disorders, topically-applied hypertonic agents will draw water from corneal epithelial cells, subepithelial spaces, and stroma into the tear film layer by osmosis (Ref. 8). Ocular hypertonicity agents, therefore, are used in the management of corneal edema (Refs. 9 and 10).

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6. *Ocular demulcents.* Demulcents, in general, are compounds of high molecular weight which are used in aqueous solution to coat mucous membranes or abraded surfaces to protect underlying cells from environmental irritants and air (Refs. 1 and 2). They also provide a mechanical means for lubricating and protecting mucous membranes or abraded surfaces by mimicking the action of mucus, which is a natural demulcent (Ref. 3).

Ocular demulcents are used to protect and lubricate the eye and to prevent drying in cases of tear insufficiency. They act as substitutes for mucin, a component of tears which normally accomplishes these functions (Refs. 4 through 7). Further, they are used to provide moisture, protection, and lubrication at the interface between artificial eyes and the inner lining of the orbit to prevent irritation and inflammation (Ref. 4).

Ocular demulcents are found in products intended to serve as tear replacements and tear substitutes (Refs. 8 through 16), and in combination with other ingredients, such as vasoconstrictors, in products intended to relieve the symptoms of irritation from airborne irritants and allergens (Refs. 7 through 22).

Ocular demulcents are sometimes used as viscosity agents in OTC ophthalmic solutions. (See part II. paragraph E. below—Formulation of OTC Ophthalmic Drug Products). High concentrations of some OTC ocular demulcents in aqueous solutions are used to facilitate certain ophthalmological examination procedures.

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(15) OTC Volume 100033.

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(20) OTC Volume 100045.

(21) OTC Volume 100062.

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7. *Ocular emollients.* Emollients, in general, are oleaginous substances, usually fats or oils which are applied to the skin or mucous membranes as protectives and for softening the skin. They also prevent drying of the skin by establishing an occlusive oil film on the stratum corneum (Refs. 1, 2, and 3).

Ocular emollients are used as lubricants in conditions of tear insufficiency, as protectives against airborne irritants and allergens, and as both protectives and agents to prevent loss of moisture in cases of exposure or paralytic keratitis (Refs. 4 and 5).

Ocular emollients are used alone or in combination with other emollients to protect or soften the tissues of eyelids to prevent drying or cracking. They are also used to protect the eye after removal of foreign particles or following surgery (Ref. 6). At times ocular emollients are used in combination with other ingredients such as ocular astringents or ocular anti-infectives (Ref. 7).

Ocular emollients are sometimes also used as ointment bases in OTC ophthalmic products. (See part II. paragraph E. below—Formulation of Ophthalmic Drug Products.)

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E. Formulation of OTC Ophthalmic Drug Products

The human eye is a particularly sensitive organ. It reacts quickly to nearly any change in environment. For this reason, solutions and ointments for use in the eye must be prepared with utmost care. Requirements which must be considered in the preparation and in the control of ophthalmic products are clarity, hydrogen ion concentration, buffering, tonicity, sterility, preservatives, viscosity, stability, packaging, and additives. Many of these requirements are interrelated and must be considered collectively in conjunction with the total requirements of a finished products. The buffer system, for example, must be considered with tonicity in mind. Stability can be related to pH, the buffer system, and the packaging material.

Ophthalmic products are generally formulated to be self-sterilizing, isotonic, buffered for stability and comfort, and sometimes viscous. From a safety standpoint, all solutions for use in the eye must be free from foreign particles.

The pH of the finished formulation and the buffer system required to establish pH comprise an important part of product design and may play a large part in stabilizing active ingredients, especially those which are acid salts of weak bases, such as ephedrine hydrochloride. A property formulated eye product should include a buffer with a capacity sufficient to maintain product pH during the proposed shelf life of the product. Even though optimal patient

comfort is at the pH of tears, which is 7.4, many formulations must be buffered on the acid side, i.e., must have a lower pH, so that product stability is not compromised. However, the buffering capacity should be minimized in order to permit the tear fluid to readily readjust to a pH of 7.4 and to reduce discomfort to the eye.

To insure stability of an active ingredient, it may sometimes be necessary to add stabilizing agents and antioxidants to the formulation.

As a general rule, ophthalmic formulations should be isotonic in order to minimize discomfort. Normally, this is not difficult to achieve. As a practical matter, exact tonicity is not a strict prerequisite for product comfort. The eye can tolerate solutions in a range of 0.5 to 1.8 percent sodium chloride.

The sterilization of eye products is a major factor in preventing serious eye infections and must be considered both the most important and the most exacting procedure in the preparation of products for the eye. To prevent the growth of micro-organisms inadvertently introduced during use, sterile ophthalmic solutions must contain a suitable antimicrobial preservative. The selection of an adequate chemical preservative for ophthalmic solutions is by no means a simple procedure. Preservative agents must be evaluated for suitability as part of the total formulation. Preservative stability and effectiveness should be evaluated on the finished product using appropriate analytical methods and tests.

The absence of ocular irritants in finished products and in manufactured batches should be determined using appropriate animal safety tests.

1. *Special consideration applicable to the formulation of OTC ophthalmic drug products.* To ensure the optimum safety and comfort of the final formulation of an ophthalmic product, the Panel has agreed upon the following requirements and standards:

a. *Clarity.* All solutions for use in the eye should be clear and essentially free from foreign particles, fibers, and filaments.

b. *Hydrogen ion concentration and buffering.* The hydrogen ion concentration of an ophthalmic solution may have considerable effect on the comfort of the patient and on the stability of the active ingredient, as well as affecting the solubility of various constituents in the formulation and the therapeutic action of the active ingredient (Refs. 1 through 7).

Normal tears have a pH of approximately 7.4 and possess some limited buffer capacity because of their protein content. The greatest comfort for the patient, or the least irritation, should logically be found at the normal pH of approximately 7.4. However, comfort is usually stated to be adequate in the pH range of 6.3 to 7.8 in unbuffered solutions. An adjustment of the pH may be necessary to improve and maintain the stability of active ingredients.

The Panel recognizes the relationship between the buffer capacity, pH of a product, and patient comfort. The eye tolerates a wider range of pH if the product has a lower buffering capacity. For example, a solution having a pH of 4 to 5 with low buffer capacity may be tolerated in the eye.

The various inactive formulation ingredients that may be used to buffer or adjust the pH of ophthalmic solutions are presented below. (See part II. paragraph E.2.a below—Buffering agents.) The various inactive formulation ingredients may also be employed in appropriate combinations to provide buffer potential and to establish either an acid or an alkaline pH.

Strong acids such as hydrochloric acid or strong bases such as sodium hydroxide should be used only in nominal amounts to make small, final adjustsments in the pH of the finished product.

As a means of limiting the amount of buffer ingredients that may be used in a preparation, the Panel recommends that the total concentration of buffer ingredients in an ophthalmic solution not exceed the osmotic equivalent of 1.0 percent sodium chloride.

c. *Tonicity.* Ophthalmic solutions should be osmotically equivalent, approximating lacrimal fluid (equivalent to 0.9 percent sodium chloride, freezing point depression of 0.52° C). An isotonic ophthalmic solution causes less discomfort than equivalent solutions that are hypertonic or hypotonic (Refs. 3, 4, 5, 8, 9, and 10).

An ophthalmic solution should have an osmotic equivalence between 0.8 and 1.0 percent sodium chloride to comply with labeling claims of "isotonic solution" or with labeling claims that allude to the solution as being isotonic or osmotically equivalent to lacrimal fluid.

Solutions that are intended for use as eye washes should have an osmotic equivalence between 0.8 and 1.2 percent sodium chloride.

An OTC ophthalmic solution intended for direct application of a limited quantity (drops) to the eye should have an osmotic equivalence between 0.5 and 1.8 percent sodium chloride.

Sodium chloride, potassium chloride, and dextrose, in addition to those buffering agents listed below, may be used to adjust tonicity. Calcium chloride (up to 0.05 percent) and magnesium chloride (up to 0.03 percent) may be used to modify the cation content of ophthalmic solutions, e.g., tear substitutes, balanced salt solutions.

The Panel has no objection to adjusting the tonicity of the final formulations of ophthalmic solutions with small amouts of glycerin or propylene glycol.

Two to 5 percent sodium chloride ophthalmic preparations are hypertonic and are acceptable OTC products when labeled as "hypertonic solutions." (See part VII. below—OCULAR HYPERTONICITY AGENT.)

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d. *Sterility and preservation.* All ophthalmic products must be sterile in accordance with § 200.50 (21 CFR 200.50).

Preservatives must be incorporated in liquid OTC ophthalmic products in multiple dose containers to maintain their sterility.

The Panel agrees that the final choice of preservatives rests with the formulator but that the final product should comply with the sterility and preservative requirements as stated

above. Presently, there is no one preservative that will satisfactorily solve the problems of all formulations and conditions of use. The various ingredients that may be used as preservative agents are presented below. (See part II. paragraph E.2.c. below—Preservative agents.)

Empirical preservative tests, such as the official U.S.P. test, must be performed to demonstrate the effectiveness of preservatives as formulated in a given preparation. the following is a summary of the U.S.P. preservative test.

Preservative Test for OTC Ophthalmic Solutions

Preservative test.....	Current USP XIX antimicrobial preservatives effectiveness test.
Products to be tested...	All OTC ophthalmic solutions.
Challenge micro-organisms.	*Staphylococcus aureus* ATCC 6538.
	Escherichia coli ATCC 8739
	Pseudomonas aeruginosa ATCC 9027.
	Candida albicans ATCC 10231.
	Aspergillus niger ATCC 16404.
Organism inoculum level.	10^5 and ^{6} cells per mL of product.
Test Formulation Sampling.	0, 7, 14, 21, 28 days after inoculation.
Criteria for Acceptance.	Bacteria- 0.1 percent survival by the 14th day. Yeasts and molds at or below initial concentrations during the first 14 days. No increase in organism counts for the remainder of the 28-day test period.

Before any formulation can be regarded as being satisfactory, the finished product must be properly tested prior to marketing.

Bacteriological trials are necessary to demonstrate that the preservative selected in the final formulation is and will be effective until its expiration date. It is essential that preservative effectiveness testing be carried out on the finished formulation in the same packaging that will be used in marketing the product. Data must not be extrapolated from one formulation to another, no matter how slight the variation. Even the material of which the container is made, including labeling inks and labeling adhesives, may affect the preservative. Thus, tests of the effectiveness of preservatives must be done with material obtained from the final market dosage form and market container.

Tamper-proof closures are necessary to insure that the contents cannot be used without destroying the seal. Such closures are considered an aid in ensuring the initial sterility of the product.

Eye cups, eye droppers, and other dispensers packaged in combination with a sterile drug should be sterile when offered for sale to the consumer.

The Panel recognizes that certain eye irritants, e.g., ethylene oxide, ethylene chlorhydrin, and ethylene glycol, are used in the sterilization procedure of ophthalmic containers. As serious harm might result if these irritants came into contact with the eye, containers sterilized with them should be thoroughly aerated and tested for residues prior to filling.

2. *Pharmaceutical necessities.* Pharmaceutical necessities are substances which are of little or no therapeutic value, but which are useful in the formulation of pharmaceutical preparations. Pharmaceutical necessities for OTC ophthalmic preparations include buffering agents, ointment bases, preservative agents, stablizing agents, antioxidants, tonicity agents, and viscosity agents. The Panel reviewed the various pharmaceutical necessities found in ophthalmic formulations and determined the suitability, unsuitability, or need for additional data regarding the suitability of each of the substances.

a. *Buffering agents.* The following inactive formulation ingredients are suitable agents for buffering or adjusting the pH of ophthalmic solutions. They may also be employed in appropriate combinations to provide buffer potential or to establish either acid or alkaline pH.

Acetic acid
Boric acid
Hydrochloric acid
Phosphoric acid
Potassium bicarbonate
Potassium tetraborate
Potassium carbonate
Potassium citrate
Potassium phosphates:
  Dibasic potassium phosphate
  Monobasic potassium phosphate
  Tribasic potassium phosphate
Sodium acetate
Sodium bicarbonate
Sodium biphosphate
Sodium borate
Sodium carbonate
Sodium citrate
Sodium hydroxide
Sodium phosphate

b. *Ointment bases—(1) Suitable ointment bases.* Vehicles for ophthalmic ointments should be nonirritating and sterile. Bland vehicles such as white petrolatum and mineral oil which have a low potential for irritation are most often used. Those ingredients listed as Category I ocular emollients are recommended as suitable ointment bases. (See part IX. below—OCULAR EMOLLIENTS.)

(2) *Unsuitable ointment bases.* Surfactant emulsifiers incorporated in absorption bases and emulsion bases may be irritating to the eye; therefore, absorption and emulsion bases are not recommended. Corn, peanut, cottonseed, and cod liver oils are not recommended because of their general instability and tendency to turn rancid.

c. *Preservative agents—(1) Suitable preservative agents.* The following substances are recommended as suitable preservative agents:

Benzalkonium chloride
Benzethonium chloride
Chlorobutanol
Phenylmercuric acetate
Phenylmercuric nitrate
Thimerosal

Ophthalmic preparations, even though sterile when dispensed, must contain suitable substances or a mixture of substances to destroy or to prevent the growth of micro-organisms accidentally introduced when the container is opened for use. The prime objective of a preservative is to minimize contamination of the preparation.

Instead of specifying a range of effective concentrations for each preparation, the Panel determined that stating maximum concentrations for safe use in the eye would be appropriate to protect the patient from possible toxicity. Suitable concentrations and combinations of preservatives in a product will depend on the various ingredients in the total formulation. Effectiveness must be determined by a suitable preservative test on the final product at the time of manufacture and after aging.

Exaggerated conditions of relative humidty, temperature, and light should be included in the final product testing to detect possible trends and necessity for precautionary label statements as to storage conditions during distribution and normal use by the consumer. Simulated opening and closing of drug containers is useful to indicate how long preservatives last and should be included in the stability data.

(i) *Benzalkonium chloride—(a) Benzalkonium chloride, maximum 0.013 percent (1:7,500) for use in the eye.* Intraocular concentrations of benzalkonium chloride above 0.013 percent (0.017 percent, 0.033 percent, 0.10 percent) have produced moderate to severe reactions in rabbits which lasted over a period of 6 to 8 weeks.

Benzalkonium chloride in a concentration of 0.1 percent (1:1,000) has been shown to produce toxicity to the corneal endothelium of rabbits when applied topically (Ref. 1).

Benzalkonium chloride should not be combined with nitrates of salicylates. Phenylmercuric nitrate or phenylmercuric acetate, 0.002 percent (1:50,000 dilution) or another compatible preservative should be used instead.

(b) *Benzalkonium chloride, 0.02 percent, not for use in the eye.* A concentration of 0.02 percent may be used in preparations for instillation in the cul-de-sac to reduce deposits on artificial eyes. Benzalkonium chloride in this concentration should not be used in the intact human eye.

(c) *Benzalkonium chloride, maximum 0.013 percent plus edetic acid, edetate calcium disodium, disodium edetate, edetate sodium, or edetate trisodium.* While edetates alone are not effective as preservatives, they enhance the activity of benzalkonium chloride against pseudomonas bacteria.

The preceding discussion of benzalkonium chloride as a preservative agent is based on a review of several sources (Refs. 1 through 13).

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(ii) *Benzethonium chloride—(a) Benzethonium chloride, maximum 0.01 percent (1:10,000) for preparations used directly in the eye.* Although not enjoying the same popularity as cationic surfactants such as benzalkonium chloride for preserving ophthalmic products, clinical and marketing experience supports the use of benzethonium chloride as being satisfactory for this purpose (Refs. 1, 2, and 3).

In general, cationic surfactants are active against a broad spectrum of gram-positive and gram-negative bacteria. Although their effectiveness against various types of pseudomonas has been questioned (Refs. 4 and 5), limited studies indicate that 0.01 percent benzethonium chloride in a vasoconstrictor product containing no other preservative satisfactorily kills five strains of pseudomonas as well as a variety of other test micro-organisms.

As is the case of other cationic surfactants, the action of benzethonium chloride is neutralized or reduced by soap, anionic detergents and organic matter such as tissue substances and pus (Refs. 6 and 7). It is ineffective against clostridial spores and has limited effectiveness against fungi and viruses (Refs. 5, 6, and 7). It can be adsorbed by cotton, rubber, and other porous materials, thus reducing its effectiveness (Ref. 7).

Benzethonium chloride can be incompatible with boric acid, fluorescein, pilocarpine nitrate, salicylates, silver nitrate, silver protein, sulfathiazole sodium, and nitrates in general (Refs. 4 and 8). For proper preservation, solutions containing benzethonium chloride should be stored in tight, light-resistant containers (Ref. 9).

(b) *Benzethonium chloride, maximum 0.02 percent (1:5,000) for use in preparations not for direct use in the eye.* Concentrations of even 0.02 percent benzethonium chloride, twice the concentration required for preservative effectiveness, are found to cause minimal irritations when instilled into the eye (Refs. 4, 5, and 10).

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(iii) *Chlorobutanol, maximum 0.5 percent.* Chlorobutanol 0.5 percent has been recommended as an ophthalmic preservative since 1939 and has been in continuous use since that time (Refs. 1 and 2). The U.S.P. recommends its use at the 0.5-percent level, and approximately 25 percent of commercial products in 1968 used chlorobutanol (Ref. 3). Chlorobutanol is effective against both gram-positive and gram-negative organisms including *Pseudomonas aeruginosa* (Refs. 4 through 8). Chlorobutanol is safe and has a low potential for sensitization (Refs. 2 and 4). Chlorobutanol significantly hydrolyzes above a pH level of 5 to 6 (Refs. 8, 9, and 10). Accordingly, the use of this preservative above pH 5 is not recommended. Care must be exercised in the use of chlorobutanol in plastic containers, since chlorobutanol has been shown to permeate polyethylene bottles (Ref. 11).

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(iv) *Mercurial preservatives (phenylmercuric acetate, maximum 0.004 percent (1:25,000); phenylmercuric nitrate, maximum 0.004 percent (1:25,000); thimerosal, maximum 0.01 percent (1:10,000)).* Phenylmercuric acetate, phenylmercuric nitrate, and thimerosal are safe when used up to their respective maximum concentrations as stated. They are moderately effective bacteriostats. However, a major disadvantage of mercurials is their relatively slow kill rates and weak antimicrobial activity. Allergic reactions to mercurials may occur.

Phenylmercuric nitrate is more active than phenylmercuric acetate or thimerosal.

An alkaline pH is required to maintain stability of the organic mercurials in solution. Phenylmercuric nitrate exists predominantly as the poorly ionized hydroxide at a pH greater than 3. It is not precipitated in slightly acid pH like other common organic mercurials.

Pursuant to the U.S.P. and N.F. recommendations, when nitrates or salicylates are used, benzalkonium chloride should be replaced with phenylmercuric nitrate or phenylmercuric acetate, 0.002 percent (1:50,000) or other compatible preservatives.

Ethylenediaminetetracetic acid (EDTA) reduces the effectiveness of phenylmercuric nitrate and should not be used with this preservative.

In view of the widespread use of organic mercurials, particularly thimerosal and phenylmercuric nitrate, and few reported adverse side effects from their use, thimerosal, phenylmercuric nitrate, and phenylmercuric actetate should be considered as useful preservatives for commercial ophthalmic solutions.

When mercury compounds are present as preservatives the labeling should state: "Warning: Do not use this product if you are sensitive to mercury compounds."

The preceding discussion of mercurial preservatives is based on a review of several sources (Refs. 1 through 17).

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(v) *Combinations of preservative agents.* The panel recommends the following guidelines for combinations of preservative agents in ophthalmic products.

An ophthalmic product may contain no more than two of the recommended preservtive agents listed above, provided the product meets the requirements for safety and preservative tests, the preservative activity of the combination is not less than any of the ingredients used singly, and the combination is not one specifically mentioned in this document as unacceptable. The use of EDTA with any approved preservative would be considered a single preservative, and another agent could be combined with these two ingredients.

(2) *Unsuitable single preservative agents.* The Panel recommends that the following substances are unsuitable if used alone as preservative agents. The Panel recognizes that these agents may be useful as part of a combination perservative system but that data are lacking at this time to make a final determination. The Panel has discussed these combinations later in this document. (See part II. paragraph E.2.c.(3) below—Preservatives for which more data are needed.)

Methylparaben
Propylparaben
Sodium benzoate
Sorbic acid

(i) *Methylparaben and propylparaben.* The Panel found methylparaben and propylparaben to be unsafe and unsuitable used alone as antimicrobial agents in OTC ophthalmic products. In concentrations that are effective against micro-organisms, these ingredients are irritating to the eye (Ref. 1); in concentrations that are not irritating to the eye, they have little or no effect against micro-organisms.

Although the parabens may be useful agents against fungi (Refs. 2 and 3), the available evidence indicates that they have limited antibacterial action (Refs. 1 and 4) and a kill rate slower than benzalkonium chloride (Refs. 5 and 6).

The parabens have questionable activity against *Pseudomonas aeruginosa* (Refs. 7, 8, and 9). Indeed, the organism can utilize the parabens as a source of carbon, thus precluding the recommendation of the parabens for widespread use (Refs. 10 and 11).

The parabens have been established as potent dermatologic sensitizers, althought there are no known reports of this effect from ophthalmic products (Refs. 12 through 15).

The parabens can be absorbed by plastic material (Ref. 12).

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(ii) *Sodium benzoate.* The Panel is unaware of any data that show that sodium benzoate used alone is safe and effective as a preservative for OTC ophthalmic preparations.

(iii) *Sorbic acid.* Sorbic acid used alone in concentrations of 0.1 to 0.2 percent is not considered an effective antimicrobial agent. Sorbic acid has been used in the food, drug, and cosmetic industry for many years as an inhibitor of fungi (Refs. 1 and 2). A review paper on sorbic acid and abstracts of a literature search indicate that sorbic acid has limited bactericidal or bacteriostatic activity (Refs. 3 and 4). Trade literature also indicates that sorbic acid and potassium sorbate have little activity against bacteria but do have broad antifungal activity (Ref. 5). The Panel concludes that there are no suitable scientific data to establish that sorbic acid used alone is a safe and effective preservative for ophthalmic preparations.

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(3) *Preservatives for which more data are needed.* The Panel recommends that more data are needed before a determination of safety and effectiveness can be made for the following preservative agents:

Cetylpyridinium chloride
Chlorhexidine gluconate
Chlorhexidine hydrochloride
Phenylethyl alcohol
Sodium propionate
Methylparaben in combination with other approved preservatives
Propylparaben in combination with other approved preservatives
Sodium benzoate in combination with other approved preservatives
Sorbic acid in combination with other approved preservatives

(i) *Cetylpyridinium chloride.* The Penel is unaware of any currently marked ophthalmic product containing cetylpyridinium chloride as a preservative agent. However, the Panel did receive investigational data on this ingredient (Ref. 1). The data indicated that certain ophthalmic formulations containing 0.01 to 0.02 percent cetylpyridinium chloride passed both the U.S.P. XVIII preservative effectiveness test and the Draize Eye Irritation test. However, all of the formulations tested also contained a sulfonamide anti-infective ingredient. The Panel is not convinced from the data presented that cetylpyridinium chloride would be an effective preservative agent in other formulations. The Panel concludes that well-designed chemical and laboratory studies are necessary to establish that cetylpyridinium chloride would be safe and effective in other ophthalmic formulations.

Reference

(1) OTC Volume 100076.

(ii) *Chlorhexidine gluconate and chlorhexidine hydrochloride.* Chlorhexidine is widely used in British Commonwealth countries, particularly Australia (Refs. 1 and 2). It is also used as an ingredient in the chemical disinfectant systems for hydrophilic soft contact lenses.

Although initial reports concerning chlorthexidine hydrochloride and chlorhexidine gluconate were enthusiastic, it now appears that there are incompatibilites and other problems, such as inactivation, associated with these compounds (Refs. 3 through 9).

Appropriate formulation and well-designed clinical studies are necessary to establish chlorhexidine hydrochloride and chlorhexidine gluconate as safe and suitable preservatives for OTC ophthalmic products.

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(iii) *Phenylethyl alcohol.* The Panel concludes that phenylethyl alcohol (0.5 percent) by itself is a relatively slow-acting bacteriostatic agent. There are conflicting reports concerning its potential for causing irritation of the eye. Phenylethyl alcohol in combination with other preservatives may be useful in opthalmic solutions when drug incompatibilities exist with other preservatives.

Although phenylethyl alcohol (0.5 percent) has been recommended as a preservative for many years, it has not been widely used in the last several years. No product containing this preservative was submitted to the Panel for review.

Appropriate formulation and well-designed clinical studies are necessary to establish phenylethyl alcohol as a safe and effective preservative alone or in combination with other preservatives for OTC ophthalmic products.

This discussion is based on a review of several sources (Refs. 1 through 5).

References

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(iv) *Sodium propionate.* The Panel is aware that sodium propionate is used extensively in the food and drug industry as a fungistatic agent (Refs. 1 through 4). However, the Panel concludes that there are no suitable scientific data to establish that sodium propionate is a safe and effective preservative in ophthalmic preparations.

Appropriate formulation studies and well-designed clinical studies are necesssary to establish the safety and effectiveness of sodium propionate as a preservative in ophthalmic preparations.

References

(1) OTC Volume 100043.

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(3) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1074–1075, 1973.

(4) "The National Formulary," 14th Ed., The American Pharmaceutical Association, Washington, DC, pp. 833–834, 1975.

(v) *Methylparaben or propylparaben or both in combination with suitable preservatives.* Methylparaben or propylparaben or a combination of the two in low concentration(s) may be a useful component of a preservative system containing other approved preservatives.

While the Panel concludes that they are not suitable preservative agents when used alone, they may be used in combination with other preservatives, provided that the concentration of each is less than its saturation solubility in water (approximately 0.25 percent for methylparaben and 0.04 percent for propylparaben).

Appropriate formulation studies and well-designed clinical studies are necessary to establish that methyl- or propylparaben in combination with other approved preservatives is a safe and effectives preservative system for OTC ophthalmic preparations. This discussion is based on a review of several sources (Refs. 1 through 14).

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(13) Eriksen, S. P., "Preservation of Ophthalmic, Nasal, and Otic Products," *Drug and Cosmetic Industry,* 98:36–40 and 147–148, 1970.

(14) OTC Volume 100057.

(vi) *Sodium benzoate in combination with suitable preservatives.* Sodium benzoate is used extensively as a preservative agent in the food and beverage industry and in the pharmaceutical industry for liquid preparations (i.e., syrups) (Ref. 1). However, the Panel concludes that there are no suitable scientific data to establish that sodium benzoate is a safe and effective preservative for OTC ophthalmic preparations. The effectiveness of sodium benzoate depends on the pH; it must be used in an acid medium with a pH which does not exceed 4 (Ref. 2).

Appropriate formulation testing and well-designed clinical studies are necessary to establish that combinations of sodium benzoate with other approved preservatives provide a safe and effective preservative system for use in OTC ophthalmic preparations.

References

(1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J.B. Lippincott, Philadelphia, pp. 1045–1046, 1973.

(2) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A., et al., Mack Publishing Co., Easton, PA, p. 1100, 1975.

(vii) *Sorbic acid in combination with suitable preservatives.* Sorbic acid is used in the food, drug, and cosmetic industry as a preservative against fungal contamination (Refs. 1 and 2). However, the Panel concludes that there are no suitable scientific data to establish that sorbic acid is a safe and effective preservative for OTC ophthalmic preparations. Sorbic acid in combination with some other approved preservative might be a useful method of obtaining a preservative system that would be

effective against a broad spectrum of possible contaminants (bacteria and fungi). The effectiveness of sorbic acid depends on the pH, and it must be used in an acid medium having a pH which does not exceed 6 (Refs. 3, 4, and 5).

Appropriate formulation and well-designed clinical studies are necessary to establish that combinations of sorbic acid with other approved preservatives provide a safe and effective preservative system for use in OTC ophthalmic preparations.

References

(1) "The National Formulary," 14th Ed., The American Pharamaceutical Association, Washington, DC, p. 834, 1975.

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(4) OTC Volume 100084.

(5) "Food Preservatives: Sorbistat, Sorbistat-K, Mycoban, Sodium Benzoate," Technical Information, Chemicals Divisions, Pfizer, Inc., New York, p. 5, 1976.

d. *Stabilizing agents and antioxidants.* The following substances are recommended as suitable stabilizing agents or antioxidants.

Edetic acid, edetate calcium disodium, edetate disodium (EDTA), edetate sodium, edetate trisodium, ethylenediaminetetraacetic acid (EDTA) (maximum 0.1 percent)
Sodium bisulfite (maximum 0.1 percent)
Sodium metabisulfite (maximum 0.1 percent)
Sodium thiosulfate (maximum 0.2 percent)
Thiourea (maximum 0.1 percent)

It is sometimes necessary to stabilize products that contain an active ingredient which may be readily oxidized. For this purpose, sodium bisulfite is most frequently used. EDTA has been found to enhance the activity of antioxidants in some cases, apparently by chelating metallic ions that would otherwise catalyze the oxidation reaction. The Panel recognizes the usefulness of the above agents in stabilizing active ingredients, including some to the vasoconstrictors. This discussion was based on a review of several sources (Refs. 1 through 7).

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(6) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD pp. 164–165 and 571, 1975.

(7) "The National Formulary," 14th Ed., The American Pharmaceutical Association, Washington, DC, p. 833, 1975.

e. *Tonicity agents.* Sodium chloride, potassium chloride, dextrose, and those substances listed above as buffering agents are suitable agents for adjusting the tonicity of ophthalmic solutions. Calcium chloride (up to 0.05 percent) and magnesium chloride (up to 0.03 percent) may be used to modify the cation content of ophthalmic solutions.

f. *Viscosity agents.* The following agents are recommended as suitable for increasing the viscosity of ophthalmic preparations:

Cellulose derivatives:
- Sodium carboxymethylcellulose
- Hydroxyethylcellulose
- Hydroxypropyl methylcellulose
- Methylcellulose

Dextran 70
Gelatin
Polyols, liquid:
- Glycerin
- Polyethylene glycol 300
- Polyethylene glycol 400
- Polysorbate 80
- Propylene glycol
- Polyvinyl alcohol
- Povidone

The safety of these substances is discussed later in this document. (See part VIII. below—OCULAR DEMULCENTS.)

There are a number of chemicals which, when added to water, decrease the fluidity (flow) of an aqueous system. Of these chemicals, methylcellulose and its derivatives plus polyvinyl alcohol are the most extensively used to increase the viscosity of ophthalmic solutions. These chemicals are polymers of varying numbers of subunits. The term used to refer to the viscosity characteristics of these chemicals in water is "centipoise." The Panel recognizes that the ingredients identified above vary in physical characteristics in that there are various grades available. The percentages of these compounds used in ophthalmic preparations will vary depending upon their molecular weight (Ref. 1).

By their alteration of surface tension, their solubility characteristics, and their consistency, viscous medications create liquid films upon ocular and prosthetic surfaces. The concentrations selected for use of these agents in ophthalmic preparations are determined by physical measurements of viscosity and wetting angle, which may be altered by infinitely variable combinations of surface-active and viscous materials.

In general, viscosity is desirable in some ophthalmic solutions for providing lubricating properties and for helping to achieve longer retention of the solutions in the eye. The most widely used polymeric substances are methylcellulose, hydroxypropyl methylcellulose, and polyvinyl alcohol (PVA). Under conditions of ophthalmic usage, these viscous drugs are virtually nontoxic.

Terms such as "water-soluble polymeric system" and "water-soluble polymers" are often used to refer to polymeric substances used as viscosity agents. When used alone, these terms are unacceptable to the Panel. The specific polymers contained in the product must be identified.

Viscosity agents are also used as ocular demulcents for their mechanical moisturizing and lubricating (physical) effect when placed in the eye and on prosthetic devices. (See part VIII. below—OCULAR DEMULCENTS.)

Reference

(1) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, pp. 667–668, 1975.

g. *Solvent vehicles.* The only solvent vehicle allowed by the Panel for OTC ophthalmic solutions is water.

3. *Nonessential ingredients.* The Panel considers it unacceptable to add odor- or color-producing substances to OTC ophthalmic preparations. Eye tissue is very sensitive, and such substances may cause adverse reactions. Common sense dictates that the fewer the number of ingredients in a product, the smaller the chance for sensitivities (allergies) or irritations to occur. There is no evidence to show that the presence of odorants or colorants adds to the safety or effectiveness of the product. The following ingredients are considered nonessential and should not be used in OTC ophthalmic drug products:

a. Colorants

Berberine preparations:
- Berberine bisulfate
- Berberine Hydrochloride
- Berberine sulfate

Hydrastine hydrochloride

b. Odorants

Camphor preparations:
- Camphor
- Camphor water

Geranium oil, Algerian
Peppermint preparations:

Peppermint oil
Peppermint water
Rose and camphor water
Rose water
Witch hazel water

4. *Acceptable OTC ocular formulations.* The Panel recommends the following formulations for OTC ophthalmic drug products:

a. Vasoconstrictor Products

Category I vasoconstrictor (only one allowed)
Suitable preservative(s)
Suitable buffers if needed
Suitable tonicity agents if needed
Suitable stabilizer if needed
Suitable viscosity agent if needed

b. Astringent Products

Zinc sulfate
Suitable preservative(s)
Suitable buffers if needed
Suitable tonicity agents if needed

c. Vasoconstrictor and Astringent Products

Category I vasoconstrictor (only one allowed)
Zinc Sulfate
Suitable preservative(s)
Suitable buffers if needed
Suitable tonicity agents if needed
Suitable stabilizer if needed
Suitable viscosity agent if needed

d. Ocular Hypertonic Solutions

sodium chloride
Suitable preservative agent(s)
Suitable viscosity agent(s) if needed

e. Ocular demulcent products

Category I demulcent agent(s)
Suitable preservative agent(s)
Suitable buffers if needed
Suitable tonicity agents if needed

f. Ocular Emollient Products

Category I emollient agent(s)
Suitable preservative agent(s)
Ointment base if needed
Adjunct(s) for proper consistency if needed

g. Eye Washes (Irrigating Solutions

No active ingredients allowed
Suitable preservative(s)
Suitable buffers
Suitable tonicity agents

F. Determination of Safety and Effectiveness of OTC Ophthalmic Drug Products.

1. *Determination of safety of OTC ocular ingredients.* In determining the safety of a drug or combination of drugs, both animal and human studies were considered.

Animal studies, especially rabbit eye irritation tests (Draize type), were considered very important. The data from the irritation test usually related to levels of the drug that did not cause irritation when applied to rabbit eyes. The drugs were usually applied as ingredient(s) in marketed products, in aqueous solutions, or, in a few instances, alone. Basic animal toxicology data were used to establish an individual drug's toxicity, or more likely, its nontoxicity to organs and tissues.

Attention was paid to information related to adverse effects in humans. Much of this type of data was abstracted from marketing information. A knowledge of the pharmacology of the drug or drugs under consideration made it possible to look specifically for adverse effects in the eye.

Final formulation safety testing in animals. The absence of ocular irritation following short-or long-term use must be demonstrated by animal or clinical testing. The testing should be done on the finished product at the time of manufacture and after long-term storage.

The Panel recommends the "Draize" test or a modification thereof to evaluate the safety of drugs that may reach the surface of the eye (Refs. 1 and 2). Testing should be done on the final formulation of the product. The test involves exposing albino rabbit eyes (the nonpigmented iris facilitates the interpretation of iritis (inflammation of the iris)) to conditions in which a drug or formulation is to be used. A 0.1-mL sample of the formulation is dropped onto the cornea and conjunctiva without rinsing. Instillation of the preparation in the manner and frequency of intended use is followed by documented observations of the cornea, conjunctiva, and iris at initially frequent intervals to identify acute ocular responses, and over a long time, e.g., 1 to 3 months, to identify chronic ocular responses. A set of colored photographs should be available to aid in the interpretation of eye lesions in the rabbit and in rating the severity of the response.

The problems with the Draize test are discussed in the literature (Refs. 1 through 9). The problems include variables such as personal error, sample size, time of release of an irritant from a formulation, sample loss from the eye, frequency of use and observations, and difficulty in correlating rabbit eye irritation with the experience found in man. The rabbit eye is considered to be more sensitive to irritants than the human eye. Agents that are mildly irritating on a single application may be moderately irritating on repeated usage in rabbits or man. Of the variables, the competence of the trained investigator is the most important.

The duration of the Draize test may be varied. For certain new formulations it may be desirable to continue the test for up to 90 days, whereas a test of 21 to 28 days could be satisfactory for other new formulations. For irritation studies of new batches of a formulation, a Draize test of 24 to 72 hours, and observation up to 7 days would be satisfactory.

In eye irritation tests, the nature of the active ingredients must be considered in the evaluation of a Draize test before going to man. For example, any product which causes an itching or burning sensation might pass the Draize test, but, in man, might result in damage from vigorous rubbing. The evaluation of the Draize test results varies, with investigators giving little uniform information. A formulation that produces marked conjunctival and corneal edema and corneal haziness for several days in the rabbit could clear in 7 days and this formulation would pass a Draize test. Such a test is most easily used to distinguish between moderate and severe irritants but is less effective when used to test for the absence of irritation.

2. *Determination of effectiveness of OTC ocular active ingredients.* In determing the effectiveness of ingredients reviewed by the Panel, it was necessary to consider each pharmacologic group separately.

Basic animal and human pharmacology studies as well as clinical studies were useful for assessing the effectiveness of anti-infectives and vasoconstrictors. Basic studies and data concerning the physical properties of demulcent and emollient agents were of value.

Important to the Panel's evaluation was the favorable acceptance, after many years of use, of certain OTC ophthalmic products containing emollient, demulcent, astringent, or vasoconstrictor agents for relieving the symptoms of minor eye irritation. Marketing data and length of time a product has been on the market were of some value.

There were only a limited number of double-blind or crossover studies and very few well-controlled studies available to the Panel. When available, comparative studies of one product versus another were of some value. Clinical experience of a general nature, if documented by qualified experts, contributed to the final decision.

References

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(2) Draize, J. H., "Dermal Toxicity," *Food Drug and Cosmetic Law Journal,* 10:722–732, 1955.

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(6) Davies, R. E., S. R. Kynoch, and M. P. Liggett, "Eye Irritation Tests—An Assessment of the Maximum Delay Time for Remedial Irrigation," *Journal of the Society of Cosmetic Chemists,* 27:301–306, 1976.

(7) Draize, J. H., "Dermal Toxicity," *in* "Appraisal of Safety of Chemicals in Foods, Drugs, and Cosmetics," Association of Food and Drug Officials of the United States, Texas State Department of Health, Austin, TX, pp. 46–59, 1959.

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(9) Conquet, P., et al., "Evaluation of Ocular Irritation in the Rabbit: Objective versus Subjective Assessment," *Toxicology and Applied Pharmacology,* 39:129–139, 1977.

G. Labeling of OTC Ophthalmic Drug Products

The Panel emphasizes the importance of informative and truthful labeling so that the consumer can select the most appropriate product for a specific ocular condition.

The Panel reviewed the general labeling requirements previously adopted by the Food and Drug Administration for OTC products (21 CFR 201.60, 201.61, and 201.62). The Panel concurs that these general requirements are appropriate for OTC ophthalmic preparations.

After reviewing all submitted labels of OTC ophthalmic preparations, the Panel recommends the following additional requirements.

1. *Ingredients.* The Panel concludes that ophthalmic products should contain only active ingredients plus such inactive ingredients (pharmaceutical necessities) as may be necessary for product formulation. All such drug products should identify the active and inactive ingredients in labeling by the established names of the ingredients. Since all OTC ophthalmic products are either solutions or ointments, the label should state the quantity of each active ingredient in percentage concentration (weight-volume, weight-weight, or volume-volume, depending on the physical characteristics of the ingredients). Preservative agent(s) should be identified in the labeling, and their concentration stated on the label as a percentage or as a ratio, e.g., "Preservative agent: Benzalkonium chloride 0.01 percent" or "Preservative agent: Benzalkonium chloride 1:10,000."

The use of a trade name alone on a label is not a meaningful description of the ingredients in the product. The term should be followed by a list of its component ingredients.

Further, the description of certain active ingredients as "water-soluble polymers" or "water-soluble polymeric system" without listing the specific ingredients making up the polymeric system is not sufficently definitive. The Panel recommends that the specific polymers making up the polymeric system be identified on the label.

The Panel strongly recommends that all inactive ingredients be listed on the label, as inactive ingredients may produce local adverse reactions such as allergy, irritation, and hyperemia. An ophthalmic drug product cannot be promoted on the basis of inactive ingredients, and the label cannot emphasize the inactive ingredients beyond the mere listing of them recommended above.

The inclusion of expiration dates in the labeling of OTC ophthalmic products is strongly recommended. Expiration dates should be supported by appropriate stability data, including the following monitored parameters: active ingredient(s), preservative(s), pH, and sterility. Additionally, the label should bear information relative to recommended conditions of storage as might be indicated from stability studies of the ingredients contained in a product.

2. *Indications and directions for use.* The indications for use of an ophthalmic preparation 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. The label should include a clear statement of the effective minimum and maximum dosage per time interval followed by "or as directed by a physician." It is axiomatic and should be emphasized that the least frequent use of even an effective ophthalmic preparation is desirable.

The Panel recognizes the importance of stating a product's indication in easily understood lay terms. The directions for use should be clear and provide the user with a reasonable expectation of the results the product might produce. No reference should be made or implied regarding the alleviation or relief of symptoms unrelated to the condition that is an indication for use of the product.

The Panel recognizes the present posture of FDA in respect specifically to appropriate and approved labeling indications and directions for use of OTC ophthalmic preparations. The Panel entirely supports FDA in its determination to review, monitor, and give approval to truthful and nondeceptive labeling to provide consumer protection.

On the other hand, the Panel believes that industry should have the opportunity to use unadorned synonyms to acceptable terminology as long as it is truthful, nondeceptive, and given prior approval by FDA.

a. *Acceptable labeling indications—*

(1) *For products containing anti-infectives.* "For the treatment of minor external infections of the eye."

(2) *For products containing astringents.* "For the temporary relief of discomfort from minor eye irritations."

(3) *For products containing emollients.* (i) "For the temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun."

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

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

(4) *For products containing demulcents.* (i) "For the temporary relief of burning and irritation due to dryness of the eye."

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

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

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

(5) *For products containing vasoconstrictors.* "For the relief of redness of the eye due to minor eye irritations."

(6) *For products containing hypertonicity agents.* "For the temporary relief of corneal edema."

(7) *For eyewash products.* "For flushing or irrigating the eye to remove loose foreign material, air pollutants, or chlorinated water."

b. *Unacceptable labeling claims.* Phrasing that promises general benefits of good health or well being or warns against the danger of physiologic states such as "fatigue," "tired eyes," or "eyes over forty" is found unproven and thus unacceptable by the Panel. The necessity for using ophthalmic (eye) medication(s) in normal visual activities, e.g., watching television, reading, close work, is an unacceptable labeling claim. The Panel considers statements

suggesting products "for continuous everyday use," "for improvement of tired eyes," or "for use before putting on makeup" to be misleading claims and not acceptable.

Undocumented claims that opthalmic (eye) medications produce cosmetic changes such as "sparkling," "bright," "diamond," or "bedroom" eyes foster the false notion among consumers that such benefits ensue from the use of these medications. Such references to "eye appearance" should not be used also because they might promote frequent or continued use.

Implications that normal eyes require prolonged medication with OTC drugs are unsupported and strongly contrary to the public interest. Hence, such claims should be considered false or misleading and subject to appropriate regulatory action.

The Panel found no evidence that astringents are indicated for treatment of stye or hay fever, and such indications are unacceptable in labeling of products containing these ingredients.

The Panel found no evidence for claims that any OTC ophthalmic product has a particular advantage for individuals simply on the basis of sex, age, or other demographic characteristics.

The Panel does not recognize the term "aromatic preservatives." Such terms as "aromatic preservatives," "other aromatics," and "peppermint" should not appear on labels as preservatives

3. *Warnings.* Because self-medication with OTC ophthalmic preparations will not prevent or treat damage from a serious eye disease, the labeling of these preparations should warn the consumer of serious symptoms which indicate disorders requiring immediate professional attention and alert him or her to seek professional advice if less serious symptoms do not respond within a reasonable period of time or worsen in reaction to an OTC medication. A reasonable period of time within which all pharmacologic classes of ophthalmic medications—except for eyewash products and hypertonicity agents—might be expected to provide symptomatic relief was judged to be 72 hours. Given the indications for eyewash products, these preparations should provide immediate symptomatic relief. Hypertonic preparations are intended to be used for prolonged periods of time once the corneal edema has been diagnosed.

In general, the Panel does not feel that isolated use of OTC opthalmics in infants and children would present any specific problem. While the Panel is not suggesting an age limitation warning in the labeling of OTC opthalmics, it recommends that any specific pediatric ocular condition be treated by a physician.

The following are general and specific warning statements recommended by the Panel for use in the labeling of OTC ophthalmic products:

a. *Statements for use in the labeling of all OTC opthalmic products.*

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

(2) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

b. *Statements for use in the labeling of OTC ophthalmic products as specified*—(1) *For all ophthalmic products except eyewash preparations and hypertonicity agents.* "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(2) *For eyewash preparations.* "If symptoms persist or worsen after use of this product, consult a physician."

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

(4) *For products containing vasoconstrictors.* (i) "If you have glaucoma, do not use this product except under the advice and supervision of a physician." The Panel recommends the inclusion of this warning because vasoconstrictors in some instances can cause dilation of the pupil which in turn may trigger an attack of narrow-angle glaucoma in a susceptible individual. The Panel did not attempt to specify narrow-angle glaucoma in the warning, because it believes that individuals who have been diagnosed as having glaucoma are often not aware which type of this disease they have, and it is therefore safer to make the warning general.

(ii) "Overuse of this product may produce increased redness of the eye." The Panel recommends inclusion of this warning to deal with the rebound hyperemia which may occur when vasoconstrictores are used excessively in the eye.

(5) *For products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(6) *For hypertonicity products containing from 2 to 5 percent sodium chloride.* (i) "This product may cause temporary burning and irritation on being instilled into the eye."

(ii) "Do not use this product except under the advice and supervision of a physician."

(7) *For products containing mild silver protein.* (i) "Prolonged or frequent use of this product may cause permanent discoloration of the eye and the skin and mucous membranes surrounding the eye.

(ii) "Keep bottle tightly closed and store away from light when not in use to prevent the product from losing potency.

4. *Labeling of product attributes.* The Panel accepts the use in labeling of terms describing certain physical and chemical qualities of OTC ophthalmic products, so long as these terms do not imply any therapeutic effect. The qualities which may be referred to pertain to the comfort and safety of the product, are usually due to specific inactive ingredients (pharmaceutical necessities) included in the final product formulation, and are described in labeling to inform the consumer.

The pH, or hydrogen ion concentration, of an ophthalmic product may have a considerable effect on the ocular comfort of the user. The Panel concludes that certain labeling claims are reasonable and informative to the consumer when they accurately reflect the pH of the solution. Terms such as "neutral solutions," "buffered to the pH of tears," "slightly acidic solution" (with actual pH in parentheses), or "slightly basic solution" (with actual pH in parentheses) are considered acceptable.

The osmotic properties of ophthalmic solutions may also have an effect on the comfort of the consumer. The Panel concludes that certain labeling claims are reasonable and informative to the consumer when they accurately reflect the osmotic or tonicity properties of the product. Terms such as "isotonic solution," "osmotically equivalent to tears," "isotonic to tears or lacrimal fluids" are considered acceptable. An ophthalmic solution should have an osmotic equivalence of between 0.8 and 1.0 percent sodium chloride to comply with labeling claims of "isotonic solution" or with labeling claims that allude to the solution's being isotonic or osmotically equivalent to lacrimal fluid. Solutions intended to be used as eye washes or irrigating fluids should have an osmotic equivalence of between 0.8 and 1.2 percent sodium chloride. (See part II. paragraph E.1.c. above—Tonicity.)

The term "hypertonic solution" is acceptable for solutions containing 2 to 5 percent sodium chloride.

Although all ophthalmic products must be sterile, the Panel accepts the use of the term "sterile solution" or "sterile ointment" on the labeling of

OTC ophthalmic products as being informative to the consumer.

The Panel concludes that certain labeling claims are informative to the consumer when they accurately reflect inherent characteristics of the marketed product. Terms such as "soothing" and "soothing relief" are considered acceptable in the labeling. However, the Panel emphasizes that these terms should not be identified as indications for use. They are merely factual statements related to product performance.

H. Principles Applicable to Combination Products

1. *General concepts.* The Panel acknowledges and concurs with the rationale expressed in the regulation at 21 CFR 330.10(a)(4)(iv), which states as follows:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concludes that, in general, the fewer the ingredients, the safer the therapy. The interests of the user of OTC drugs are best served by exposure to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

OTC durgs containing safe and effective single ingredients are preferred to those having multiple active ingredients because of the reduced risks of toxic effects, synergistic effects, allergic, or idiosyncratic reactions, and possible unrecognized and undersirable drug interaction(s).

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions. However, the Panel recognizes that combinations of active ingredients may be desirable in some circumstances.

The Panel concludes that OTC ophthalmic drugs should contain only such inactive ingredients as are necessary for formulation.

The Panel's combination policy is based on those combination products submitted pursuant to the notice published in the **Federal Register** of April 26, 1973 (38 FR 10306). The Panel recognizes that other combination products may be in the market place but it has either no knowledge of insufficient data to make a reasonable judgment of the safety or effectiveness of such products.

2. *Safety of combinations.* In its consideration of active ingredients, the Panel reviewed the safety and effectiveness of all the combinations submitted. All combinations that meet the criteria for Category I as set forth below are considered safe.

3. *Effectiveness of combinations.* Combination products are regarded as effective if each active ingredient is present in the product within the dosage set by the Panel for each Category I active ocular ingredient, as set forth elsewhere in this document.

The Panel considers it important that the minimum effective dose be established for each ingredient in a combination product. If the dosage level for any active ingredient in a combination product is below the minimum set by the Panel for that ingredient when used alone, data should be developed by appropriate, well-controlled clinical studies to demonstrate its effectiveness.

4. *Active ingredients not reviewed by the Panel.* Each claimed active ingredient must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient that has not been reviewed by the Panel and is consequently not found in this docment, such ingredient is automatically classified as a Category II ingredient, i.e., not safe or not effective or both for use in OTC ophthalmic drug products. Appropriate animal and human testing and prior approval by FDA is required before a product containing such an ingredient may be marketed.

5. *Criteria for determining Category I combination drug products.* To qualify as a Categroy I combination, i.e., one that is generally recognized as safe and effective, the combination must meet the following conditions:

a. Each active ingredient in the combination must be a Category I ingredient.

b. Each ingredient in the subject combination must be present within the dosage range for a Category I active ingredient, as set forth elsewhere in this document.

c. The final marketed product must be shown to be safe and effective.

d. The Panel concludes that the following combinations of ocular active ingredients are Category I:

(1) *Zinc sulfate (ocular astringent) combined with an ocular vasoconstrictor.* The Panel considers it rational to combine a Category I ocular astringent with a Category I ocular vasoconstrictor because such a combination would better accomplish the overall effect of reducing redness and irritation of the eyes. The Panel is limiting the ocular astringent to zinc sulfate since it is the only Category I ocular astringent recognized at this time. There are several different products currently on the market which combine zinc sulfate with various ocular vasoconstrictors. The experience with these marketed products does not suggest any incompatibility problems. The Panel is unaware of any reason to restrict zinc sulfate-vasoconstrictor combinations to only those that are currently marketed. Therefore, zinc sulfate may be combined with any Category I vasoconstrictor.

(2) *Combinations of any two or three ocular demulcent ingredients.* The Panel considers it rational to allow up to three ocular demulcent ingredients to be combined in OTC drug products. The Panel recognizes that severl demulcent ingredients may be necessary for formulation purposes. However, the Panel finds no reason for allowing more than three of these ingredients in any one product.

(3) *Ocular demulcents combined with an ocular vasoconstrictor.* The Panel considers it rational to combine any Category I ouclar demulcent or Category I ocular demulcent combination with any Category I ocular vasonstictor. The demulcent will aid in relieving the discomfort of the eye irritation. In addition, the viscous nature of the demulcent will prolong the action of the vasoconstrictor by keeping the vasoconstrictor in contact with the eye for a longer period.

(4) *Zinc sulfate (ocular astringent) combined with an ocular vasoconstrictor and ocular demulcents.* The Panel has discussed in (1) above the rationale of the zinc sulfate-vasoconstrictor combination. The addition of a Category I demulcent or Category I demulcent combination will aid in producing further relief from the irritation and in prolonging the action of the other ingredients.

(5) *Combinations of two or more ocular emollient ingredients.* The Panel considers it rational to allow ocular emollient active ingredients to be combined when necessary. The Panel recognizes that several emollient ingredients may be necessary to give a product a proper consistency for application to the eye.

6. *Criteria for Category II combination drug products.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe or not generally recognized as effective or both, if any of the following apply:

a. The combination contains active ingredients each of which is safe and effective when used alone, but in combination is found to be not safe. The Panel concludes that combining two different vasoconstrictor agents in a single product would be such a combination.

b. The combination contains any ingredient that is listed elsewhere in this document as a Category II ingredient.

c. The combination contains any ingredient in excess of the maximum dosage set by the Panel for such ingredient.

d. The combination contains any active ophthalmic ingredient that has not been reviewed by the Panel and accordingly not listed in this document.

7. *Criteriq for Category II combination drug products.* A combination is classified as a Category III combination if any of the following apply:

a. If any Category I ingredient falls below the established minimum dosage set.

b. If one or more ingredients are Category III ingredients, as set forth else forth elewhere in this document for single active ingredients.

III. Ocular Anesthetics

The Panel concludes that ocular anesthetics are effective but are unsafe for OTC use because the potential risks to the consumer that can arise from the OTC use of these ingredients for out weigh the benefits.

The Panel recognizes that ocular anesthetics have a purpose and justifiable use in ophthalmologic practice, but the Panel concludes that anesthetics should be used only under the direction and supervision of a physician. Professional use of local anesthetics in ophthalmic conditions include (1) obtaining transient loss of corneal and conjunctival sensitivity, e.g., in routine tonometric and gonioscopic procedures, removal of foreign bodies, conjuctival and corneal scrapings, removal of sutures, and paracentesis of the anterior chamber; and (2) relieving severe blepharospasms produced by irritants to allow thorough examination and irrigation of the eye.

One of the risks associated with OTC use of ocular anesthetics is the masking of the symptoms associated with serious eye problems, such as foreign bodies embedded in the eye, corneal abrasions, or eye diseases which require professional attention.

Ocular anesthetics can mask such significant symptoms as severe pain, reduced visual acuity, or major ocular discomfort, and the use of such preparations may prevent or delay definitive treatment of an ocular disease that requires prior diagnosis by a physician to establish proper medical therapy.

It has been well established in animal and in vitro studies that ocular anesthetics generally have toxic effects on the epithelium of the cornea, depress respiration and glycolysis of the epithelial cells, interfere with regeneration of corneal epithelium, increase permeability, induce sensitization reactions, decrease the blink frequency, cause edema of corneal epithelium, and produce dryness of corneal and conjuctival surfaces (Refs. 1 and 2). Self-medication with local anesthetic preparations may lead to irreversible ocular damage if the medication is used for prolonged periods (Ref. 3). Even short-term use can hinder the healing process (Ref. 1).

Ocular anesthetics may remove patches of corneal epithelial cells with even a single application. Repeated use of these anesthetics can lead to severe corneal erosions (Ref. 2). Serious problems, such as corneal ulcerations with scarring and consequent permanent visual loss, have resulted from long-term lay use of ocular anesthetics. While the corneal changes are usually mild and transient after a single instillation of an ocular anesthetic, repeated application of ocular anesthetics following injury to the cornea may seriously delay or prevent regeneration of the corneal epithelium.

The use of ocular anesthetics promotes a vicious cycle in which an anesthetic agent applied to relieve discomfort due to toxic or mechanical injury to the epithelium actually interferes with the healing of the injury and causes the condition to worsen. In addition, the effective potency of an ocular anesthetic agent is diminshed with continued application (Ref. 4). Under these circumstances reapplication of the anesthetic provides a shorter duration of relief of the discomfort, leading to more frequent application. This more frequent application eventually may lead to ulceration of the cornea and conjuctiva.

Chronic use of anesthetics in the eye can lead to changes that begin with keratitis and may end in permanent reduction of visual acuity. Loss of corneal epithelium by sloughing and edema of the corneal stroma, opacification, and marked inflammatory changes in the anterior segment of the eye are the sequence of events that follow days or weeks of such treatment (Ref. 3).

Epstein and Paton (Ref. 3) demonstrated in their case studies that the misuse and abuse of ocular anesthetics could lead to serious eye damage. The development of corneal degeneration and, in one case, irreversible loss of visual acuity was shown to occur after chronic use of local anesthetics (Ref. 2).

Allergic reactions to ocular anesthetics occur and very somewhat with drug used. For example, allergic reactions are less common with proparacaine than with tetracaine. Reactions such as widened intrapalpebral fissures, changes in accommodation, and pupillary dilation occur with cocaine but do not occur with most of the other topical anesthetics (Ref. 2).

The Panel reviewed two submitted ingredients as ocular anesthetics: Antipyrine (which the Panel reviewed in this category because if its inclusion in a submitted product as a claimed pain reliever, rather than for its pharmacologic activity which is not truly anesthetic) and piperocaine hydrochloride.

The Panel noted that antipyrine in a 0.4-percent solution was found to have only slight local anesthetic effect on the eye (Ref. 5). Piperocaine hydrochloride in a 2-percent solution or a 4-percent ointment is an effective ocular anesthetic (Ref. 6).

In keeping with the Panel's belief that an anesthetic effect, no matter how slight, can mask symptoms of serious ocular disorders and that misuse or overuse of ocular anesthetic ingredients may ultimately be injurious to the eye, the Panel concludes that the entire class of ocular anesthetics is unsafe for OTC use, and therefore, all ocular anesthetics are classified as Category II. Because the entire anesthetic class is in Category II, all labeling associated with ocular anesthetic ingredients is also in Category II.

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IV. Ocular Anti-Infectives

A. General Discussion

Topical anti-infective agents are applied to the eye to inhibit the growth of infecting organisms. Body mechanisms then remove the infecting organisms and act to repair the tissue damage. The anti-infective drugs act to interfere preferentially with the metabolism of the micro-organism in comparison with the normal cells of the eye. The preferred treatment of ocular infection depends on isolating and determining the infecting organism, so that the proper anti-infective agent will be used.

The Panel believes that anti-infective preparations should not be used to self-treat serious ocular infections such as corneal ulcers and intraocular infections, since these infections require vigorous and appropriate treatment by a physician. The Panel recognizes, however, that many minor ocular infections such as blepharitis, conjunctivitis, and hordeolum (stye) may not require immediate attention by a physician since these conditions are normally self-limiting, and serious complications from self-treatment are rare. Therefore, the Panel believes it is theoretically reasonable to recommend the OTC use of ocular anti-infective drug products to treat minor infections of the eye. However, the Panel recognizes that at the present time there are no anti-infective ingredients that can be generally recognized as safe and effective.

Because the Panel believes that the consumer would not be able to diagnose conjunctivitis, blepharitis, or stye, the indications for use of these products should be limited to "for the treatment of minor external infections of the eye." In addition, since the signs and symptoms of infections amenable to OTC treatment are often similar to conditions that are not amenable to OTC treatment, the labeling of OTC anti-infective drug products must warn the user of the product's limitations, so that if a more serious underlying ocular problem exists, professional treatment will not be delayed. The Panel concludes that the general warning statements required on all OTC ophthalmic drug products are sufficient to alert consumers to the potential seriousness of ocular problems and to encourage them to seek professional help if the condition worsens or persists for more than 72 hours.

B. Categorization of Data

1. *Category I conditions under which ocular anti-infective active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

None.

Category I Labeling

The Panel recommends the following labeling for OTC ocular anti-infectives:

a. *Indication.*

"For the treatment of minor external infections of the eye."

b. *Warnings*—(1) *For all OTC ophthalmic anti-infective drug products.*

(i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(ii) "If you experience severe eye pain, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

(2) *For OTC ophthalmic anti-infective drug products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(3) *For OTC ophthalmic anti-infective solutions.* "If solution changes color or becomes cloudy, do not use."

2. *Category II conditions under which ocular anti-infective active ingredients are not generally recognized as safe and effective or are misbranded.*

The Panel recommends that the Category II conditions be eliminated from OTC ocular anti-infective drug products effective 6 months after the date of publicaiton of the final monograph in the **Federal Register.**

Category II Actie Ingredient

Sulfacetamide sodium

Sulfacetamide sodium.—While sufacetamide sodium was not included in the original submissions of data pursuant to the call for data as published in the **Federal Register** of April 26, 1977 (38 FR 10306), the Panel specifically requested data from the manufacturer on this ingredient, which is currently limited to prescription use, to determine the feasibility of recommending OTC marketing. It is marketed in 10-, 15-, and 30-percent concentrations.

Sulfacetamide sodium is a sulfonamide having a solubility of 1 g in 2.5 mL of water. The drug has a bitter taste, and Scruggs, Wallace, and Hanna (Ref. 1) noted that, following application to the eye, sulfacetamide sodium will pass into the nose, and the throat, where a bitter taste will be noted. The drug then can be systemically absorbed from the nasal cavity and oral pharynx.

The preparation, stabilization, and sterilization of sulfacetamide sodium solutions may be difficult (Ref. 2). Solutions of sulfacetamide sodium in water are alkaline (Ref. 3); a 30-percent solution of sulfacetamide sodium has a pH of 8 (Ref. 4). Ophthalmic solutions of this drug are buffered by the addition of phosphates and borates. Both buffered and unbuffered solutions, on standing, experience the formation of sulfanilamide and can turn brown (Ref. 5). Clarke (Ref. 5) studied the extent of decomposition of sulfacetamide sodium solutions, and Fletcher and Norton (Ref. 6) found that buffered sulfacetamide sodium was stabilized by the addition of 0.1 percent sodium metabisulfite.

The sterility of sulfacetamide sodium solutions is difficult to maintain upon exposure to the environment. Whittet (Ref. 7) found fungi, including common molds, in sulfacetamide solutions which included the 30-percent concentration. The sterility of these can only be maintained by the addition of preservatives and by storage in a cool place.

Sulfacetamide ophthalmic ointment preparations are sterile and contain preservatives. There is no need for buffers or stabilizers when this drug is suspended in anhydrous ointment.

Sulfacetamide sodium ophthalmic preparations are incompatible with silver preparations.

(1) *Safety.* Sulfacetamide sodium has been widely used as a prescription drug to treat external eye infections. The incidence of severe ocular toxicity and systemic side effects has been low (Refs. 8 and 9). The Panel recognizes, however, that the use of sulfacetamide sodium has been limited to a small segment of the population which is usually under the medical supervision of an ophthalmologist and generally for a short period of time. Also, those patients known to be sensitive to sulfonamides are usually treated with other drugs. The exact incidence of sensitization in the general population, if this drug were marketed OTC, is not known, but it most likely would be higher than at present.

Sollman (Ref. 10) states that local application of sulfonamides to skin, conjunctiva, and nasal mucosa presents a special hazard of sensitization, in that future internal or external use of sulfonamides may produce serious local or generalized exfoliative dermatitis.

The Panel is aware that the current ophthalmic solutions of sulfacetamide sodium produce a burning and smarting sensation when instilled into the eye. This effect was first noted by Benedict and Henderson (Ref. 9). A 30-percent sulfacetamide sodium solution is equivalent in tonicity to a hypertonic sodium chloride solution of 9 percent (Ref. 11). Luxenburg and Green (Ref. 12) reported that every patient studied complained of stinging and burning, lasting for about 5 minutes, when a 30-percent solution of sulfacetamide was instilled into the eye. Occasionally, the 30-percent solution may produce epithelial cell injury to the cornea and conjunctiva which can cause ocular irritation lasting from several hours to days. It is not surprising that most subjects experience a burning and smarting sensation following the ocular instillation of even a 10-percent sulfacetamide sodium solution (Ref. 11). Repeated, unsupervised use could lead to persistent ocular irritation.

Cases of Stevens-Johnson syndrome were reported in reaction to sulfacetamide sodium by Ban and Bose (Ref. 13) in 1965 and Gottschalk and Stone (Ref. 14) in 1976. There are also recent reports of bloody tear production following sulfacetamide instillation into the eye (Ref. 15).

(2) *Effectiveness.* Sulfonamides exert a bacteriostatic action against a variety of gram-positive and gram-negative pathogenic bacteria (Refs. 16, 17, and 18), including some strains of pseudomonas grown in culture (Ref. 19). There is only one double-blind study related to the value of topical sulfacetamide sodium in the treatment of blepharitis (Ref. 20). While this study was not designed to show the antibacterial effectiveness of sulfacetamide, it did show that the post-treatment bacterial cultures of the conjunctiva were negative.

Sulfacetamide is ineffective in treating fungal and viral infections of the eye and has been known to give rise to resistant strains of micro-organisms when given orally (Ref. 21). It is possible that long-term unsupervised use of sulfacetamide could lead to the development of resistant strains of bacteria and fungi, and a proliferation of fungi in the conjunctival sac.

Sulfacetamide sodium has been used since the late 1930's in the treatment of many types of infections which include those of the eye, skin, and urinary tract (Refs. 21 through 24). It is now primarily used to treat eye infections (Refs. 20 and 21). There are a number of reports suggesting that sulfacetamide is effective in treating ocular infections, including trachoma (Refs. 4, 8, 21, 22, 23, and 25 through 33). In 1969 the National Academy of Sciences-National Research Council concluded that sulfacetamide sodium is effective in treating acute and chronic conjunctivitis and corneal ulcers. This conclusion was published in the **Federal Register** on September 10, 1969 (34 FR 14248). There are numerous publications on the possible effectiveness of sulfacetamide sodium in animal experimental models of infection, but these experiments are always difficult to evaluate (Refs. 16, 17, 18, 24, 31, 33, 34, and 35).

(3) *Evaluation.* After review of the data, the Panel concludes that sulfacetamide sodium (either 10-, 15-, or 30-percent concentrations) is not safe for OTC use as an ocular anti-infective due to its irritating and allergic sensitization potential. In addition, while the prescription product is currently effective, sanctioning the OTC marketing of sulfacetamide sodium could lead to the emergence of resistant strains of organisms. Therefore, the Panel concludes that sulfacetamide sodium should remain limited to prescription use.

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Category II Labeling

The Panel concludes that the use of certin labeling claims related to the safety and effectiveness of ocular anti-infective ingredients in ophthalmic products is unsupported by scientific data.

The use of the term "stye" as a product name or as a part of a product name is unacceptable to the Panel because it implies that the product will cure a stye infection. There is no scientific evidence to support this implication, and the use of this term as a product name could be misleading to the consumer.

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

The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

Boric acid
Mild silver protein
Yellow mercuric oxide

a. *Boric acid.* The Panel concludes that boric acid is safe for use as an OTC ocular anti-infective when used within the dosage limits set forth below, but there are insufficient effectiveness data available to permit final classification.

Boric acid, also known as boracic acid, or orthoboric acid, is a colorless, odorless material which is in the form of scales, crystals, or white powder. When dry, it is 99.5 percent boric acid (Refs. 1 and 2). Boric acid is readily prepared from borax (sodium borate).

Boric acid and sodium borate are used as a buffer system for many ophthalmic solutions. Boric acid solution has also been used extensively as an eyewash (Refs. 3 and 4).

(1) *Safety.* The Panel concludes that boric acid is safe when used in the amounts contained in ophthalmic solutions or ointments.

Boric acid has enjoyed great popularity in the form of powders, lotions, ointments, and pastes. Solutions for irrigation of bladder, rectum, and serous cavities also have been used. Within a few years after the use of boric acid became established in medicine, reports of poisonings began to appear in the literature (Refs. 5 and 6). Many of the early reports of poisoning were from the application of boric acid-containing medicaments to burns or wounds (misuse) and not from accidental ingestion. More recently, however, boric acid poisoning has occurred accidently rather than from its use as a medication (Ref. 6).

By the mid 1940's any use of boric acid was questioned. For example, Watson (Ref. 7) wrote a paper entitled "Boric Acid: A Dangerous Drug of Little Value." Pfeiffer, Hallman, and Gersch (Ref. 8) wrote a paper entitled "Boric Acid Ointment: A Study of Possible Intoxication in the Treatment of Burns."

The significant risk of toxicity associated with either absorption of boric acid through broken skin, or through inadvertent oral ingestion, has prompted some medical authorities to discourage the use or the distribution of boric acid for any medical purpose (Refs. 5 and 9).

Poisoning from the minimal lethal dose of boric acid has occurred accidently rather than from its use as medication (Ref. 6). Accidental poisoning has been reported to occur in infants from the oral ingestion of as little as 3 g boric aid (Ref. 10). Much larger doses have been administered to adults without dangerous toxic effects (Refs. 6 and 11). Frost and Richards (Ref. 12) found that low concentrations of boric acid injected over long periods of time in animals produced no toxic effects. He concluded that boric acid would not exert toxic effects until the renal threshold is exceeded and accumulation occurs in the tissues.

The Panel recognizes that OTC ophthalmic products contain much less boric acid than is required to produce toxicity. It would be necessary to ingest the contents of a number of commercial containers of OTC ophthalmic boric acid preparations for toxicity to occur. Therefore, the Panel concludes that boric acid is safe for OTC ophthalmic use.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available on effectiveness to permit final classification of boric acid as an OTC ocular anti-infective.

Many consumers have used boric acid solution as eye drops to treat minor ocular infections. Many professionals who treat ocular infections have prescribed saturated boric acid solution or 5-percent boric acid ointment to treat minor ocular infections. Yet, there are no reports to indicate that boric acid preparations are effective in treating ocular infections. Many minor ocular infections disappear without treatment with drugs.

Throughout history, boric acid has been used to treat infections. Borax was used by Arab physicians in A.D. 875 to cleanse wounds, and it was taken internally as well (Ref. 13). Homberg, in 1702, heated borax and converted it into boric acid and gave it the name *sal sedativum* (Ref. 5). Borax and boric acid have been used as a panacea by the early physicians and surgeons to treat illness. Godlee (Ref. 14), in 1873, recommended that boric acid be used as a companion agent with Lister's anti-infective, carbolic acid (phenol). Boric acid was used as an anti-infective in the pre-bacteriological era prior to the germ theory of disease. Boric acid became widely accepted as a germicide without laboratory and clinical studies to document its effectiveness (Ref. 15).

At the beginning of the 20th century, boric acid was used to clean teeth and preserve meat (Ref. 16). Soon afterwards toxicity to the borate was noted. Bernstein (Ref. 17) in 1910 tried 0.3 percent boric acid to preserve pork. He found some beneficial effect by noting a lack of odor of the stored pork. Later a number investigators questioned whether saturated boric acid solution would kill micro-organisms. Tanner and Funk (Ref. 18), in 1919, reported a bacteriostatic effect of one-tenth saturated solution of boric acid on several bacterial pathogens.

Allen (Ref. 19), in 1929, investigated 21 commonly used germicides for their bactericidal activity. He found boric acid to be the least effective of the 21 germicides studied.

Browning (Ref. 20) determined the effect of various dilutions of boric acid on the growth of pathogenic bacteria in broth cultures. He reported both bacteriostatic and bactericidal activity but only after 24 hours of incubation.

In 1958, Kingma (Ref. 13) reviewed the pharmacology and toxicology of boron compounds. At that time about 95 percent of the dermatologists surveyed were using boric acid preparations in their practice. Kingma cultured *Staphylococcus aureus, Streptococcus haemolyticus,* and *Bacillus (Escherichia) coli* in the presence of various concentrations of boric acid for 24 hours. An extrapolation of the preliminary results of his data indicated a 50-percent inhibition of growth with a 0.1- to 0.5-percent concentration of boric acid. Half of the bacteria were killed by incubation for 24 hours with 0.4- to 0.75-percent boric acid solution. Kingma noted that the bacteriostatic effect of boric acid solutions requires at least 24-hour contact with pathogenic bacteria, and to shorten this time interval would require a much higher concentration of boric acid.

It has become recognized that boric acid solutions are at best bacteriostatic when in contact with pathogenic bacteria for less than one hour.

Boric acid and its sodium salt are presently used as a buffer system in ophthalmic preparations. This buffer system is effective and well tolerated when used in eye drops. However, to

claim that boric acid is useful in the treatment of infections of the conjunctiva, cornea, and eyelid requires studies using current clinical experimental methods as discussed below. (See part IV. paragraph C. below—Data Required for Evaluation.) For example, the bacteriostatic effects of boric acid must be demonstrated to be sufficiently rapid to be useful in infections of the eye. Furthermore, eye drops are diluted by the tears, and this dilution is so great that component ingredients in the drop are diluted ten times in a matter of minutes (Refs. 21 and 22). There is no evidence to indicate that boric acid crystals, when suspended in ointment, reach a concentration in the tears that is adequate to exert a bacteriostatic effect (Ref. 23). However, ointments do provide a method of delivering rather high concentrations of drug to the eye (Ref. 24). Should evidence be gained to demonstrate that a bacteriostatic concentration of boric acid can be maintained in the tear film, it will then be necessary to obtain clinical evidence supporting claims of efficacy in the treatment of infections of the conjunctiva and lids.

(3) *Proposed dosage.* Adults and children: Instill a 5-percent boric acid ointment or solution in the affected eye(s). As the Panel is recommending drug release studies to be done as part of the Category III testing, the Panel is unable to propose a dosage frequency at this time. The drug release data will determine the frequency of application required to produce the required effect.

(4) *Labeling.* The panel recommends the Category I labeling for products containing ocular anti-infective active ingredients. (See part IV. paragraph B.l. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC ocular anti-infectives. (See Part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Mild silver protein.* The Panel concludes that mild silver protein is safe when used within the dosage limits set forth below, but effectiveness data are lacking to permit final classification at this time.

Marketed mild silver protein products contain either 20 or 40 mg of silver per mL of solution. The silver ion is stabilized with gelatin and edetate but the silver ion is unstable when exposed to light. Therefore, the Panel concludes that mild silver protein solutions should be packaged in tight, light-resistant containers to avoid changes in potency. Also, the labeling should instruct the user to tightly close the container after each use and to store away from light. Mild silver protein is a colloidal complex of silver and protein in which the protein serves to regulate or reduce the corrosive properties of the silver ion.

(1) *Safety.* Mild silver protein has been used for decades without reports of toxicity. However, prolonged or frequent use of any silver preparation may produce a condition known as argyria or argyrosis. In the eye, this condition develops as an unsightly, long-lasting, ashen-grey-to-brown color of the skin and mucous membranes and is caused by the accumulation of silver granules in the membranes or tissues of the body. the Panel considers it reasonable to require statement on the label concerning this side effect.

Hanna, Fraunfelder, and Sanchez (Ref. 1) found that long-term use of mild silver protein leads to staining of the conjunctiva, cornea, and the region around the punctum, but that normal eye function is not altered by the staining effect.

Because there are no toxicity concerns from use of mild silver protein, the Panel concludes that it is safe for OTC use as an anti-infective, provided that the labeling contains a statement warning of the argyria side effect with prolonged use.

(2) *Effectiveness.* In the preantibiotic era, silver preparations were used in the treatment of infections. Mild silver protein has in vitro activity against many bacteria (Refs. 2 through 7). Development of resistance of micro-organisms sensitive to this agent has not been reported. However, some strains of *Staphylococcus aureus* and pseudomonas species are always resistant (Ref. 4). Its effectiveness as an ocular anti-infective has not been documented (Refs. 5, 6, and 7). Solutions of mild silver protein do not require

preservative agents since the silver ion has intrinsic antibacterial activity.

The Panel concludes that the claim that mild silver protein is useful in the OTC treatment of minor eye infections requires clinical studies as outlined below. (See part IV. paragraph C. below—Data Required for Evaluation.)

(3) *Proposed dosage.* Adults and children: Instill 1 to 2 drops of mild silver protein solution, containing 20 to 40 mg of silver per mL of solution, into the affected eye(s). Repeat every 2 to 4 hours as necessary.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing ocular anti-infective active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends that labeling of mild silver protein products contain the following warnings:

(a) "Prolonged or frequent use of this product may cause permanent discoloration of the eye and the skin and mucous membranes surrounding the eye."

(b) "To prevent medicine from deteriorating, keep bottle tightly closed and store away from light when not in use."

(5) *Evaluation.* The Panel concludes that when used within the dosage limit set forth above, mild silver protein is safe for use as an OTC ocular anti-infective. However, there are insufficient data on effectiveness to permit final classification at this time. Data to demonstrate effectiveness will be required in accordance with guidelines set forth for OTC ocular anti-infectives. (See part IV. paragraph C. below—Data Required for Evaluation.)

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c. *Yellow mercuric oxide.* The Panel concludes that there are insufficient data to make a final determination that yellow mercuric oxide is safe and effective for use as an OTC ocular anti-infective.

The bacteriostatic property of mercuric salts is considered to be due to the mercuric ion content of the solution (Ref. 1). Mercuric oxide exists in red and yellow crystalline forms. Both forms are practically insoluble in water, having a solubility of 0.52 mg per 100 mL of water at 25° C (Ref. 2). However, mercuric oxide contains 92 percent mercury for ionization and becomes highly soluble in water at 100° C. On cooling to 25° C, only 0.48 mg mercuric ion will be in 100 mL solution, which is a concentration of 0.0048 mg per mL water or a dilution of 1 part of mercuric ion in approximately 200,000 parts of water (Ref. 2).

(1) *Safety.* The Panel concludes that there are insufficient data available to determine the safety of yellow mercuric oxide for use as an OTC ocular anti-infective.

Mercury has been used for centuries to treat infections (Ref. 3). Inorganic mercury salts were recommended by Robert Koch in 1861 as antiseptic drugs. The soluble mercury salts are bacteriostatic, but these compounds are also toxic when applied to mucous membranes (Ref. 1).

Yellow mercuric oxide was introduced into ophthalmology by Pagenstecher in 1866 as a 0.1- to 1.0-percent concentration suspended in ointment. Pagenstecher's ointment contained yellow mercuric oxide and small amounts of mercuric chloride. In 1933, Hosford and McKenney (Ref. 4) noted that Pagenstecher observed that the immediate effect of this ointment was "undoubtedly irritant" and that the ointment produced tissue sloughing if applied too freely and left too long in contact with the tissue. Hosford and McKenney suggested that Pagenstecher's ointment was more often harmful than useful.

The Panel received a report from a practicing ophthalmologist that, because of a delay in medical attention, serious problems resulted in patients using an ointment containing yellow mercuric oxide to self-treat minor infections of the eye, including stye (Refs. 5 and 6).

There is a recent submission indicating that over 1 million units of an ophthalmic preparation containing yellow mecuric oxide have been marketed with only a small number of minor patient complaints (Ref. 7).

(2) *Effectiveness.* The Panel concludes that there are insufficient data to determine the effectiveness of yellow mercuric oxide for use as an OTC ocular anti-infective.

The antibacterial action of mercurial salts is a function of the amount of free mercuric ion that is delivered. Therefore, the water insoluble-mercurials, such as yellow mercuric oxide, do not produce immediate effects (Ref. 1). While the water-insoluble mercurials are gradually dissolved by the proteins and salts of the tissues, the concentration of available mercuric ion from yellow mercuric oxide is insufficient to prevent growth of staphylococcus (Ref. 8). A more recent limited in vitro bacteriologic study suggests that yellow mercuric oxide may have anti-infective properties (Ref. 7).

The Panel notes that in the past, yellow mercuric oxide ointment which was marketed OTC contained small amounts of mercuric chloride. Hosford and McKenney (Ref. 4) suggested that the effectiveness of the ointment was due to the mercuric ion released from the mercuric chloride and not from the yellow mercuric oxide. However, in 1889 Geppert confirmed that, while mercuric chloride has a high bacteriostatic potency and prevents the multiplication of many bacteria in dilutions of 1:300,000, it is not a reliable germicide, for the bacteria are not killed but resume growth when the mercuric chloride is removed or further diluted (Ref. 1). The National Formulary now requires that yellow mercuric oxide be used in pure form—not "contaminated" by the presence of any other ingredient—and the Panel recognizes that any effectiveness which the mercuric chloride might have contributed is now removed (Ref. 7).

(3) *Proposed dosage.* Adults and Children: Instill a small amount of a 1-percent yellow mercuric oxide ointment into the affected eye(s) twice a day.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing ocular anti-infective ingredients. (See part IV. paragraph B.1. above—Category I Labeling).

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to determine whether yellow mercuric oxide is safe because of the sensitizing properties of mercuric salts. In addition, the Panel concludes that there is also insufficient evidence to determine whether this ingredient is effective as an ocular anti-infective.

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Category III Labeling

None.

C. Data Required for Evaluation

The Panel considers that the following guidelines for moving Category III ingredients into Category I are in accordance with the present state of the art and do not preclude the use of improved methodology in the future.

1. *Clinical trials.* The Panel has given careful consideration to the types of studies and data required to reclassify Category III ocular anti-infectives as Category I. It is sufficient to perform a well-controlled, double-blind clinical study of adequate size to determine if the Category III ocular anti-infectives are effective.

The final appraisal of effectiveness should take place under circumstances conforming to actual expected use in the community. The study should include a sufficient number of patients to substantiate effectiveness as an ocular anti-infective. "Before-treatment" data should be obtained for each subject to note any conditions which might bias analyses. The study should include patients diagnosed as having minor external eye infections, i.e., conjunctivitis, blepharitis, or stye. Patients with more serious ocular infections should not be included in the study since the OTC ocular anti-infectives are not indicated for serious infections. Patients should be observed closely for any adverse effects.

Animal and human model studies when appropriate can give useful information concerning the effectiveness of a product, but the final appraisal must take place in a well-controlled clinical study. The Panel agrees that § 314.111(a)(5)(ii) (21 CFR 314.111(a)(5)(ii)) outlines the features of a well-defined clinical trial.

All data, including both favorable and unfavorable results, should be submitted to FDA.

2. *Drug release studies.* The Panel recognizes the value of drug release studies where appropriate on formulations prior to conducting a clinical study (where appropriate) to determine dosage frequency to be used in the clinical study. Under the varying conditions of ophthalmic ointment preparation, the amount of drug available for ocular contact can be greatly altered. Ophthalmic ointments are designed to melt at body temperature (Refs. 1, 2, and 3); for example, the standard ophthalmic ointment, a 60:40 mixture of white petrolatum, U.S.P., and mineral oil, U.S.P., melts readily when applied to the eye. Ophthalmic drugs which are suspended in this ointment base dissolve on contact with the tears. Other ointment bases may contain varying amounts of water so that it is possible that the drug is dissolved in the aqueous phase (Refs. 3 and 4). It is important that data be obtained concerning the length of time it takes before the anti-infective agent is diluted to noninhibitory antibacterial concentrations in the tear film. Some drugs have been known to be diluted to one-tenth the original strength in a matter of minutes (Refs. 5 and 6). The manner of administering the ocular preparations can greatly affect the rate of loss of material from the tear film (Ref. 7). The experimental clinical protocol and the labeling of the finished product should indicate exactly how the formulation is to be given. Animal and human model studies (where appropriate) could also be used to validate the results of the drug release study before conducting the clinical trial.

3. *Animal and human models.* It is the consensus of the Panel that animal and human model studies (where appropriate) could give useful information as to the effectiveness of a product. Information derived from these studies could be helpful, for example, in predicting appropriate dosage levels for desired response in clinical trials.

Experimental animal models of antibacterial activity involve injuring the superficial cornea or conjunctiva or both. This is followed by ocular drops of pathogenic bacteria of the type the drug is expected to be used to treat. The treatment is begun after the infectious process develops. Furgiuele, Kiesel, and Martyn (Ref. 8) in 1965 infected rabbits by scarifying the cornea and then dropping in 1,000,000 cells per mL of pseudomonas organisms. One day later, treatment was begun with gentamicin ocular drops and the treatment continued for 5 days. Clinical signs of inflammation such as edema, hyperemia, and discharge were graded. The double-blind, cross-over experiment using nontreated eyes as a control and with the amount of inflamation evaluated by a trained observer were used to make statistically valid conclusions about the effectiveness of the therapy. Similar animal studies using minor external eye infections can be used to determine the effectiveness of the anti-infective.

A human study could involve the use of certain ocular ointments which form an occlusive shield over the surface of the eye. Grayston et al. (Ref. 9) found that the use of these ointments for several hours on the cornea and conjunctival surfaces fostered the development of bacterial conjunctivitis. Bacterial growth in the conjunctival sac can also be increased if the eye if bandaged (Ref. 10). Quantitative bacterial counts are obtained prior to bandaging. The eyes are then treated with randomly selected anti-infective ophthalmic preparations or controls during the period of patching which may continue for several days. Repeated quantitative bacterial counts are obtained at selected times.

While the human model studies may be useful in predicting the dosage regimen for some clinical trials, it may not be applicable for all drugs (Ref. 11).

Testing of Category III ingredients should be done on the final formulation product.

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V. Ocular Vasoconstrictors

A. *General Discussion*

Irritation of the external tissues of the eye (cornea and conjuctiva) results in the production of copious tears which are intended to dilute the irritating substance to a nonirritating concentration. When the noxious substances are not sufficiently diluted by tears, white blood cells migrate to the area, and a dilation of the underlying blood vessels (resulting in hyperemia or redness of the eye) occurs.

Minor reaction of the eye to noxious agents may be recognized as ocular itching and tearing with sensations of smarting and burning.

Sometimes this minor ocular irritation can be alleviated by the use of buffered, neutral, aqueous eye drops. If redness persists along with itching, the redness 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.

B. Categorization of Data

1. *Category I conditions under which ocular vasoconstrictor active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

Sympathomimetic amines
- Ephedrine hydrochloride
- Naphazoline hydrochloride
- Phenylephrine hydrochloride (0.08 to 0.2 percent concentrations)
- Tetrahydrozoline hydrochloride

The four sympathomimetic amines listed above have been widely used in OTC ocular preparations to treat minor redness of the eye. Many other sympathomimetic amines might be demonstrated to be effective and safe for use as OTC ocular vasoconstrictors (Refs. 1 and 2); however, the Panel had no data to support OTC use for other vasoconstrictor amines.

Safety. The Panel finds this group of sympathomimetic amines generally safe for OTC use at concentrations specified in the individual ingredient sections below. The Panel recognizes that the ingredients in this group have had a long OTC marketing history without causing undue side effects; however, it strongly recommends against too-frequent or prolonged use of these ingredients. One danger is that such use may delay proper medical treatment for more serious conditions that are also characterized by redness of the eyes. Also, excessive use may produce such adverse side effects as excessive cell loss, prolonged constriction of conjunctival blood vessels followed by dilation of these blood vessels (rebound hyperemia), and subjective effects of ocular stinging and burning. On encountering the symptoms of rebound hyperemia, the user would be led to believe that more vasoconstrictor is needed, when actually deleting the vasoconstrictor is necessary to relieve this condition. The Panel believes that the labeling of ocular vasoconstrictor products should warn the consumer against excessive use and delaying medical treatment if symptoms persist.

At concentrations higher than recommended for OTC use, the sympathomimetic amines will cause mydriasis (dilation of the pupil) (Refs. 3 through 7). Even at the low concentrations specified for OTC use, these ingredients, occasionally, may cause some mydriasis, especially in those subjects who wear contact lenses, whose cornea is abraded, or who have lightly colored irises (Refs. 5, 8, and (9). This mydriasis may in turn trigger an attack of narrow-angle glaucoma in a susceptible individual (Ref. 10).

The Panel recognizes the possibility of systemic toxicity if sympathomimetic amines are ingested orally but believes systemic effects from short-term ocular use are highly unlikely especially at the concentrations used in OTC opthalmic products (Refs. 11 through 15).

Effectiveness. The Panel is aware that concentrations of sympathomimetic amines higher than those recommended for OTC use have a purpose in opthalmology. In higher concentrations, these drugs are used to dilate the pupil as an examining procedure, to decrease intraocular pressure in treatment of open-angle glaucoma, and to decrease the incidence of posterior synechiae in uveitis. In concentrations specified for OTC use, ocular vasoconstrictor amines function by constricting the conjunctival blood vessels, resulting in the relief of redness of the eye.

a. *Ephedrine hydrochloride.* Ephedrine occurs naturally in the MaHuang plant and was used in China for over 5,000 years before being introduced into Western medicine in 1924 (Ref. 16). It is now usually produced synthetically. A 0.123-percent concentration of ephedrine hydrochloride in aqueous solution is generally nonirritating and has been used for many years to treat cases of minor eye irritation (Ref. 17). This concentration is recognized by the Panel as safe for OTC use. Theodore (Ref. 18) reported that ephedrine hydrochloride is a valuable agent for the treatment of allergic manifestations of the eye because of its vasoconstricting properties.

Dosage. Adults and children: Instill 1 to 2 drops of a 0.123-percent concentration in the affected eye(s) up to four times daily.

b. *Naphazoline hydrochloride.* The Panel concludes that naphazoline hydrochloride in concentrations of 0.01 to 0.03 percent is safe for use in eye drops as an OTC ocular vasoconstrictor. In the OTC concentrations this ingredient is generally well tolerated and nonirritating (Refs. 5 and 19 through 23). Occasionally naphazoline hydrochloride in concentrations of 0.02 and 0.03 percent may, however, produce minimal mydriasis (Ref. 5). Concentrations above 0.1 percent will cause both constriction of the blood vessels and dilation of the pupils (Ref. 24). Schiller (Ref. 25) and others (Refs. 26 and 27) reported rebound congestion from prolonged use of naphazoline nasal proudcts. However, rebound hyperemia has not been reported from use of naphazoline opthalmic products.

This ingredient has been confirmed to be an effective vasoconstrictor. One study compared naphazoline hydrochloride in 0.1 and 0.012 percent concentrations for ocular vasoconstrictor activity against chlorine water and histamine. The results showed both strengths to be effective, with little difference between the two (Ref. 20). Another study was conducted using naphazoline in 0.012 percent concentration in one eye and nothing in the other eye prior to exposure to chlorine water. The conjuctival blood vessels in the treated eye were not abnormally dilated by exposure to chlorine water (Ref. 5).

Dosage. Adults and children: Instill 1 to 2 drops of a 0.01- to 0.03-percent concentration in the affected eye(s) up to four times daily.

c. *Phenylephrine hydrochloride (concentrations of 0.08 to 0.2 percent).* Phenylephrine hydrochloride, in concentrations of 0.08 to 0.2 percent, has a long marketing history as an OTC ocular vasoconstrictor. Concentrations of 2 to 10 percent of phenylephrine hydrochloride are used by physicians to dilate the pupil (Refs. 28 and 29). The significantly lower concentrations used in OTC ocular vasoconstrictor products constrict the conjunctival blood vessels

without producing pupillary dilation. A number of human and animal studies have in fact shown phenylephrine hydrochloride to be effective as an ocular vasoconstrictor at 0.08- to 0.2-percent concentrations (Ref. 30). In two studies, a 0.12-percent solution of phenylephrine hydrochloride was compared to a tear-like solution for providing relief from hyperemia induced by histamine; in four studies these two medications were compared in treating hyperemia induced by chlorinated water. All six studies showed the 0.12-percent phenylephrine hydrochloride solution to be more effective than the tear-like solutions in reducing redness of the eyes.

Dosage. Adults and children: Instill 1 to 2 drops of a 0.08- to 0.2-percent concentration in the affected eye(s) up to four times daily.

d. *Tetrahydrozoline hydrochloride.* The Panel found that 0.01- to 0.05-percent concentrations of tetrahydrozoline hydrochloride used in OTC aqueous eye drops usually produce no dilation of the pupil in healthy eyes and have not been reported to cause rebound hyperemia. In one study, 348 patients with allergic conjunctivitis and 808 patients with chronic conjunctivitis were treated with a 0.05-percent aqueous solution of tetrahydrozoline hydrochloride (Ref. 31). In the first group 336 out of the 348 patients and 717 of the 808 in the second group found this treatment to be effective in providing temporary relief from redness of the eyes. Another study compared a 0.05-percent solution of tetrahydrozoline hydrochloride with a 0.1-percent solution in treating eyes reddened by chronic conjunctivitis, ocular allergies, or exposure to chemical or physical irritants. Both solutions were shown to be effective in reducing redness, with the 0.05-percent solution providing the same degree of relief as the 0.1-percent solution and having a similar duration of action (Ref. 32).

Dosage. Adults and children: Instill 1 to 2 drops of a 0.01- to 0.05-percent concentration in the affected eye(s) up to four times daily.

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Category I Labeling

a. *Indication.* "For the relief of redness of the eye due to minor eye irritations."

b. *Warnings*—(1) *For all OTC ophthalmic vasoconstrictor drug products.* (i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

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

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

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

(v) "If you experience eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

(2) *For OTC ophthalmic vasoconsitrictor drug products containing mercury.* "Do not use this product if you are sensitive to mercury."

(3) *For OTC ophthalmic vasoconstrictor solutions.* "If solution changes color or becomes cloudy, do not use."

2. *Category II conditions under which ocular vasoconstrictor ingredients are not recognized as safe and effective or are misbranded.*

The Panel recommends that the Category II conditions be eliminated from OTC ocular vasoconstrictor drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients.

None.

Category II Labeling.

The Panel recommends that the following labeling not be permitted for use in marketing of OTC ocular vasoconstrictor ingredients:

a. *Claims for cosmetic purposes or enhancement of vision.* The Panel finds any labeling which states or implies that certain cosmetic benefits may be derived from use of ocular vasoconstrictor products unacceptable. Labeling claims of this nature are scientifically unfounded and misleading to the consumer, as are labeling claims which imply relief of a tired state (e.g., "for tired eyes"). For the same reasons, the Panel finds unacceptable claims which imply a need for ocular vasoconstrictors in normal visual activities or for continuous everyday use of these products.

b. *Claims for treatment of hay fever.* The Panel opposes the use of claims which state or imply that ocular vasoconstrictor products are used to treat the actual state of hay fever because such claims are scientifically unfounded and may delay the consumer in seeking the advice of a physician.

c. *Claims relating to demographic characteristics.* The Panel finds no evidence in support of claims that the use of an ocular vasoconstrictor product has a particular advantage to the consumer solely on the basis of such demographic characteristics as sex or age.

d. *Claims for relief of symptoms within a period of time not supported by scientific data.* The Panel concurs with the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products that claims for relief of symptoms within a period of time that is not specific (e.g., "fast-action") and not supported by scientific data are unacceptable.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredient .

Phenylephrine hydrochloride (concentrations below 0.08 percent.)

Phenylephrine hydrochloride (concentrations below 0.08 percent). The Panel is aware that at least one ocular vasoconstrictor product containing phenylephrine at a concentration below 0.08 percent is marketed OTC. As the Panel found this ingredient safe for OTC ocular vasoconstrictor use at concentrations of 0.08 to 0.2 percent, there is no question of its safety at lower concentrations. However, the Panel is aware of no data that demonstrate the effectiveness of phenylephrine hydrochloride at concentrations below 0.08 percent. The Panel concludes that clinical studies, as outlined below, are required to determine at what concentrations below 0.08 percent phenylephrine hydrochloride is effective as an ocular vasoconstrictor. (See part V. paragraph C. below—Data Required for Evaluation.)

Category III Labeling

None.

C. Data Required for Evaluation

The Panel considers that the following guidelines for moving Category III ingredients into Category I are in accordance with the present state of the art and do not preclude the use of improved methodology in the future.

The Panel has given careful consideration to the types of studies and data required to move phenylephrine hydrochloride from Category III to Category I. It is sufficient to perform a well-controlled, double-blind clinical study of adequate size to determine at what concentrations below 0.08 percent phenylephrine hydrochloride is effective as an ocular vasoconstrictor. Model studies demonstrating the effectiveness of phenylephrine hydrochloride at concentrations below 0.08 percent will be also be acceptable.

The Panel agrees that 21 CFR 314.111(a)(5)(ii) outlines the features of a well-controlled clinical trial. The final appraisal of effectiveness should take place under circumstances conforming to actual expected use in the community. The study should include a sufficient number of patients to substantiate effectiveness, and "before-treatment" data should be obtained for each subject to note any conditions which might bias analysis. The study should include patients diagnosed as having redness of the eye from minor causes—not redness indicative of injury or severe infection. Patients should be watched closely for any adverse effects.

The test formulation should be compared to a standard OTC ocular vasoconstrictor preparation that is recognized as effective, such as a 0.2-percent solution of phenylephrine hydrochloride. Formulations must be used according to directions provided on their labels, and the test formulation must be shown to provide clinically significant relief of the redness of the eyes tested in order to be recognized as effective.

In an acceptable model study, redness can be induced by instilling a drop of histamine hydrochloride or 0.07 percent chlorine water ("swimming pool water") in each of the subject's eyes. This should be followed 5 minutes later by instillation of a drop of the test formulation in one eye and a drop of an effective OTC vasoconstrictor preparation in the other eye. Any changes in the degree of redness in each eye should be graded by trained observers and the data analyzed for significant differences.

Testing of Category III ingredients should be done on the final formulation product.

VI. Ocular Astringents

A. General Discussion

An astringent is a topically applied protein precipitant which has a low cell penetrability. Its action is essentially limited to the surface cells and the interstitial spaces (Ref. 1).

Many astringents are irritants or caustics in moderate to high concentrations. Consequently, strict attention must be paid to the appropriate concentration of ocular astringents.

The principal astringents are (1) the salts of aluminum, zinc, manganese, iron, and bismuth; (2) certain others salts that contain these metals such as permanganates; and (3) tannins, or related polyphenolic compounds. Acids, alcohols, phenols, and other substances that precipitate proteins may be astringent in the proper concentration; however, such substances are generally not employed for their astringent effects, because they readily penetrate cells and promote tissue damage. Strongly hypertonic solutions dry the affected tissues and are thus often wrongly called astringents, as these solutions do not appear to precipitate protein (Ref. 2).

The Panel recognizes that the ingredients it has classified as ocular astringents do not produce a true astringent action in the eye. A true astringent action is not desirable as this would cause damage to the corneal epithelium. However, historically these ingredients have been designated and promoted as astringents. The Panel believes that any astringent action of these ingredients is extremely mild and is limited in helping to remove mucus from the eye, thus providing subjective relief from minor eye irritations. The Panel recommends that the indications for use of these products be limited to "for the temporary relief of discomfort from minor eye irritations."

B. Categorization of Data

1. *Category I conditions under which ocular astringent active ingredients are generally recognized as safe and*

effective and are not misbranded. The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredient

Zinc sulfate

Zinc sulfate. The Panel concludes that zinc sulfate is safe and effective for use as an active ingredient in OTC ocular astringents when used within the dosage limit set forth below.

Zinc sulfate occurs as colorless, transparant prisms, or small needles that are efflorescent in dry air. It is very soluble in water, freely soluble in glycerin, insoluble in alcohol, and its solutions are acid to litmus. There is a tendency for solutions of zinc sulfate to form a slight cloudiness due to the separation of a boric salt formed through partial hydrolyzation (Ref. 3).

Zinc sulfate ophthalmic solution is a sterile solution of zinc sulfate in water rendered isotonic by the addition of suitable salts and having a final pH of between 5.8 and 6.2. Available solutions contain zinc sulfate in concentrations of 0.1, 0.2, or 0.25 percent, with the 0.25-percent concentration used most often (Ref. 4).

Some ophthalmic preparations use zinc sulfate as a single active ingredient, but most use zinc sulfate in combination with a vasoconstrictor and at times other ingredients. OTC zinc sulfate ophthalmic products are intended to relieve symptoms of minor eye irritation (Refs. 5 through 11).

The Panel recognizes that zinc sulfate is generally considered as having some mild astringent properties when applied topically to the eye (Refs. 12 and 13). The Panel also believes that the safety of zinc sulfate has been well documented based on the fact that millions of bottles of ophthalmic perparations containing zinc sulfate have been used with few adverse effects.

(1) *Safety.* Zinc sulfate, in a concentration of 0.25 percent, has been used in OTC eye drops for decades to relieve minor ocular irritations (Refs. 5 through 11).

A 20-day "Draize" irritation test was conducted on nine rabbits using an ophthalmic solution containing 0.25 percent zinc sulfate, a vasoconstrictor, and a lubricating agent (Ref. 11). The test solution was administered to the left eyes of the rabbits, with the untreated right eyes serving as controls. Three rabbits received one drop of the preparation containing 0.25 percent zinc sulfate four times daily; three rabbits received two drops four times daily; and three rabbits received three drops four times daily. There was no mucosal irritation noted in any of the animals' eyes. Slit lamp examinations of all animals revealed no untoward ocular reactions.

In a controlled study conducted on 56 volunteers in July 1967, 11 physicians instilled into the subjects' eyes an ophthalmic solution containing 0.25 percent zinc sulfate, a vasoconstrictor, and a lubricating agent (Ref. 11). All of the test subjects displayed symptoms of a particular ocular condition or inflammation, and the physicians who conducted the study diagnosed each test subject and noted their symptoms. The product containing 0.25 percent zinc sulfate was instilled into the eyes of the test subjects at prescribed intervals. The only side effects noted were sensations of stinging or burning on instillation, with one patient complaining of a headache.

Marketing experience with an ophthalmic product containing 0.25 percent zinc sulfate in solution indicates that zinc sulfate is safe for the relief of minor eye irritation. From 1963–1973, over 250,000 bottles of this product were sold, and there have been few inquiries or complaints received (Ref. 7).

(2) *Effectiveness.* Zinc sulfate does not produce a vasoconstriction of conjunctival blood vessels (Refs. 9, 10, and 11). The 0.25-percent zinc sulfate solution inhibits the growth of some bacteria and has been suggested for use in the treatment of angular conjunctivitis (Morax-Axenfeld bacillus) and acute catarrhal conjunctivitis ("pink eye"—pneumococcus or Koch-Weeks bacillus) (Refs 14 and 15). However, there are no recent studies to support these uses of zinc sulfate (Ref. 16).

Zinc sulfate, in a concentration of 0.25 percent in an aqueous solution, is used in many OTC eye drops for the temporary relief of minor eye irritations (Refs. 5 through 10). It has been found to be effective in the treatment of experimental ocular irritations in man.

In July of 1967, a controlled study was conducted on 56 volunteers who displayed symptoms of various ocular conditions. A large majority of the subjects were relieved of their minor eye irritations with the use of the ophthalmic product containing 0.25 percent zinc sulfate (Ref. 11).

The Panel concludes that zinc sulfate is effective in relieving minor eye irritations.

(3) *Dosage.* Adults and children: Instill 1 to 2 drops of a 0.25-percent concentration in the affected eye(s) up to four times per day.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular astringent active ingredients. (See part VI. paragraph B.1. below—Category I Labeling.)

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Category I Labeling

The Panel recommends the following Category I labeling for OTC ocular astringent active ingredients.

a. *Indication.* "For the temporary relief of discomfort from minor eye irritations."

b. *Warnings*—(1) *For all OTC ophthalmic astringent drug products.* (i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

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

(iii) "If you experience servere eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to

light, or double vision, consult a physician at once."

(2) *For OTC ophthalmic astringent drug products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(3) *For OTC ophthalmic astringent solutions.* "If solution changes color or becomes cloudy, do not use."

2. *Category II conditions under which ocular astringent active ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC ocular astringent drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

None.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of ocular astringent ingredients in ophthalmic products is unsupported by scientific data.

a. *Claims for treatment of a disease state or infection* The Panel opposes the labeling indication "relief from hay fever" because such a claim implies that the ocular astringent product can be used to treat this disease state. The Panel recognizes that ocular astringents can be used for the relief of symptoms of hay fever, such as itching and watering, but astringents are not effective in treating the disease state.

The Panel is aware of the use of ophthalmic products containing ocular astringent ingredients for the relief of discomfort due to styes. However, the use of the term "stye" as a product name or as a part of a product name is unacceptable to the Panel because it implies that the product will cure a stye infection. There is no scientific evidence to support this implication.

b. *Claims for a decongestant effect.* The Panel opposes the labeling indication, "relief of congestion," because ocular astringents do not have a vasoconstrictive action.

c. *Claims for a physiological effect.* Claims implying a physiological effect that is meaningless or has no foundation are unacceptable to the Panel. Examples of such claims are "relief for most forms of minor eye distress" and "relief from tired eyes."

d. *Claims for relief of symptoms within a period of time not supported by scientific data.* Claims for relief of symptoms within an indeterminate period of time, e.g., "fast action," which are not supported by scientific data are unacceptable.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredient

Infusion of rose petals.

Infusion of rose petals. Infusion of rose petals is an extract of *Rosa gallica* buds; the extract contains volatile oil, mucilage, coloring matter, sugar, guercitrim, and guercitannic acid (Ref. 1). An older edtion of "The National Formulary" describes the raw material but fails to define its constitutents (Ref. 2). While data from studies with a marketed product containing infusion of rose petals imply that infusion of rose petals would be a safe and effective Ocular astringent, the Panel concludes that there are insufficient data to permit final classification at this time. The Panel is unable to determine from the data submitted the concentration of infusion of rose petals in the marketed product. The Panel is also unclear as to the actual active principle contained in infusion of rose petals that produces the claimed astringent effect. "The Dispensatory of the United States of American" states that the astringency of infusion of rose petals is due chiefly to a tannin (Ref. 3). However, recent chemical studies performed on infusion of rose petal preparations have failed to give a positive test for tannins (Ref. 4). While the manufacturer claims three procedures for assuring batch-to-batch uniformity, the Panel was not presented with data to show that these procedures assure uniformity between batches.

(1) *Safety.* Two lots of an ophthalmic product containing infusion of rose petals were evaluated for ocular irritation in albino rabbits (Ref. 4). A 0.05 ml dose was instilled into six rabbit eyes at 20-minute intervals for 6 hours. A separate group of six untreated eyes served as negative controls. The conjunctiva was graded by the Draize method at 2, 4, and 6 hours. The Baldwin method was utilized to grade changes in the iris, cornea, lens, and anterior chamber. Results of the study showed the test eyes to have a slightly greater minimal conjuctival congestion when compared to the negative controls. There were no changes in the iris, anterior chamber, lens, or cornea for any test eye.

A controlled study was conducted on 51 individuals who were experiencing eye irritation resulting from adaptation to contact lenses (Ref. 5). A marketed product containing infusion of rose petals was used to treat the symptoms. There were no allergic reactions, side reactions, or systemic disturbances as a result of the use of the product.

It is the opinon of the Panel that the marketed product containing infusion of rose petals meets the eye irritation safety tests. Furthermore, the Panel feels that the safety record of this product is favorable, based on the low incidence of reported complaints (Ref. 5). Therefore, the Panel concludes that infusion of rose petals is safe for OTC ophthalmic use.

(2) *Effectiveness.* The clinical studies reviewed by the Panel regarding the effectiveness of infusion of rose petals for use as an OTC ocular astringent dealt with the marketed product containing infusion of rose petals. There was no information either in the literature or submitted by the manufacturer on the effectiveness of the individual active component(s) in infusion of rose petals.

The marketed product has been shown to be effective in reducing irritation encountered in adapting to corneal contact lenses (Ref. 4)

A double-blind clinical trial was conducted on 47 patients with mild ocular irritation (Ref. 5). One-half of the patients used a mild astringent containing a vasoconstrictor, and the other half used the marketed product containing infusion of rose petals. Both were used four times a day for 7 days. The results of this study showed that both preparations demonstrated a significant improvement in clinical symptomatology and that the product containing infusion of rose petals had an appreciably lower incidence of complaints (Ref. 5). The Panel questios the design and the statistical analysis of this study.

It is claimed that infusion of rose petals is effective in treating the symptoms of hay fever. Histamine and other amines react with a variety of compounds including tannic acid and polyphenols to form a precipitate. Infusion of rose petals also yields a precipitate when mixed with a solution of histamine phosphate. It is theorized that infusion of rose petals is effective in treating the symptoms of hay fever by removing histamine through precipitation from tears of hay fever patients (Refs. 4 through 7). However, the Panel is not convinced from the data presented that enough histamine is released during a hay fever episode to account for ocular redness, excessive tearing, and swollen tissues.

The Panel is unable to determine the active ingredient(s) in infusion of rose petals. The Panel concludes that additional data are needed on an assay

procedure or chemical analysis of the active ingredient(s) before a determination can be made regarding the effectiveness of the active component(s) in infusion of rose petals.

(3) *Proposed dosage.* The Panel is unable to propose a dosage since the concentration of active constituents of infusion of rose petals in marketed products is unknown.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular astringent active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends testing in accordance with the guidelines set forth below for infusion of rose petals to move from Category III to Category I. (See part VI. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

None.

C. *Data Required for Evaluation*

Infusion of rose petals is the only ocular astringent ingredient placed in Category III by the Panel. While the data submitted with a marketed product containing infusion of rose petals imply that this ingredient would be a safe ocular astringent, the Panel is concerned that the quality control procedures currently used are not sufficient to assure uniformity of batches. The Panel recognizes that infusion of rose petals is derived from natural sources and that different batches will contain varying amounts of each constituent. However, the Panel believes that the active ingredients in the infusion and the effective concentration need to be identified. After determining the active ingredients in infusion of rose petals, the manufacturer should develop quality control procedures to ensure that each batch of final formulation delivers the same concentration of the active ingredients.

Testing of Category III ingredients should be done on the final formulation product.

VII. Ocular Hypertonicity Agent

A. General Discussion

The Chief determinant of the passage of fluid from one body compartment to another is a change in osmotic pressure.

Osmosis is the movement of fluid through a semipermeable membrane from a compartment with a lower concentration of dissolved particles (molecules or ions) to a compartment with a higher concentration of such particles to equalize the concentration of particles in each compartment.

A hypertonic ophthalmic solution has a higher concentration of dissolved particles than the fluid in the corneal area. When such a solution is instilled into the eye, it causes fluid to be drawn from the cornea. In cases of corneal edema, the edematous area is thus decreased by loss of excess fluid, and visual acuity may improve to a level approaching normal.

The utilization of osmotic therapy in cases of chronic edema is not an attempt to cure the underlying disease but rather to supply symptomatic relief of corneal sweeling. Therapy is symptomatic and may have to be continued on a permanent basis (Ref. 1).

A number of ingredients are used as hypertonicity agents, but only preparations of sodium chloride in 2- and 5-percent concentrations are available as OTC hypertonicity agents (Refs. 2 and 3).

B. Categorization of Data

1. *Category I conditions under which active ingredients for use as ocular hypertonicity agents are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredient

Sodium chloride in 2- to 5-percent concentrations

Sodium chloride. The Panel concludes that preparations containing sodium chloride in 2- to 5-percent concentrations are safe and effective for use as OTC ocular hypertonicity agents when used within the dosage limits set forth below.

When applied to the eye, sodium chloride solutions in concentrations of 2- to 5-percent act as hypertonicity agents because of their osmotic effect on edematous tissue (Ref. 4).

(1) *Safety.* Hypertonic sodium chloride has been used by physicians for decades as an aid in reducing corneal edema. In recent years 2- and 5-percent concentrations of sodium chloride have been available for OTC use. When instilled into a normal eye, these concentrations produce a burning and stinging sensation. Concentrations of sodium chloride above 5 percent are not used in therapy as they could be excessively irritative (Ref. 5), while concentrations below 2 percent have not been found to be effective. (See part VII. paragraph B.1.(2) below—Effectiveness).

A number of studies have shown a 5-percent concentration of sodium chloride, both in solution and ointment forms, to be well-tolerated by patients with chronic corneal edema. The great majority of patients were able to use preparations of this concentration without suffering excessive burning of the eyes, excessive ocular irritation, pain, photophobia, foreign body sensation, and adverse changes in vision (Refs. 1, 5, and 6). One study reported an obvious allergic reaction in one patient to a 5-percent sodium chloride marketed preparation, and a burning sensation in another patient so acute that when the same solution was applied the medication could not be continued (Ref. 1). Accidental instillation into a normal eye will result in temporary discomfort and redness but will not produce permanent damage.

A study of 52 chronic corneal edema patients treated with hydrophilic lenses showed that hypertonic sodium chloride solutions were safely used in conjunction with this treatment (Ref. 7).

Because hypertonic sodium chloride preparations may produce a stinging and burning sensation upon instillation in the eye, the Panel concludes that the labeling should warn the user of this side effect. The Panel believes that this uncomfortable sensation would prevent too frequent application or "overdose" by the consumer, and therefore, concludes that preparations of 2- to 5-percent sodium chloride are safe for OTC use.

(2) *Effectiveness.* Of seven commercially available hypertonic preparations evaluated in a study of chronic corneal edema, a 5-percent sodium chloride ointment was found to be the most effective in achieving a reduction of corneal edema. This ointment utilized a petrolatum and wool fat vehicle which enabled it to remain in the vicinity of the cornea for a prolonged period of time. The degree of reduction of corneal edema treated with this ointment was 20 percent. As the petrolatum and wool fat vehicle used alone was found to achieve a 10-percent reduction of corneal edema, the 20-percent effectiveness of the sodium chloride ointment cannot be attributed entirely to the sodium chloride (Ref. 6). However, the addition of sodium

chloride to the ointment base can be said to have substantially enhanced the effectiveness of the product.

Another study evaluated visual acuity of 75 chronic corneal edema patients treated with a 5-percent sodium chloride solution over a period of 18 months. The drops were administered four to eight times daily as required to maintain acuity, and patients were evaluated at 1-week, 1-month, and finally 3-month intervals. An improvement in visual acuity—as a result of a reduction in edematous corneal tissue—occurred in 61 percent of the eyes tested (Ref. 1).

While an ointment form of sodium chloride preparation has the advantage of keeping the sodium chloride in contact with the eye for long periods of time, the consistency of an ointment will vary with change in temperature. An excess of ointment may actually reduce visual auity for several minutes by forming a film over the corneal surface. Hypertonic sodium chloride solutions, when used in conjunction with hydrophilic bandage lenses, are preferred over a ointment which may become trapped in the contact lens-cornea interface and be an impediment to visual acuity (Ref. 1).

Concentrations of sodium chloride of less than 2 percent have been shown to be ineffective in reducing corneal thickness (Ref. 5). Albino rabbits treated with a 2-percent concentration of sodium chloride in a solution containing a water-soluble polymer showed a reduction of corneal thickness by 8.66 percent after 4 hours. As the effect of such treatment in rabbits is half that in man, a 17.32-percent corneal edema reduction in man can be inferred with the 2-percent sodium chloride solution (Ref. 5).

The Panel concludes that sodium chloride preparations in 2- to 5-percent concentrations are effective ocular hypertonicity agents, drawing fluid from edematous corneal tissue by osmosis.

(3) *Dosage.* Adults and children: Instill 1 or 2 drops of a 2- to 5-percent concentration in the affected eye(s) every 3 or 4 hours, or as directed by a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for OTC ocular hypertonicity agents. (See part VII. paragraph B.1 below—Category I Labeling.)

References

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Category I Labeling

The Panel recommends the following labeling for OTC ocular hypertonicity agents.

a. *Indication.* "For the temporary relief of coreal edema."

b. *Warnings*—(1) *For all OTC ophthalmic hypertonicity drug products.* (i) "Do not use this product except under the advice and supervision of a physician."

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

(iii) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

(2) *For OTC ophthalmic hypertonicity drug products containing mercury.* "Do not use this product if you are sensitive to mercury.

(3) *For OTC ophthalmic hypertonicity solutions.* "If solution changes color or becomes cloudy, do not use."

2. *Category II conditions under which active ingredients for use as ocular hypertonicity agents are not generally recognized as safe and effective or are misbranded.* None.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* None.

VIII. Ocular Demulcents

A. General Discussion

Demulcents are agents that are employed primarily to alleviate irritation and dryness of the eye (Refs. 1, 2, and 3). They are generally applied to the eye as aqueous solutions. A variety of substances possess demulcent properties, including high molecular weight substances, water-soluble polymers, or water-soluble polyols. Mucus is a natural demulcent. When applied locally to irritated tissue, demulcents tend to coat the surface and protect the underlying cells from external stimuli. They also prevent drying of the affected tissue. These substances are indicated for dry or irritated eyes and also act as ocular lubricants, their demulcent and lubricating actions being related to their physical characteristics rather than to their chemical activity.

Ocular demulcents are used as tear substitutes and as viscosity agents in OTC ophthalmic solutions, their viscous consistency assisting in increasing retention time of other therapeutic ingredients in the eye. (See part II. paragraph E. above—Formulation of OTC Ophthalmic Drug Products.) They are also used in dry eyes for their lubricating properties and in professional eye examination techniques which require the use of viscous fluids to separate the examining instruments from the surface of the eye and to establish an ocular seal. (See part II. paragraph C.2.g. above—Professional examination.) The Panel recommends limiting this use to professional labeling only. Such information would be unhelpful and possibly confusing to the consumer.

Generally, the selection of a demulcent agent or a combination of demulcent agents rests with the formulator, with the final demulcent/lubricant action of the product depending not only on the demulcent agent, but also on such other ingredients in the product as electrolytes, buffering agents, and preservatives.

References

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(2) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A., et al., Mack Publishing Co., Easton, PA, p. 715, 1975.

(3) Havener, W. H., "Ocular Pharmacology," 3d Ed., C. V. Mosby Co., St. Louis, pp. 494–497, 1974.

B. Categorization of Data

1. *Category I conditions under which ocular demulcents are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients.

Cellulose derivatives:

Carboxymethylcellulose sodium

Hydroxyethylcellulose
Hydroxypropyl methylcellulose
Methylcellulose
Dextran 70
Gelatin
Polyols, liquid:
Glycerin
Polyethylene glycol 300
Polyethylene glycol 400
Polysorbate 80
Propylene glycol
Polyvinyl alcohol
Povidone

a. *Cellulose derivatives (carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropyl methylcellulose, and methylcellulose).* The Panel concludes that cellulose derivatives (carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropyl methylcellulose, and methylcellulose) are safe and effective for use as OTC ocular demulcents when used within the dosage limits set forth below.

Methylcellulose is prepared from wood pulp or chemical cotton by treatment with alkali and methylation of the alkali cellulose with methyl chloride. Methylcellulose is in the form of colorless and odorless granules. It is soluble in cold water and insoluble in hot water (Ref. 1).

Carboxymethylcellulose sodium occurs as white granules, and its solubility is equally good in hot and cold water. Solutions are stable between pH 2 and 10 (Ref. 2).

The cellulose derivatives are water-soluble derivatives of cellulose that form viscous, transparent solutions.

(1) *Safety.* The cellulose derivatives are used in pharmacy as suspending agents for oral and external preparations and for preparing bland vehicles for ophthalmic drugs. Manufacturers of prescription ophthalmic products add water-soluble cellulose derivatives or other macromolecular compounds or both to almost 50 percent of their preparations (Ref. 3). Methylcellulose and carboxymethylcellulose sodium have been used for many years as bulk laxatives in daily oral doses of 1 to 6 g (Refs. 4, 5, and 6). These bulk-forming laxatives are essentially devoid of systemic effects (Ref. 4). Cellulose derivatives are chemically inert and virtually nontoxic to living tissue, including the eyes. Swan (Refs. 7 and 8) first reported on the ophthalmic use and safety of methylcellulose solutions. Swanson, Jeter, and Cregor (Ref. 9) reported that methylcellulose and polyvinyl alcohol, when used as ophthalmic vehicles, were neither toxic nor irritating to corneal tissue and surrounding ocular tissue. Havener (Ref. 10) summarized the safety of methylcellulose,"Methylcellulose is nonirritating to ocular tissue and may be used without fear of eye damage. Topical instillation of a 1-percent solution can be continued indefinitely without altering the appearance of the normal eye."

Subconjunctival injection of 0.1 mL of a 1.0-percent methylcellulose solution in rabbits causes practically no irritation (Ref. 7). The healing of experimental corneal epithelial wounds is not slowed by a 2-percent methylcellulose solution (Ref. 11). When 0.1 mL of 0.5-percent methylcellulose in balanced salt solution was injected into the anterior chamber of rabbit eyes, no irritation resulted other than would be expected from the trauma of the needle. After such injection, traces of methylcellulose were detectable in the aqueous humor for 3 days (Ref. 12).

Although intensive safety and toxicity studies have not been reported for the other cellulose derivatives, they have been used extensively in prescription and OTC products for many years (Ref. 3 and 13 through 30). Animal and human use and safety tests have been carried out on finished products containing the various cellulose derivatives, and there is no indication that the other cellulose derivatives would be less safe than methylcellulose (Ref. 13 through 30). After many years of extensive consumer use of ophthalmic products containing these gums, the Panel knows of no adverse reactions that can be attributed to the cellulose derivatives. The only side effect that can be attributed to products containing cellulose derivatives, especially the more viscous preparations, is that dry crusts of the material may form on eye lids. These crusts may be annoying or irritating to some patients, but they can be wiped off easily.

(2) *Effectiveness.* Swan (Refs. 7 and 8) first reported on the effective use of methylcellulose solutions as ocular lubricants and demulcents. Methylcellulose and other cellulose derivative solutions are effective when used to augment deficient tear secretions. They are also effective as protective lubricants in the postenucleation socket for the prosthesis, as protective medicaments for various pathologic conditions, and as gonioscopy ointments (Refs. 10 and 31 through 38). Limited human studies have been carried out to establish effectiveness of final products containing cellulose compounds (Refs. 13 through 30). Ophthalmic vehicles containing a cellulose derivative may remain in the eye from 2 to 4 minutes after instillation. A 1-percent hydroxpropyl methylcellulose solution is reported to have remained an average of 210 seconds after instillation (Ref. 39). Methylcellulose and hydroxypropyl methylcellulose solutions are recognized in the official compendium as ophthalmic protectants and tear substitutes (Ref. 40).

The demulcent and lubricant actions of these cellulose derivatives are due to their physical properties in aqueous solutions. The Panel is aware that the cellulose derivatives can vary in physical characteristics according to the concentration used. Mims (Ref. 38) found that a concentration of 0.33 percent methylcellulose (4000 centipoise (cP)) was most satisfactory as a tear substitute, whereas concentrations of 0.25, 0.5, or 1 percent were either insufficiently viscous or too viscous. A wide range of concentrations is used in commercial products ranging from 0.24 to 2.5 percent of cellulose derivative (Refs. 13 through 30).

It has been reported that pH and buffer ingredients can influence the viscosity of methylcellulose solutions (Ref. 41). Although high concentrations of cellulose derivatives would probably have no serious effect on the eye, there are practical limitations to the concentrations that may be used as effective demulcents and lubricants. A 2.5-percent methylcellulose (4000 cP) solution has a consistency of a thin ointment and can be used in gonioscopy (Ref. 37). The Panel agrees that a 2.5-percent total concentration limit on cellulose derivatives will allow adequate flexibility for the formulator, but will prevent the use of higher concentrations that have not been adequately tested for safety and effectiveness. A lower limit of 0.2 percent would also allow the necessary flexibility to obtain adequate effectiveness with the higher molecular weight varieties of cellulose derivatives.

(3) *Dosage.* Adults and children: Instill 1 or 2 drops in the affected eys(s) of an aqueous solution containing 0.2 to 2.5 percent total cellulose derivatives.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

References

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(15) OTC Volume 100007.

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(19) OTC Volume 100024.

(20) OTC Volume 100032.

(21) OTC Volume 100035.

(22) OTC Volume 100036.

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(26) OTC Volume 100051.

(27) OTC Volume 100052.

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(30) OTC Volume 100084.

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b. *Dextran 70.* Dextran is a term that is applied to polysaccharides that are produced by bacteria growing on a sucrose substrate. Several organisms produce dextrans, but only *Leuconostoc mesenteroides* and *Leuconostoc dextranicum* have been used commercially. The chemical and physical properties of the dextrans vary with the methods of production. The average molecular weight of dextran 70 is 70,000 (Ref. 1).

(1) *Safety.* The Panel is not aware of any adverse effects associated with the products containing dextran that have been marketed for several years. Dextran 70 is a polymer of glucose with an average molecular weight of about 70,000. It has been used for many years as a plasma volume expander, usually in a 6-percent concentration in 0.9 percent saline solution. Dextran 70 is a potent antigen. Such allergic reactions as hives, angioedema, bronchospasm, and anaphylaxis have been observed after injection of dextran 70 (Ref. 2). However, the Panel is not aware of allergic responses occurring after topical application in the eye. No significant irritation or adverse effects were observed in rabbit eyes after topical irritation studies of 1-day and 21-day durations were carried out using products containing 0.1 percent dextran 70 (Refs. 3 and 4). No significant adverse effects were observed when the dextran 70 concentration was increased to 0.3 percent (Refs. 3 and 4). Limited 1-day human safety and comfort studies, using 15 to 40 subjects, were conducted to test products containing 0.1 percent dextran 70 (Refs. 3 and 4).

The only adverse effects noticed in all the dextran 70 products tested were transient stinging and temporarily blurred vision.

(2) *Effectiveness.* The Panel agrees that the colloidal properties of dextran 70 would probably have demulcent and lubricant activity. However, no data are available to establish that dextran alone in solution, especially at the 0.1-percent concentration level, would be effective. Its effective use in combination with other approved polymers is apparently due to the additive physical properties of the combined ingredients.

In-house, single-dose, comparative-comfort studies, which were considered by the manufacturer as a means of assessing effectiveness, were carried out using 40 healthy human subjects (Refs. 3 and 4). The data indicated that the products containing 0.1 percent dextran 70 and another polymer were comfortable but not significantly more comfortable than products to which they were compared. Comparative-comfort studies did not indicate that products containing dextran 70 have significantly increased effectiveness or unique activity as compared with other products containing polymers without dextran 70 (Refs. 3 and 4). Because a 0.1-percent concentration of dextran alone would not be effective as a demulcent, it should be used only in combination with another approved polymeric demulcent agent.

(3) *Dosage.* Adults and children: Instill 1 or 2 drops in the affected eye(s) of an aqueous solution containing 0.1 percent dextran 70 plus another approved polymeric demulcent agent.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

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(3) OTC Volume 100050.

(4) OTC Volume 100052.

c. *Gelatin.* The Panel concludes that gelatin is safe and effective for use as an OTC ocular demulcent when used within the dosage limits set forth below.

Gelatin is a heterogeneous mixture of water-soluble proteins of high average molecular weight. Gelatin is a product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissues, and bones of animals (Ref. 1). Gelatin derived from an acid-treated precursor is known as gelatin A.

Gelatin is a colorless or slightly yellow substance that is transparent, brittle, practically odorless, and

tasteless. It may be processed into sheets, flakes, or coarse powder (Ref. 1).

(1) *Safety.* Gelatin is used widely in the food and drug industry and is considered a safe and nontoxic foodstuff (Ref. 2). Acacia, tragacanth, and gelatin solutions were the most used ophthalmic vehicles before the introduction of methylcellulose. However, these solutions have the disadvantages of having high refractive indices, of being chemically unstable, and of being good growth media for micro-organisms (Ref. 3). A concentration of 0.01 percent gelatin, when used as a demulcent agent in a product containing an effective preservative agent, would not display these disadvantages. A 20-day Draize eye irritation study for a product containing 0.01 percent gelatin indicated no irritation to rabbit eyes (Ref. 4). The Panel concludes that concentrations greater than 0.01 percent would not be practical because of the disadvantages mentioned above in this section.

(2) *Effectiveness.* The probable basis for adding gelatin to a demulcent tear substitute or tear-like preparation is to include a protein component in an attempt to simulate the protein composition of tears. No studies have been carried out to determine the value and effectiveness of adding gelatin to a demulcent tear replacement. Its effective use as a demulcent in combination with other approved polymers would apparently be due to the additive physical properties of the ingredients. There are no studies to indicate that products containing gelatin have significantly greater effectiveness or more unique activity than other demulcent products. Because gelatin alone would not be effective as a demulcent, it should be used only in combination with another approved polymeric demulcent agent.

(3) *Dosage.* Adults and children: Instill 1 or 2 drops in the affected eye(s) of a 0.01-percent concentration in aqueous solution plus another approved polymeric demulcent agent solution as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

References

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(4) OTC Volume 100040.

d. *Polyols, liquid (glycerin, polyethylene glycol 300, polethylene glycol 400, polysorbate 80, and propylene glycol).* The Panel concludes that liquid polyols (glycerin, polyethylene glycol 300, polyethylene glycol 400, polysorbate 80, and propylene glycol) are safe and effective for use as OTC ocular demulcents as specified in the dosage section discussed below.

Glycerin, the polyethylene glycols, and propylene glycol are clear, colorless, water-soluble, viscous liquids. Glycerin has a sweet warm taste and is about 0.6 times as sweet as cane sugar. Glycerin absorbs moisture from the air (Ref. 1).

The polyethylene glycols are bland and have low toxicity. They do not hydrolyze or deteriorate on storage, and they will not support mold growth (Ref. 2).

Propylene glycol is a hygroscopic, viscous liquid with a slightly acrid taste. It is miscible with water, acetone, and chloroform. Under ordinary conditions, propylene glycol is stable (Ref. 3).

Polysorbate 80 is often used as an emulsifying agent because of its hydrophilic and lipophilic characteristics (Ref. 4).

(1) *Safety.* Glycerin, the polyethylene glycols, and propylene glycol are extensively used as solvents and vehicles for external, oral, and parenteral drug products. The nontoxicity of glycerin and propylene glycol in food and pharmaceutical use has been established both by marketing experience and clinical data. The polyethylene glycols are important ingredients in the drug industry because of their blandness, water solubility, wide compatibility, and low order of toxicity (Refs. 5 through 10). A repreated eye irritation study was conducted in rabbits and humans using a product containing 0.33 percent glycerin. After the product was instilled five times a day, 5 days a week, for a total of 3 weeks, no significant irritation was noted (Ref. 11). A 21-day Draize study in rabbits was carried out for a product containing 0.33 percent glycerin, and again the data indicated no significant irritation (Ref. 11). Two 20-day Draize tests in rabbits and a safety test in 80 human subjects were carried out on a product containing 3 percent polyethylene glycol 300, and the data indicated no significant irritation (Ref. 12).

(2) *Effectiveness.* Glycerin, polyethylene glycols, and propylene glycol have been recognized for many years as demulcents and have been incorporated into lotions and ointments for application to the skin and gargles and lozenges for the throat (Refs. 5, 6, and 7). Because of their ability to coat tissue surface, the Panal concludes that these ingredients are effective as demulcents and lubricants when applied to the eye. Glycerin and propylene glycol are used in tear substitute products which contain other viscous demulcent agents, such as the cellulose derivatives.

The Panel concludes that a 0.2- to 1.0-percent concentration range for glycerin and the liquid glycols will allow adequate flexibility for the formulator but will prevent the use of higher concentrations that have not been adequately tested for safety and effectiveness.

(3) *Dosage.* Adults and children: Instill 1 or 2 drops of a 0.2-to 1.0-percent concentration in aqueous solution in the affected eye(s) as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

References

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(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ p. 1017, 1976.

(4) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A., et al., Mack Publishing Co., Easton, PA, p. 1252, 1975.

(5) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S., and A. Gilman, Macmillan Publishing Co., New York, p. 947, 1975.

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(7) "The United States Pharmacopeia." 19th Ed., United States Pharmacopeial Convention, Rockville, MD, pp. 565–566, 1975.

(8) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 560–561, 933, and 974, 1973.

(9) Gosselin, R. B., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins Co., Baltimore, section II, p. 120, section III, pp. 149–150, 1976.

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(11) OTC Volume 100006.
(12) OTC Volume 100059.

e. *Polyvinyl alcohol.* Polyvinyl alcohol (PVA) is a long-chain plastic polymer that is readily soluble in water. It is widely used as an ophthalmic vehicle and can lower surface tension (Refs. 1, 2, and 3).

(1) *Safety.* Polyvinyl alcohol is widely used as an ophthalmic vehicle and is regarded as nontoxic to ocular tissues. Injections of polyvinyl alcohol solutions into the anterior chamber of rabbit eyes caused no significant irritation or corneal edema (Ref. 4). Subcutaneous and subconjunctival implants of polyvinyl alcohol in rabbits caused some tissue response after three months (Ref. 5). Studies on the regeneration of damaged corneal epithelium suggest that instillation of polyvinyl alcohol solutions caused only slight retardation of regeneration (Ref. 6). Another report indicated that regeneration was not impaired (Ref. 7).

Acute (13-day) and extended (20-, 21-, 51-, and 90-day) rabbit-irritation (Dranze-type) studies have been conducted. Comfort and effectiveness studies in human subjects which have been carried out using products containing 1.4 to 3.0 percent polyvinyl alcohol involved 632 patients in a clinical evaluation of a product containing 2.5 percent polyvinyl alcohol for safety and comfort when used with hard contact lenses (Refs. 8 through 16). In the above studies, no significant irritation that could be attributed to polyvinyl alcohol in rabbit or human eyes was reported. From 1963 to 1974, 5.5 million units of a product containing 4.0 percent polyvinyl alcohol have been distributed, and the manufacturer reports very few instances of discomfort from the use of this product (Ref. 17). A 20-day Draize irritation study indicated that the above product was not toxic or irritating to rabbit eyes (Ref. 17). Polyvinyl alcohol at 2-, 4-, and 6.8-percent concentrations was evaluated for ocular irritation (an acute 1-day study and a 5-day study) and found to be nonirritating to rabbit eyes (Ref. 18). The Panel concludes that polyvinyl alcohol, in concentrations up to 4 percent in aqueous solution, is safe and nontoxic to the eye.

(2) *Effectiveness.* Polyvinyl alcohol in aqueous solution has been recognized for many years as an effective ocular demulcent and lubricant, as a form of treatment for tear insufficiency, and as a vehicle for ophthalmic drugs (Refs. 2, 3, 6, 19, and 20). In general, polyvinyl alcohol solutions are much less viscous than methylcellulose solutions. The demulcent and lubricant action of polyvinyl alcohol appears to depend on its ability to form a film over the eye surface and on hard contact lenses which helps to protect underlying tissue (Ref. 6). Polyvinyl alcohol lowers surface tension and can wet the hydrophilic surface of hard contact lenses (Ref. 21). Numerous human safety and comfort evaluations have been carried out on finished polyvinyl alcohol products, and a wide range of concentrations is used in these products (from 0.125 to 4 percent polyvinyl alcohol) (Refs. 8 through 16). Many preparations contain more than one polymer, such as polyvinyl alcohol and hydroxypropyl methylcellulose (Refs. 8 through 18). The Panel is aware that polyvinyl alcohol is available in various viscosity grades, and that the viscosity and wetting ability of the polymer may be influenced by other ingredients in the finished product. The Panel agrees that a 4-percent total concentration limit on polyvinyl alcohol will allow adequate flexibility for the formulator, but will prevent the use of higher concentrations that have not been adequately tested for safety and effectiveness.

(3) *Dosage.* Adults and children: Instill 1 or 2 drops of an aqueous solution containing 0.1 to 4.0 percent polyvinyl alcohol in the affected eye(s) as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

References

(1) "Ophthalmology Prescription Handbook," 2d ED., Browning Medical Publishers, Pasadena, CA, 1968.
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(8) OTC Volume 100020.
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(19) Lofholm, P. W., "Ophthalmic Products," *in* "Handbook of Nonprescription Drugs," 5th Ed., American Pharmaceutical Association, washington, DC, pp. 226–235, 1977.
(20) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, pp. 391–392, 1975.
(21) Lemp, M. A., and F. J. Holly, "Ophthalmic Polymers as Ocular Wetting Agents," *Annals of Ophthalmology,* 4:15–20, 1972.

f. *Povidone.* The Panel concludes that povidone is safe and effective for use as an OTC ocular demulcent as specified in the dosage section discussed below.

Povidone is a synthetic polymer, occurring as a faintly yellow, solid substance. It is soluble in water, yielding a colloidal solution (Ref. 1).

(1) *Safety.* Povidone is used as an ophthalmic vehicle and is widely used as a pharmaceutical aid as a tablet binder, coating agent, and dispersing and suspending agent (Refs. 2 through 5). Povidone is essentially an inert material with extremely low acute toxicity and does not cause organic disturbances on long-term administration (Ref. 6). A report from the National Academy of Sciences—National Research Council (NAS–NRC Report, Drug Efficacy Study, Log 2694, NDA 11126, accession number 1968) on a product containing 3 percent povidone indicated that this product may well be safe for use in soothing and lubricating dry eyes and in making the wearing of contact lenses more comfortable. A very limited eye irritation test (one instillation of dilute material in three rabbits) was carried out for a contact lens cleaning solution containing 2 percent povidone (Ref. 7). No significant irritation was observed.

(2) *Effectiveness.* Aqueous solutions of povidone have been recognized as suitable vehicles for ophthalmic products (Refs. 2 and 3). The FDA, after considering the NAS–NRC report mentioned earlier as well as other available evidence, published in the **Federal Register,** May 22, 1971 (36 FR 9344), its conclusion that povidone ophthalmic solution is probably effective in soothing and lubricating dry eyes and in making the wearing of contact lenses more comfortable. In 1956 a report indicated that a product containing povidone reduced or prevented the development of irritation during anesthesia (Ref. 8). The Panel

concludes that povidone has an effective demulcent and lubricating action similar to that of polyvinyl alcohol. The viscosity of solutions containing 10 percent or less of povidone is essentially the same as that of water (Ref. 8). Two-percent solutions of povidone and polyvinyl alcohol have almost the same viscosity (Ref. 9). The Panel agrees that a 2.0-percent total concentration limit on povidone will allow adequate flexibility for the formulator but prevent the use of higher concentrations that have not been adequately tested for safety and effectiveness. Lower concentrations of the agent in aqueous solutions will still maintain some demulcent/lubricant effect. Additive demulcent/lubricant action would be obtained when demulcent agents are used in combination. Therefore, the Panel recommends a range of 0.1 to 2.0 percent for povidone as a demulcent/lubricant agent.

(3) *Dosage.* Adults and children: Instill 1 or 2 drops of a 0.1- to 2.0-percent concentration of an aqueous solution in the affected eye(s) as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular demulcent active ingredients. (See part VIII paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 996, 1976.

(2) "Ophthalmology Prescription Handbook," 2d Ed., Browning Medical Publishers, Pasadena, CA, pp. 29–30, 1968.

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(4) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 395, 1975.

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Category I Labeling

The Panel recommends the following Category I labeling for ocular demulcent active ingredients.

a. *Indications.* (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 relieve dryness of the eye."

b. *Warnings*—(1) *For all OTC ophthalmic demulcent drug products.* (i) "Do not use this product more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

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

(iii) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

(2) *For OTC ophthalmic demulcent drug products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(3) *For OTC ophthalmic demulcent solutions.* "If solution changes color or becomes cloudy, do not use."

2. *Category II conditions under which ocular demulcent agents are not generally recognized as safe and effective or are misbranded.*

None.

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

None.

IX. Ocular Emollients

A. General Discussion

Emollients are bland oleaginous substances used for their local action on the skin and mucous membranes (Refs. 1 and 2). They are employed as softening agents and render the skin and tissue more pliable. Emollients soften surface tissue by forming an occlusive film on the surface and thus prevent drying from evaporation of the water that diffuses to the surface from underlying layers of tissue. They can act as protectants by excluding water-soluble irritants, air, and airborne bacteria. Emollients are indicated for the dry or irritated eye. They also act as lubricants. Emollient products are of such consistency that they should be packaged in appropriate ophthalmic ointment tubes having special tips for easy application to the eye.

The Panel is aware that emollient ingredients are widely used as vehicles for ophthalmic ointment products. Their inertness and blandness are such that repeated and prolonged use of these ingredients would not be harmful to the eye. Ocular emollient preparations should be instilled into the eye by pulling down the lower lid and applying a small amount of ointment to the inside of the lid (one-fourth inch from ophthalmic tube applicator) or as directed by a physician.

References

(1) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S., and A. Gilman, Macmillan Publishing Co., New York, p. 947, 1975.

(2) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A., et al., Mack Publishing Co., Easton, PA, p. 715, 1975.

B. Categorization of Data

1. *Category I conditions under which ocular emollient active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients.

Lanolin preparations:
- Anhydrous lanolin
- Lanolin
- Nonionic lanolin derivatives

Oleaginous ointment base ingredients:
- Light mineral oil
- Mineral oil
- Paraffin
- White ointment
- White petrolatum
- White wax

a. *Lanolin preparations (anhydrous lanolin, lanolin, and nonionic lanolin derivatives).* The Panel concludes that lanolin preparations (anhydrous lanolin, lanolin, and nonionic lanolin derivatives) are safe and effective for use as OTC ocular emollients as specified in the dosage section discussed below.

Lanolin is a purified unctuous material obtained from the wool of sheep and it contains 25 to 30 percent water. It is a yellowish-white, smooth, greasy mass with a slight odor and is practically insoluble in water. Anhydrous lanolin is lanolin that contains essentially no water. Anhydrous lanolin is a yellowish, semisolid fat which has a slight odor or is practically odorless. It mixes with

about twice its weight of water without separation (Ref. 1).

(1) *Safety.* Most OTC and prescription ophthalmic ointment products are prepared with a base of petrolatum and mineral oil, often with added lanolin or anhydrous lanolin (Refs. 2 and 3). Anhydrous lanolin is used when the formulator wishes to have an anhydrous base for an active ingredient. Lanolin materials have been used for centuries in dry skin softening products and in protective ointments. Because of their physical properties, 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 such as petrolatum. Because certain individuals are allergic to lanolin substances, these substances have been deleted from several official formulations (Refs. 4, 5, and 6). However, the Panel is not aware of any significant number of allergic reactions associated with the topical ocular use of ointments containing lanolin materials. Nonionic lanolin derivatives, because of their more refined and purified state, are less sensitizing than lanolin (Ref. 7). An ophthalmic emollient ointment containing nonionic lanolin derivatives has been on the market for many years, and the Panel is not aware of any significant adverse effects associated with this product. A Draize eye irritation test (0.2 cm^3 of ointment) in rabbits was carried out for 20 consecutive days, and no damage or irritation was observed (Ref. 8).

Lanolin and other oleaginous ointment bases are toxic to the interior of the eye, causing endothelial damage, corneal edema, vascularization, and scarring (Refs. 9 and 10). For this reason, ophthalmic medications in ointment or oily liquid vehicles should not be introduced into the interior of the eye or used in such a way during surgery that they may accidentally enter the eye. On the other hand, a survey of ophthalmologists indicated that ointments are routinely used immediately after surgery, after the first dressing change, for corneal abrasions, and for corneal ulcers (Ref. 11). The safety of immediate postoperative ophthalmic ointment application is supported by the experience of a noted surgeon who saw no side effects secondary to ointment usage in over 20,000 postsurgical patients (Ref. 12). A study on the effect of ointments on wounded corneas of rats, rabbits, and monkeys indicated that nonemulsion ointment bases containing white petrolatum or mineral oil with or without lanolin did not interfere with corneal healing (Ref. 13).

The Panel is aware that temporary blurring of vision will occur when preparations containing lanolin and other oleaginous materials are applied to the eyes as the result of an oily film that covers the eye surface. This condition may last only a few minutes after application and is not harmful to the eye, even after prolonged use.

(2) *Effectiveness.* Preparations containing lanolin have been recognized for many years as emollients and have been incorporated into lotions and ointments for application to the skin and mucous membranes. They have been used in the preparation of ointment vehicles for various medications, including ophthalmic preparations. Because of their intrinsic lubricating and protectant properties, the Panel concludes that these ingredients are effective as emollients and lubricants when applied to the eye.

(3) *Dosage.* Adults and children: Pull down the lower lid of the affected eye and apply a small ribbon (one-fourth inch) of ointment to the inside of the eyelid.

(4) *Labeling.* The Panel recommends the Category I labeling for ocular emollient active ingredients. (See part IX. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 704, 1976.

(2) Deardorff, D. L., "Ophthalmic Preparations," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A., et al., Mack Publishing Co., Easton, PA, pp. 1503–1504, 1975.

(3) "Ophthalmology Prescription Handbook," 2d Ed., Browning Medical Publishers, Pasadena, CA, 1968.

(4) Blaug, S. M., "Medicated Applications," *in* "The Pharmaceutical Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S., and A. Gilman, Macmillan Publishing Co., New York, pp. 1531–1532, 1975.

(5) Masters, E. J., "Allergies to Cosmetic Products," *New York State Journal of Medicine,* 60:1934–1940, 1960.

(6) Clark, E. W., "Estimation of the General Incidence of Specific Lanolin Allergy," *Journal of the Society of Cosmetic Chemists,* 26:323–335, 1975.

(7) "Amerchol CAB," Amerchol Corporation, Amerchol Park, Edison, NJ, p. 19, 1978.

(8) OTC Volume 100041.

(9) Havener, W. H., "Ocular Pharmacology," 3d Ed., C. V. Mosby Co., St. Louis, pp. 22–23, 1974.

(10) Scheie, H. G., R. A. Rubenstein, and J. A. Katowitz, "Ophthalmic Ointment Bases in the Anterior Chamber," *Archieves of Ophthalmology,* 73:36–42, 1965.

(11) Fraunfelder, F. T., and C. Hanna, "Ophthalmic Ointment," *Transactions of the American Academy of Ophthalmology and Otolaryngology,* 77:467–475, 1973.

(12) Castroviejo, R., "Ointment Bases in the Anterior Chamber," *Archives of Ophthalmology,* 74:143–144, 1965.

(13) Hanna, C., et al., "The Effect of Ophthalmic Ointments on Corneal Wound Healing," American Journal of Ophthalmology, 76:193–200, 1973.

b. *Oleaginous ingredients (light mineral oil, mineral oil, paraffin, white ointment, white petrolatum, white wax).* The Panel concludes that oleaginous ingredients (light mineral oil, mineral oil, paraffin, white ointment, white petrolatum, white wax) are safe and effective for use as OTC ocular emollients as specified in the dosage section discussed below.

The oleaginous substances include the hydrocarbons (mineral oils, paraffin, and white petrolatum), the purified wax from the honeycomb of the bee (white wax), and a mixture of 5 percent white wax in white petrolatum (white ointment).

Light mineral oil and mineral oil are colorless, oily liquids that are practically tasteless and odorless. The density of light mineral oil is usually 0.83 to 0.86, as compared to the density of mineral oil, which is 0.875 to 0.905 (Ref. 1).

Paraffin is a whitish mass which is somewhat translucent and odorless (Ref. 2). White petrolatum is a semisolid, unctuous mass that is transparent in thin layers and is practically odorless and tasteless (Ref. 1).

White wax is yellowish-white in color, with a texture that varies from soft to brittle. It has a honey-like odor and melts at 62 to 65° C (Ref. 3).

(1) *Safety.* The oleaginous substances have been used widely for a long period of time as occlusive coverings for the skin, and as vehicles for ophthalmic drugs and for certain antibiotics that are unstable in the presence of water (Refs. 4, 5, and 6). Essentially all of the marketed prescription ophthalmic ointments contain one or more of these oleaginous materials (Ref. 7). White petrolatum and white ointment are frequently employed without modification for external application to the skin surface. These materials are considered inert and practically nontoxic (Refs. 8 and 9). A 20-day Draize irritation test was carried out on an ocular emollient product containing petrolatum, mineral oil, and a lanolin derivative, and no damage or irritation was observed (Ref. 10).

Oleaginous ointment bases are toxic to the interior of the eye, causing endothelial damage, corneal edema, vascularization, and scarring (Refs. 11 and 12). For this reason, ophthalmic medications in ointment or oily liquid

vehicles should not be introduced into eyes with open wounds. On the other hand, a survey of ophthalmologists indicated that ointments are routinely used immediately after surgery, after the first dressing change, for corneal abrasions, and for corneal ulcers (Ref. 13). The safety of immediate postoperative ophthalmic ointment application in most instances is supported by the experience of a noted surgeon who saw no side effects secondary to ointment usage in over 20,000 postsurgical patients (Ref. 14). A study on the effect of ointments on wounded corneas of rats, rabbits, and monkeys indicated that nonemulsion ointment bases containing white petrolatum or mineral oil with or without lanolin did not interfere with corneal healing (Ref. 15).

The Panel is aware that temporary blurring of vision will occur when these oleaginous materials are applied to the eye as a result of an oily film that covers the eye surface. This condition may last only a few minutes after application and is not harmful to the eye, even after prolonged use.

(2) *Effectiveness.* Oleaginous substances have been recognized for many years as emollients and protectants. They have been incorporated into lotions and ointments for application to the skin and mucous membranes and have been used as bland vehicles for ophthalmic drugs (Refs. 4 through 7, 9, and 13). Most ophthlamic ointments are prepared with a base of white petrolatum and mineral oil with or without lanolin. Paraffin and white wax are used to increase the consistency of ointment products and are not used alone as emollients. By virtue of their intrinsic lubricating and protectant properties, the Panel concludes that oleaginous substances, properly formulated into ointment dosage forms suitable for application to the eye, are effective as emollients and lubricants.

(3) *Dosage.* Adults and children: Pull down the lower lid of the affected eye and apply a small ribbon (one-fourth inch) to the inside of the eyelid.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing ocular emollient active ingredients. (See part IX. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 931, 1976.

(2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 910, 1976.

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(7) "Ophthalmology Prescription Handbood," 2d Ed., Browning Medical Publishers, Pasadena, CA, 1968.

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(9) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 755–756, 832, 888, and 1253–1254, 1973.

(10) OTC Volume 100041.

(11) Havener, W. H., "Ocular Pharmacology," 3d Ed., C. V. Mosby Co., St. Louis, pp. 22–23, 1974.

(12) Scheie, H. G., R. A. Rubenstein, and J. A. Katowitz, "Ophthalmic Ointment Bases in the Anterior Chamber," *Archives of Ophthalmology,* 73:36–42, 1965.

(13) Fraunfelder, F. T., and C. Hanna, "Ophthalmic Ointment," *Transactions of the American Academy of Ophthalmology and Otolaryngology,* 77:467–475, 1973.

(14) Castroviejo, R., "Ointment Bases in the Anterior Chamber," *Archives of Ophthalmology,* 74:143–144, 1965.

(15) Hanna, C., et al., "The Effect of Ophthalmic Ointments on Corneal Wound Healing," *American Journal of Ophthalmology,* 76:193–200, 1973.

Category I Labeling

The Panel recommends the following Category I labeling for ocular emollient active ingredients:

a. *Indications.* (1) "For the temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun."

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

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

b. *Warnings* —(1) *For all OTC ophthalmic emollient drug products.* (i) "Do not use for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(ii) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

(2) *For OTC ophthalmic emollient drug products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

2. *Category II conditions under which ocular emollient active ingredients are not generally recognized as safe and effective or are misbranded.*

None.

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

None.

X. Eyewashes

A. *General Discussion*

Eyewashes, eye lotions, and eye-irrigating solutions are sterile, aqueous solutions intended for washing, bathing, irrigating, or mechanically flushing the eye. They are used to dilute or remove irritants such as foreign bodies, pollen, and noxious chemicals from the eye. They are not used to treat even minor infections of the eye. These preparations should be neutral and comfortable to the eye, and should not contain therapeutically active ingredients such as vasoconstrictors, anti-infectives, astringents, etc. A rational formulation for an OTC eyewash preparation includes water, sodium chloride, and other tonicity agents to establish isotonicity with tears, agents for establishing pH and buffering to achieve the same pH as tears, and a suitable preservative agent. A discussion of tonicity, buffering, and formulation ingredients is presented earlier in this document. (See part II. paragraph E. above—Formulation of OTC Ophthalmic Drug Products.)

The tears are the first line of defense for the conjunctiva, the cornea, and, to some extent, the eyelids. The tears maintain the hydration of the corneal and conjunctival surfaces. The output of tears greatly increases when the cornea and conjunctiva become irritated, but occasionally it is necesssary to flush the irritants from the cornea, conjunctiva, and lids. For this purpose, isotonic, neutral aqueous solutions which contain no therapeutically active ingredients are used.

When the eye is exposed to certain adverse environmental conditions, symptoms of irritation can develop. Foreign material in the eyes can result in a foreign body sensation, inflammation, swelling, tearing, uncontrolled blinking

of the eyelids, or symptoms of irritation, discomfort, burning, stinging, smarting, and itching. When such symptoms occur, foreign material may be present in an undissolved form, such as dust or an eyelash; as suspended particulate material in tears, such as pollen or smog; or as noxious materials such as airborne pollutant gases and chemicals, dissovled in tears.

Provided the eye is not damaged by such debris, the relief of symptoms occurs with removal of the causative substance. Treatment consists of washing or flushing the exposed eye and conjunctival sacs with an irrigating solution to remove tangible foreign material and substances dissolved or suspended in the tears.

Many of the symptoms of irritation, including a foreign body sensation, occur with various anterior eye disease conditions, such as conjunctivitis, keratitis, and blepharitis, which result in inflammation and other changes in ocular tissue. There is little danger of such conditions becoming exacerbated through use of irrigating solutions alone. However, exacerbation of the underlying condition through delayed professional attention is a distinct possibility.

Eyewashes, eye lotions, and eye-irrigating solutions are not only used by consumers for cleaning and washing irritants from the eyes, but they are also used for the emergency flushing of chemicals or foreign bodies from the eye(s) in homes, places of work, first aid stations, clinics, and hospitals. These products are important components of first aid and emergency kits in industrial settings, clinics, and hospitals. Terms such as "eye-wash," "eye lotion," and "irrigating solution" or fluid are very descriptive and inform the user (whether patient or professional) what the solution is used for. One of the above terms should be prominently displayed on the label of such products.

In the absence of or in addition to using these products, copious flushing of the eye with water is required in the emergency treatment of chemical burns or in cases where gross amounts of foreign material have entered the eye.

In addition to their emergency first aid use, irrigating fluids are used by medical personnel for irrigation following diagnostic procedures and for postoperative irrigation.

Eyewash and eye lotion products are usually packaged in screwcapped glass or plastic containers with an appropriate sterile eye cup included as part of the total package. Irrigating solutions or fluids are packaged in flexible plastic containers equipped with an appropriate nozzle to facilitate application of the fluid to the eye. The label should have appropriate directions for applying the solution.

B. Category I Labeling

The Panel recommends the following Category I labeling for eye wash preparations.

1. *Indication.* "For flushing or irrigating the eye to remove loose foreign material, air pollutants, or chlorinated water."

2. *Warnings*—a. *For all eyewash products.* (1) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

(2) "If symptoms persist or worsen after use of this product, consult a physician."

(3) "Not for use in eyes with open wounds."

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

b. *For preparations using an eye cup.* "Rinse cup with clean water immediately before and after each use, and avoid contamination of rim and inside surfaces of cup."

c. *For preparations using a nozzle applicator.* "Do not touch nozzle to any surface since this may contaminate the solution."

d. *For preparations containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(3) *Directions for use.* The Panel recommends the following directions for the various types of eye wash products.

a. For solutions intended to be applied with an eye cup. "Apply the half-filled cup, pressing it tightly to the affected eye to prevent the escape of the liquid, and tilt the head backward. Open eyelids wide and rotate eyeball to insure thorough bathing with the wash or lotion."

b. For solutions intended to be applied as a stream to flush the eye. "Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle."

The agency has determined that in accordance with 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 349, to read as follows:

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

Subpart A—General Provisions

Sec.
349.1 Scope.
349.3 Definitions.

Subpart B—Active Ingredients

349.10 Ophthalmic Anti-infectives. [Reserved]
349.12 Ophthalmic astringents.
349.14 Ophthalmic demulcents.
349.16 Ophthalmic emollients.
349.18 Opthalmic hypertonicity agent.
349.20 Ophthalmic vasoconstrictors.
349.22 Eyewashes.
349.30 Permitted combinations of active ingredients.

Subpart C—[Reserved]

Subpart D—Labelling

349.50 Labeling of products containing ophthalmic anti-infectives.
349.55 Labeling of products containing ophthalmic astringents.
349.60 Labeling of products containing opthalmic demulcents.
349.65 Labeling of products containing opthalmic emollients.
349.70 Labeling of products containing ophthalmic hypertonicity agents.
349.75 Labeling of products containing opthalmic vasoconstrictors.
349.80 Labeling of eyewash products.

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

Subpart A—General Provisions

§ 349.1 Scope.

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 the Part 349 and each of the general conditions established in § 330.1 of this chapter.

§ 349.3 Definitions.

As used in this part:

(a) *Ophthalmic drug product.* A drug product applied to or instilled in the eye which should be sterile in accordance with 21 CFR 200.50.

(b) *Anti-infective.* A therapeutic agent which destroys or limits the multiplication of micro-organisms.

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

(d) *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.

(e) *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.

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

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

(h) *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 hypertonicitiy agent creates an osmotic gradient which draws water out of the cornea.

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

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

Subpart B—Active Ingredients

§ 349.10 Ophthalmic anti-infectives. [Reserved]

§ 349.12 Ophthalmic astringent.

The active ingredient of the product consists of the following when used within the concentration limit established: Zinc sulfate 0.25 percent.

§ 349.14 Ophthalmic demulcents.

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

(a) Cellulose derivatives (sodium carboxymethylcellulose, hydroxyethylcellulose, hydrxypropyl methylcellulose, and methylcellulose) 0.2 to 2.5 percent.

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

(c) Gelatin 0.01 percent.

(d) Polyols, liquid (glycerin, polyethylene glycol 300, polyethylene glycol 400, polysorbate 80, and propylene glycol) 0.0 to 1.0 percent.

(e) Polyvinyl alcohol 0.1 to 4.0 percent.

(f) Povidone 0.1 to 2.0 percent.

§ 349.16 Ophthalmic emollients.

The active ingredients of the product consist of the following:

(a) Lanolin preparations (anhydrous lanolin, lanolin, and nonionic lanolin derivatives).

(b) Oleaginous ingredients (light mineral oil, mineral oil, paraffin, white petrolatum, white wax).

§ 349.18 Ophthalmic hypertonicity agent.

The active ingredient of the product consists of the following when used within the concentration limits established: Sodium chloride 2 to 5 percent.

§ 349.20 Ophthalmic vasoconstrictors.

The active ingredients of the product consist of the following when used within the concentration limits established 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.

§ 349.22 Eyewashes.

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

§ 349.30 Permitted combinations of active ingredients.

(a) Any single ocular astringent active ingredient identified in § 349.12 may be combined with any single ocular vasoconstrictor active ingredient identified in § 349.20.

(b) Any two or three ocular demulcent active ingredients identified in § 349.14 may be combined.

(c) Any single ocular demulcent active ingredient identified in § 349.14 or any ocular demulcent combination identified in paragraph (b) of this section may be combined with any single ocular vasoconstrictor identified in § 349.20.

(d) Any single ocular astringent active ingredient identified in § 349.12 may be combined with any single ophthalmic vasoconstrictor active ingredient identified in § 349.20 and any single ophthalmic demulcent identified in § 349.14 or ophthalmic demulcent combination identified in paragraph (b) of this section.

(e) Any two or more emollient active ingredients identified in § 349.16 may be combined as necessary to give the product proper consistency for application to the eye.

Subpart C—[Reserved]

Subpart D—Labeling

§ 349.50 Labeling of products containing ophthalmic anti-infectives.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug(s) and identify the product as an "ophthalmic anti-infective."

(b) *Indications.* The labeling of the product shall contain the following indication, under the heading "Indications": "For the treatment of minor external infections of the eye."

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

(1) *For all ophthalmic anti-infective drug products.* (i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(ii) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

(2) *For ophthalmic anti-infective drug products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(3) *For ophthalmic anti-infective drug products containing mild silver protein.* (i) "Prolonged or frequent use of this product may cause permanent discoloration of the eye and the skin and mucous membranes surrounding the eye."

(ii) "Keep bottle tightly closed and store away from light when not in use to prevent the product from losing potency."

(4) *For ophthalmic anti-infective solutions.* "If solution changes color or becomes cloudy, do not use."

(d) *Directions for use.* The labeling of the products shall contain under the heading "Directions," the recommended dosage per time interval, e.g., every 4 hours, or other time interval, e.g., 3 times

daily, broken down by age groups if appropriate, followed by "or as directed by a physician."

§ 349.55 Labeling of products containing ophthalmic astringents.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug(s) and identify the product as an "ophthalmic astringent."

(b) *Indications.* The labeling of the product shall contain the following indication, under the heading "indications": "For the temporary relief of discomfort from minor eye irritations."

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

(1) *For all ophthalmic astringent drug products.* (i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(ii) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

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

(2) *For ophthalmic astringent drug products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(d) *Directions for use.* The labeling of the product shall contain the following statement under the heading "Directions": "Adults and children: Instill 1 to 2 drops in the affected eye(s) up to four times per day."

§ 349.60 Labeling of products containing ophthalmic demulcents.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug(s) and identify the product as an "ophthalmic demulcent."

(b) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

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

(1) *For all opthalmic demulcent drug products.* (i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(ii) "If you experience severe eye pain, headache rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

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

(2) *For ophthalmic demulcent drug products containing mercury compounds.* "Do not use this product if you are sensitive to mecury."

(d) *Directions for use.* The labeling of the product shall contain the following statements under the heading "Directions": "Adults and children: Instill 1 or 2 drops in the affected eye(s) as needed."

(e) *Professional labeling.* The labeling of any OTC ophthalmic demulcent 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).

§ 349.65 Labeling of products containing ophthalmic emollients.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug(s) and identify the product as an "ophthalmic emollient."

(b) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

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

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

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

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

(1) *"For all ophthalmic emollient products.* (i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(ii) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

(2) *For ophthalmic emollient products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(d) *Directions for use.* The labeling of the product shall contain the following statement under the heading "Directions": "Adults and children: Pull down the lower lid of the affected eye and apply a small ribbon (one-fourth inch) of ointment to the inside of the eyelid."

§ 349.70 Labeling of products containing ophthalmic hypertonicity agents.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug and identify the product as an "ophthalmic hypertonicity agent."

(b) *Indications.* The labeling of the product shall contain the following indication under the heading "Indications": "For the temporary relief of corneal edema."

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

(1) *For all ophthalmic hypertonicity drug products.* (i) "Do not use this product except under the advice and supervision of a physician."

(ii) "If you experience severe pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

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

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

(2) *For ophthalmic hypertonicity agent products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(d) *Directions for use.* The labeling of the product shall contain the following statement under the heading "Directions": "Adults and children: Instill 1 or 2 drops in the affected eye(s) every 3 or 4 hours, or as directed by a physician."

§ 349.75 Labeling of products containing ophthalmic vasoconstrictors.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug(s) and identify the product as an "ophthalmic vasoconstrictor."

(b) *Indications.* The labeling of the product shall contain the following indication, under the heading "Indications": "For the relief of redness of the eye due to minor eye irritations."

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

(1) *For all ophthalmic vasocostrictor drug products.* (i) "Do not use this product for more than 72 hours except under the advice and supervision of a physician. If symptoms persist or worsen, discontinue use of this product and consult a physician."

(ii) "If you experience severe eye pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

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

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

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

(2) *For ophthalmic vasoconstrictor products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(d) *Directions for use.* The labeling of the product shall contain the following statements under the heading "Directions": "Adults and children: Instill 1 to 2 drops in the affected eye(s) up to four times per day."

§ 349.80 Labeling of eyewash products.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug(s) and identify the product with one or more of the following terms: "eyewash," "eye lotion," or "irrigating solution."

(b) *Indications.* The labeling of the product shall contain the following indication, inder the heading "Indications": "For flushing or irrigating the eye to remove loose foreign material, air pollutants, or chlorinated water."

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

(1) *For all eyewash products.* (1) "If symptoms persist or worsen after use of this product, consult a physician."

(ii) "Not for use in open wounds."

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

(iv) "If you experience severe pain, headache, rapid change in vision (side or straight ahead), sudden appearance of floating spots, acute redness of the eyes, pain on exposure to light, or double vision, consult a physician at once."

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

(2) *For eyewash products containing mercury compounds.* "Do not use this product if you are sensitive to mercury."

(3) *For eyewash products intended for use with an eye cup.* "Rinse cup with clean water immediately before and after each use, and avoid contaimination of rim and inside surfaces of cup."

(d) *Directions for use.* The labeling of the product shall comtain the following statements under the heading "Directions":

(1) *For eyewash products intended for use with an eyecup.* "Apply the half-filled cup, pressing tightly to the affected eye to prevent the escape of the liquid, and tilt the head backward. Open eye lids wide and rotate eyeball to ensure thorough bathing with the wash or lotion."

(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."

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before August 4, 1980. Such comments should be addressed to the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before September 3, 1980. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: April 11, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

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