

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 349

[Docket No. 80N-145B]

RIN 0910-AA01

**Over-the-Counter Ophthalmic Drug Products for Emergency First Aid Use;
Proposed Amendment of Final Monograph for Over-the-Counter Ophthalmic
Drug Products**

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the final monograph for over-the-counter (OTC) ophthalmic drug products to include OTC emergency first aid eyewash drug products. These products are used to flush or irrigate the eye to remove acid and alkali chemicals or particulate contamination. This proposal is part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments by *[insert date 90 days after date of publication in the Federal Register]*. Submit written or electronic comments on the agency's economic impact determination by *[insert date 90 days after date of publication in the Federal Register]*. Please see section IX of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061,

DMB
Display Date 2-18-03
Publication Date 2-19-03
Certifier R. LEDESMA

NPR 1

Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Marina Y. Chang, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of March 4, 1988 (53 FR 7076), FDA published a final monograph for OTC ophthalmic drug products in part 349 (21 CFR part 349). The monograph provides for eyewash drug products in § 349.20, but does not include emergency first aid eyewash drug products because there were no submissions or comments on these products during the rulemaking process.

After the final monograph was published, the agency received a request for an advisory opinion (Ref. 1) concerning the status of a product used for emergency first aid treatment of chemical burns of the eyes and skin. This product was described as a sterile phosphate buffered solution containing sodium phosphate, USP and monobasic potassium phosphate, NF, preserved with edetate disodium, USP 1:2,000 and benzalkonium chloride, USP 1:5,000, for use immediately following a chemical burn to thoroughly flush the eyes and skin for the express purpose of removing the chemical irritant, and to relieve the discomfort and burning caused by the irritating chemical prior to seeking medical treatment.

As a result, the agency published a request for data and information on this category of drugs in the **Federal Register** of December 5, 1989 (54 FR 50240). The agency stated that it was unaware of sufficient data to make a

determination as to the safety, effectiveness, and proper labeling of these ophthalmic drug products. Specifically, the agency noted that the majority of these products: (1) Are not intended to be marketed directly to individual consumers; (2) are often packaged in large volume containers not normally found at the retail level of distribution, especially for OTC ophthalmic drug products; (3) may be stored for long periods of time under different environmental conditions; (4) may be marketed in different types of containers and closure systems; and (5) may be used with plumbed, nonplumbed, self-contained emergency eyewash, or shower equipment/stations. The agency noted it was not aware of all of the various labeling formats, labeling statements, and formulations of all the various emergency first aid eyewash products.

In response to the request for data and information, three manufacturers and one manufacturer's association provided submissions (Refs. 2 through 7) that included several journal articles in support of the safety and effectiveness of products that provide immediate emergency care by neutralization and dilution to the most serious burns due to strong acids and alkalis. The submitted literature explained that acid burns cause instantaneous coagulation of protein and result in limited damage, whereas strong alkalis penetrate the ocular tissues rapidly and produce damage that is widespread, uncontrolled, and progressive (Ref. 8). The literature (Ref. 2) included a quote from the National Institute of Occupational Safety and Health occupational health guidelines which states: "If (chemical) gets into the eyes, wash eyes immediately with large amounts of water, lifting the lower and upper lids occasionally. Get medical attention immediately." The comment included an excerpt from the regulations of the Occupational Safety and Health

Administration (OSHA) entitled “Requirements for Medical and First Aid” (42 CFR 1910.151). This portion of the OSHA regulations assures that workers exposed to injurious corrosive materials be provided with “suitable facilities for quick drenching or flushing of the eye.” One manufacturer also provided sample labeling of several marketed products (Ref. 5).

II. Comments Received and the Agency’s Responses

A. Neutralization

Three comments addressed the term “neutralization.” One comment stated that it removed this term from the principal display panel of its product’s labeling and replaced it with “Wash/Flush” because the latter term better expressed the action of the product. Another comment considered the term “neutralization” to be relative and not absolute. The third comment believed that neutralizing was part of the action of the product and provided a chart demonstrating the buffering capacity of a neutralizer solution towards strong acids and bases versus purified water (Ref. 7).

The agency reviewed available medical literature (Refs. 8 through 15) and found the treatment of choice for acid and alkali burns listed in this literature to be copious and continuous irrigation of the area with water or a pH balanced solution for at least 20 to 30 minutes. According to the American Academy of Ophthalmology (Ref. 8), “Specific neutralizing agents are not useful; simple dilution (with water or saline solution) is the most effective and practical way of neutralizing strong chemicals.” *Casarett and Doull’s Toxicology: The Basic Science of Poisons* (Ref. 9) states: “Attempts to obtain some special buffered solution or mildly alkaline wash will only delay the start of treatment. Washing should begin as close in time and place to the site of the accident as possible.” *Conn’s Current Therapy 1990* (Ref. 10) states:

The severity of the chemical burn is related directly to length of time that a given agent is exposed to the skin * * *. Exact identification of the burning chemical may suggest appropriate specific measures; but an acid should not be neutralized with a base or vice versa.

The agency is concerned that attempts to adjust the pH of the affected area, such as by testing with litmus paper and then adding drops of neutralizing solution, would delay or, at a minimum, reduce the vigorous flushing needed to prevent further eye damage. Therefore, the agency tentatively concludes that initial treatment is best accomplished by copious and continuous amounts of water or saline solution. Any attempt to provide a corrective solution, if necessary, should be left to health care professionals following transport of the accident victim to the facility's first aid station or a hospital. Accordingly, the agency considers the term neutralization as inappropriate to describe the pharmacological action of these products.

B. Water Lavage

Four comments emphasized the importance of immediate and continuous water lavage for emergency care of the eye following chemical burns. The Tulane University Research Report (Ref. 7) compared administration of 50 milliliters (mL) of distilled water and a test product, called "Neutralize" (exact formulation not provided), to each eye 10 seconds after acid was dropped on the eye. The studies showed no significant difference in the rate of healing or in the final condition of both eyes.

The agency agrees that the medical literature and the American Academy of Ophthalmology support the use of copious amounts of fluid as the best approach for emergency eyewash care. The agency also recognizes the value

of providing a sterile and stable product in large quantities in an industrial setting where flowing water may not be available.

C. Container Size and Ease of Opening

One comment referred to a 32-ounce (oz) container, intended for only one use, as having a closure that requires 1 1/4 turns. The comment explained that a 38-millimeter unrestricted opening is approximately the diameter needed to cover an average adult eye. The comment added that this product is easily opened by a small stature adult under stress. The comment noted that a tamper evident plastic heat shrink seal that breaks away easily is used.

All eyewash products must comply with the monograph standards in part 349. The products must also meet current good manufacturing practices (CGMPs) as stated in 21 CFR parts 210 and 211.

The agency believes that emergency eyewash products must contain enough fluid to permit adequate flushing of the eye. While a maximum volume may depend on the configuration of the container or the plumbing system, the minimum volume should be no less than 16 oz (473 mL (500 mL or 1/2 liter is acceptable)). Because of concerns about sterility, the product should be for a single individual's use unless it is part of a plumbing system with a one-way valve.

D. pH Adjustment

Several comments supported the pH range of 6.6 to 7.4 as appropriate for these products. One comment mentioned a lack of adverse event reports in the many years of use of these products as an indicator that the present pH is appropriate. Another comment stated it was unlikely that the pH of a product would have a clinically significant impact on the outcome of a chemical burn. One comment, however, felt that the agency should not require

a specific range but define the requirement as “needing to be at or near neutral pH, 6.6 to 7.4.”

The agency agrees that 6.6 to 7.4 is an appropriate pH range for emergency eyewash solutions. The agency believes this pH range provides sufficient flexibility for manufacturers to adjust agents to maintain stability, yet provides a solution that does not cause further harm or additional irritation to the accident victim. The agency, however, agrees that the pH within this range is not likely to impact on the outcome of a chemical burn. The agency believes that the inclusion of an antimicrobial preservative would aid the stability of the product.

Accordingly, the agency is proposing the following in new § 349.22 *Emergency first aid eyewashes*: “These products contain water, agents to achieve the pH within a range of 6.6 to 7.4, and a suitable antimicrobial preservative agent.”

E. Buffering

One comment noted that buffering is an added feature to help neutralize the chemical burn but that both buffered and unbuffered solutions can be extremely beneficial to achieve dilution and neutralization because the main treatment is by dilution. Another comment added that buffers help ensure product integrity during storage in an industrial setting, while another comment was unaware of any superiority of either buffering or not buffering.

The product that led to the request for data was described as a sterile phosphate buffered solution (Ref. 1) for use immediately following a chemical burn to thoroughly flush the eyes and skin for the express purpose of removing the chemical irritant, and to relieve the discomfort and burning caused by the irritating chemical prior to seeking medical treatment. The comment provided

excerpts from studies presented in a Tulane University Research Report (Ref. 7) to demonstrate the superiority of its product when compared to water as an emergency first aid eyewash to treat a caustic acid splash.

The agency notes that a medical dictionary (Ref. 16) defines “buffering” as “a chemical system that prevents change in concentration of another chemical substance, e.g., proton donor and acceptor systems serve as buffers preventing marked changes in hydrogen ion concentration (pH).” The agency acknowledges the buffer system contributes to the tonicity of the ophthalmic product but adds that the tonicity of the entire formulation should approximate lacrimal fluids.

The agency agrees with the comment that stated it was unaware of any superiority of either buffering or not buffering these products. Accordingly, the agency is proposing in § 349.22 that emergency first aid eyewash products may contain agents for buffering the pH.

F. Phosphate Treatment of Chemical Burns

One comment provided references to support “phosphate therapy” to treat burns caused by acidic or basic substances (Ref. 1). The references reported a phosphate buffer is prepared by dissolving 70 grams (g) of monobasic potassium phosphate (KH_2PO_4) and 180 g of dibasic sodium phosphate ($\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$) in 850 mL of water. The concentration of the solution is molar with respect to phosphate, but as the phosphates are physiologically occurring substances they can be safely employed in such high concentrations and provide prompt neutralization. The comment contended that some antidotes are too acidic or alkaline; that burns caused by acids or bases require different treatment; and that the phosphate buffer is neutral in its reaction,

and thus is well suited for the treatment of injuries caused by acidic or basic chemicals.

At this time, the agency considers a phosphate buffered solution acceptable for emergency first aid eyewash products. The increased concentration of phosphates would not alter the pH range but could be more effective against an acid or alkali burn.

G. Industrial Glare

One comment briefly referred to emergency first aid eyewash solutions to treat industrial glare (i.e., from welder's arc) but did not provide any data to support this use. At this time, the agency is not including this use as an indication for these products without adequate supporting documentation. The agency requests interested parties to provide supporting data.

H. Five to 15-gallon Container Plus Preservative Concentrate

One comment explained that a 15-minute emergency eyewash requires 14 gallons (gal) of potable water and a 5-minute eyewash requires 9 1/2 gal of potable water. The comment stated that the unit would be filled with potable water and the preservative concentrate added. The comment offered that a concentrate will preserve 5 to 20 gal of potable water for up to 180 days. The comment further stated that potable eyewash units should be flushed and cleaned and the water and concentrate replaced every 60 days.

All emergency eyewash products must be able to meet monograph requirements, which include safety and effectiveness, a pH range of 6.6 to 7.4, and compliance with CGMPs. The agency is aware that there are preservative concentrates in the marketplace for use in potable eyewash units, as the comment noted. Under § 349.82(d)(3), the agency is proposing that the labeling contain the word "concentrate" in bold type. The labeling must provide

adequate directions for adding the concentrate to potable water to obtain a solution that meets the requirements of § 349.22. The directions should also state that the concentrate should be added to potable water to have a fully constituted solution available in advance of an emergency. The agency is unaware of data to support the length of time that any particular preservative concentrate is safe and effective. Manufacturers of these products are advised to follow CGMPs.

I. Labeling

One comment proposed several labeling revisions under § 349.78. Under § 349.78(a), the comment added to the statement of identity the terms “neutralizer” and “neutralizing solution.”

As stated in section II.A of this document, the agency does not believe that the term “neutralize” properly describes the action of these products and, therefore, is not proposing this term or any variation of this term in the monograph.

Under § 349.78(b)(1) and (b)(2), the comment added the terms “acid” and “alkali.” Under § 349.78(b)(5), the comment provided for indications for eyes that have been subjected to industrial glare such as welder’s arc and “other workplace irritants.” The comment argued that demulcents have a long history of use for soothing the burning sensation associated with welder’s arc and other workplace irritants that dry the eye. The comment explained that this indication is an extension of § 349.60(b)(2), which provides for temporary relief due to exposure to the sun.

The agency agrees that if an emergency first aid eyewash will assist in the prevention of permanent damage to the eye(s) due to industrial glare, this indication should be included in the uses section of the labeling. However,

as stated in section II.G of this document, the agency needs supporting documentation for this use.

The agency believes the term “particulate contamination” is a general term that could include the comment’s request for an indication for “other workplace irritants.” The agency agrees that there are potential instances in the industrial setting where particulate matter could cause eye damage and that an eyewash solution could alleviate the seriousness of the condition. Accordingly, the agency is proposing the terms “acid,” “alkali,” and “particulate contamination” in new § 349.82(b) as examples of causes of injury.

Under § 349.78(d)(3), the comment suggested the following directions for emergency first aid eyewash products:

For eyewash products packaged in a container that also serves as an eyecup. Remove safety seal and cap. Avoid contamination of rim of bottle. Place rim over affected eye, pressing tightly to prevent the escape of the liquid, and tilt the head backward. Open eyelid wide and rotate eyeball to ensure thorough bathing with the solution. Use only unopened bottle on the eyes.

The comment explained that many large volume (up to 32 oz) first aid eyewash solutions are packaged in containers with wide flanged rims that fit over the eye.

The agency agrees that containers that also serve as eyecups should be addressed in the monograph and is including this information, with a few modifications, in § 349.82(d)(1). The agency notes that eyecups generally promote retention of material that may be injurious to the eye instead of allowing the injurious material to be washed away and down the face. The use of eyecups in the setting of workplace irritants should be discouraged. The

agency also obtained and reviewed representative current labeling for a number of these products (Ref. 17) to develop the labeling in this proposal.

III. The Agency's Proposal

The agency tentatively concludes that the references support the safety and effectiveness of emergency first aid eyewash drug products to remove acid or alkali chemicals and that, in particular, immediate flushing of the eye with fluid is urgently needed to lessen the impact of the alkalis. The agency also acknowledges that burns from alkalis penetrate the ocular tissues rapidly and produce damages that are widespread, uncontrolled, and progressive. However, the agency does not believe that a chemical irritant should be counteracted with another chemical. The agency believes that immediate and copious irrigation with fluid is the most important step and that the amount of time prior to irrigation is a critical factor in determining the amount of residual damage.

The effectiveness of an emergency eyewash appears dependent upon the steady flow of copious amounts of fluid to the injured eye(s). Emergency first aid eyewashes serve as an interim step in first aid care by providing immediate flushing of the eye and allowing the accident victim to be transported to the facility's first aid station or a hospital while the flushing treatment is in progress. Accordingly, the agency is proposing to amend the final monograph for OTC ophthalmic drug products to include a section on emergency first aid eyewashes.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the

Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. In addition, the proposed rule is not a significant regulatory action as defined by the Executive order. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this proposed rule because the proposed rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted annually for inflation. The current inflation adjusted statutory threshold is approximately \$110 million.

With respect to the Regulatory Flexibility Act, FDA does not believe that the proposed rule would have a significant economic impact on a substantial number of small entities. However, the agency recognizes the uncertainty of its estimates with respect to the number of affected small entities as well as the economic impact of the rule on those small entities. The agency therefore

requests detailed public comment regarding any substantial or significant economic impact that this rulemaking would have on manufacturers of OTC emergency first aid eyewash drug products.

The purpose of this proposed rule is to amend the final monograph for OTC ophthalmic drug products to include OTC emergency first aid eyewash drug products. This proposed rule may increase OTC availability of these products and may, as a result, lower the costs to industrial facilities and individuals that use such products.

Manufacturers of the affected products should incur only minor costs to relabel their products to meet the monograph requirements. These manufacturers can make the required changes whenever they are ready to order new product labeling within the 12 months after the final rule is issued. Manufacturers of products with annual sales of less than \$25,000 will have 24 months to complete the required relabeling. The agency has been informed that this type of relabeling generally costs approximately \$3,000 to \$4,000 per stockkeeping unit (SKU) (i.e., individual products, packages, and sizes). The agency estimates that there are approximately 25 manufacturers or marketers of 40 to 45 products and 50 to 60 SKUs that would be affected by this proposed rule.

Based on this information, the total one-time costs of relabeling would be between \$150,000 (\$3,000 per SKU x 50 SKUs) and \$240,000 (\$4,000 per SKU x 60 SKUs). Assuming an equal distribution of these costs across the 25 affected entities results in an average cost burden of \$6,000 to \$9,600 per firm. The agency believes that actual costs would be lower for several reasons. First, most of the required changes will be made by private label manufacturers that tend to use relatively simple and less expensive labeling. Second, the agency

is proposing a 12-month implementation period that would allow manufacturers to coordinate the required changes with routinely scheduled label printing and/or revisions. Labeling changes for these products would not be required until 12 months after the monograph amendment is issued as a final rule and becomes effective. Furthermore, products with less than \$25,000 per year in sales would not need to be relabeled until 24 months after the rule becomes final. Thus, manufacturers would have time to use up existing labeling stocks and plan for new labeling, thereby mitigating some of the costs of this proposed rule. Third, manufacturers may be able to implement the new labeling required by this proposal at the same time that they implement the new standardized format and content labeling required by 21 CFR 201.66. Thus, the total relabeling costs associated with two different but related final rules may be reduced by implementing the required changes at the same time.

According to standards established by the Small Business Administration, a small pharmaceutical preparations manufacturer (NAICS code 325412) employs fewer than 750 people. FDA has determined that approximately 88 percent (22 out of 25) of OTC ophthalmic drug product manufacturers meet these criteria and can therefore be categorized as small entities. The average annual revenue of small entities affected by this rule was found to be approximately \$10.7 million. Thus, the cost of the rule per affected small entity would be between 0.056 percent ($\$6,000 \div \10.7 million) and 0.09 percent ($\$9,600 \div \10.7 million) of average annual revenues. FDA is aware of one small entity that has average annual revenues of approximately \$1 million and produces 3 SKUs. The total cost of the final rule for this small entity would be between 0.9 percent ($3 \text{ SKUs} \times \$3,000 \text{ per SKU} \div \1 million) and 1.2 percent ($3 \text{ SKUs} \times \$4,000 \text{ per SKU} \div \1 million) of annual revenues. Thus the economic

impact of the proposed rule on the majority of small entities is expected to be much less than 1 percent of annual revenues. While these estimates are uncertain, it appears that this proposed rule would not have a significant economic impact on a substantial number of small entities.

The agency considered but rejected several alternatives: (1) A shorter or longer implementation period, and (2) an exemption from the requirements for small entities. While the agency believes that industries and accident victims who use these products would benefit from having the new labeling in place as soon as possible, the agency also acknowledges that coordination of the labeling changes with implementation of the new OTC “Drug Facts” labeling may significantly reduce the costs associated with this proposed rule. Thus, an alternative specifying a shorter implementation period was rejected due to its inflexibility and potentially greater cost. A longer implementation period was also rejected because it would unnecessarily delay the benefits of new labeling and revised formulations, where applicable, to parties who use these OTC drug products. The agency also rejected an exemption for small entities because the new labeling and revised formulations, where applicable, would also generate benefits for parties who purchase products marketed by those entities. Furthermore, the vast majority of firms affected by this proposed rule can be classified as small entities. However, an additional year is being allowed for products with annual sales of less than \$25,000 to implement the required changes in order to reduce the potential impact of the rule on small entities.

This proposed rule allows for continued marketing of affected products without the risk of regulatory action provided the following conditions are met:

- (1) The product or similarly formulated and labeled products were marketed

as OTC drugs at the inception of the OTC drug review on May 11, 1972, a date that was later extended to on or before December 4, 1975 (see 21 CFR 330.13); (2) such product does not constitute a hazard to health; (3) the product formulation is not regarded to be a prescription drug within the meaning of section 503(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)); (4) the product is an OTC drug and does not bear claims for serious disease conditions that require the attention and supervision of a licensed practitioner.

Emergency first aid eyewash products and eye irrigating solutions that do not meet the previous criteria may not be marketed OTC pending evaluation of these products for the treatment of chemical burns and for irrigation of the eye(s) unless the product is the subject of an approved new drug application (NDA).

This analysis of impacts shows that the proposed rule is not economically significant under Executive Order 12866 and that the agency has undertaken important steps to reduce the burden to small entities. This analysis of impacts, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required by the Regulatory Flexibility Act. The agency will reassess the economic impact of this rulemaking in the preamble to the final rule.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling statements are a "public disclosure of information originally supplied

by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action 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.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

VIII. Request for Comments

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments to <http://www.fda.gov/dockets/ecomments> or three hard copies of any written comments, except that individuals may submit one hard copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may

be accompanied by a supporting memorandum or brief. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

IX. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 12 months after its date of publication in the **Federal Register**.

X. References

The following references are on display in the Dockets Management Branch (see **ADDRESSES**) under Docket No. 80N-145B and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. AP.
2. Comment 1.
3. Comment 2.
4. Comment 3.
5. Comment 4.
6. Comment 5.
7. Comment 6.
8. "External Disease and Cornea," 1989-1990, *Basic and Clinical Science Course*, American Academy of Ophthalmology, San Francisco, CA, pp. 130-133, 1989.
9. Potts, A. M., "Toxic Responses of the Eye," *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 3d ed., Macmillan Publishing Co., New York, NY, pp. 478-485, 1986.
10. Raker, R. E., *Conn's Current Therapy 1990*, W. B. Saunders Co., Philadelphia, PA, p. 1035, 1990.

11. Dreisbach, R. H., and W. O. Robertson, "Emergency Management of Poisoning," *Handbook of Poisoning: Prevention, Diagnosis & Treatment*, 12th ed., Appleton & Lange, Norwalk, CT, pp. 28–29, 1987.
12. Siverston, K. T., "Ocular Toxicity," *Manual of Toxicologic Emergencies*, Year Book Medical Publishers, Inc., Chicago, IL, pp. 115–118, 1989.
13. Tapley, D. F. et al., "The Eyes," *The Columbia University College of Physicians and Surgeons Complete Home Medical Guide*, Crown Publishers, Inc., New York, NY, pp. 696–697, 1989.
14. Behrman, R. E., and V. C. Vaughan, "Injuries to the Eye," *Nelson Textbook of Pediatrics*, 13th ed., W. B. Saunders Co., Philadelphia, PA, pp. 1472–1473, 1987.
15. "Occupational Health Guidelines for Ethyl Chloride," National Institute for Occupational Safety and Health, pp. 1–4, September 1978.
16. *Dorland's Illustrated Medical Dictionary*, 27th ed., W. B. Saunders Co., Philadelphia, PA, p.252, 1988, s.v. "buffer."
17. Comment 7.

List of Subjects in 21 CFR Part 349

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 349 be amended as follows:

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

1. The authority citation for 21 CFR part 349 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 349.22 is added to subpart B to read as follows:

§ 349.22 Emergency first aid eyewashes.

These products contain water, agents to achieve the pH within a range of 6.6 and 7.4, and a suitable antimicrobial preservative agent. Additionally, they may contain tonicity agents to establish isotonicity with tears and agents for buffering the pH.

3. Section 349.82 is added to subpart C to read as follows:

§ 349.82 Labeling of emergency first aid eyewash drug products.

(a) *Statement of identity.* The labeling of the product identifies the product with one of the following: “Emergency first aid eyewash,” “First aid eye rinse,” or “Emergency eyewash.”

(b) *Indications.* The labeling of the product states, under the heading “Uses”, “for” [select one of the following: “flushing,” or “irrigating”] “the eye to reduce chances of severe injury caused by acid, alkali, or particulate contamination”.

(c) *Warnings.* In addition to the warnings in § 349.50 (the “Replace cap after using,” warning in § 349.50(c)(1) should only be used if applicable), the labeling of the product contains the following warnings under the heading “Warnings” for all emergency eyewash products:

(1) “Do not use [in bold type] [bullet]¹ for injection [bullet] in intraocular surgery [bullet] internally [bullet] if solution changes color or becomes cloudy”.

(2) “Ask a doctor if you have [in bold type] [bullet] eye pain [bullet] changes in vision [bullet] redness or irritation of the eye after use [bullet] an injury caused by an alkali”.

(d) *Directions.* The labeling of the product states, as appropriate, under the heading “Directions”, “[bullet] do not dilute solution or reuse bottle [in

¹ See § 201.66(b)(4) of this chapter for definition of bullet symbol.

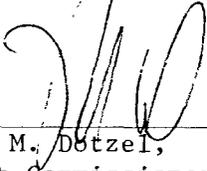
bold type] [bullet] hold container a few inches above the eye [bullet] control rate of flow by pressure on bottle [bullet] flush affected area for a minimum of 20 minutes [bullet] continue flushing with water if necessary [bullet] obtain medical treatment”.

(1) *For products packaged in a container that also serves as an eyecup.* The labeling states “[bullet] use only unopened bottle [bullet] remove safety seal and cap [bullet] avoid contamination of rim of bottle [bullet] place rim over affected eye [bullet] tilt head backward [bullet] open eyelids wide [bullet] thoroughly bathe eye with solution [bullet] allow solution to flow away from eye”. The directions in this paragraph shall be placed in sequence with the directions provided in paragraph (d) of this section, as appropriate.

(2) *For products intended for use with a nozzle applicator.* The labeling states “[bullet] flush affected eye as needed [bullet] control flow of solution by pressure on bottle”.

(3) *For products that use a concentrate with potable water.* The word “concentrate” shall be in bold type. Labeling must provide adequate directions for adding the concentrate to potable water to obtain a solution that meets the requirements of § 349.22. The directions shall also state that the concentrate should be added to potable water to have a fully constituted solution available in advance of an emergency.

Dated: 1/31/03
January 31, 2003.



Margaret M. Dotzel,
Assistant Commissioner for Policy.

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