May 14, 2021

David Palmer, MD
Clinical Associate Professor
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Alan L. Robin, MD
Executive Vice President
American Glaucoma Society
Professor, University of Michigan
Ann Arbor, Michigan

Dear Drs. Palmer and Robin,

Thank you for your letter dated April 15, 2021. Your letter describes confusion regarding the proper use of preserved multidose topical ophthalmic drug products in both the clinic and the operating room. You state that there is concern about whether a bottle should be discarded after each patient because of the risk of contamination and if discarded, the waste of the medication and the bottle. In addition, you ask about the role of The Joint Commission (TJC) and ask "Is there any rationale from a regulatory perspective to discard a bottle either after every use or after 28 days.

In 1953, the FDA (the Agency) first published in the Federal Register a notice to manufacturers and re-packers of ophthalmic solutions that liquid preparations for ophthalmic use contaminated with viable microorganisms had been responsible for serious eye injuries [18 FR 351 (1953), Friday, January 16, 1953]. The Agency concluded that liquid ophthalmic preparations packed in multiple-dose containers should (1) contain one or more suitable and harmless substances that will prevent the growth of micro-organisms, or should (2) be so packaged as to volume and type of container and so labeled as to duration of use and necessary warnings as will afford adequate protection and minimize the hazard of injury resulting from contamination during use.

In June, 1963, the FDA proposed a regulation which was finalized in September, 1964 [29 FR 12458 (1964)], requiring liquid preparations offered or intended for ophthalmic use to be sterile and that liquid ophthalmic preparations packed in multiple-dose containers should: (1) Contain one or more suitable and harmless substances that will inhibit the growth of micro-organisms; or (2) Be so packaged as to volume and type of container and so labeled as to duration of use and with such necessary warnings as to afford adequate protection and minimize the hazard of injury resulting from contamination during use. The implementation of this regulation has been incorporated into the approval process which permits multidose ophthalmic drug products to be approved and safely used in the United States.

Prior to approval, multidose ophthalmic products are required to establish the minimum concentration of an antimicrobial preservative which can be included in the topical ophthalmic drug product formulation to inhibit the growth of potential microbiological contaminants. The criteria for this demonstration are specified in the United State Pharmacopeia [USP 51] and include bacteria, yeasts, and molds. The concentration of the antimicrobial preservative is then monitored throughout the entire established shelf life of the product to ensure that the product is capable of continually affording adequate protection from injury should contamination occur during use. Monitoring of the necessary concentration of the antimicrobial preservative as well as periodic contamination testing as specified in the USP is routinely completed during ongoing stability studies following the release of commercial product. The established shelf life of the product is reviewed and included in the FDA's approval of each specific drug product application. The lot number and expiration date of the product is required to be included on the bottle of every approved new drug product.

The inclusion of an antimicrobial preservative might seem unnecessary in a setting such as the operating room or professional office where trained paraprofessionals and professionals will be administering the drug product, but this added protection is designed to further minimize any chances of injury should a contamination event occur. This additional level of protection also enables the drug product to be administered to multiple different patients over the course of time **until the bottle's stated expiration date**. While the number of different individuals is not limited, the duration of use is limited by the expiration date included on the bottle.

The FDA uses established testing methodology to set appropriate expiration dating periods. To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, the United States Code of Federal Regulations (21 CFR 211.137) states that the drug product shall bear an expiration date determined by appropriate stability testing described in 21 CFR 211.166. You have asked in your letter about artificial expiration dates, such as 28 days after opening on ophthalmic drug bottles, or restricting the use of ophthalmic

drug bottles to single patient use. To the best of our knowledge, there is no scientific data to support these expiration dates or restrictions in use for topical ophthalmic drug products.

There are some topical ophthalmic drug products which have a defined limited shelf life. These products are clearly marked with labeling which describes expected storage conditions and the supported shelf life. There are ophthalmic drug products which are only appropriate for administration to a single patient. These products are also clearly marked with labeling which describes that the product is intended to be used only on a single patient. Products not labeled as single dose ophthalmic products are not intended to be limited in use to a single patient and when stored as labeled, can be expected to be able to be safely used after opening until the expiration date included on the bottle. Many, although not all, of these bottles are specifically labeled with statements clarifying that after the bottle is opened, they can be used until their identified expiration date.

The location of the use of an ophthalmic drug product does not influence the expiration date included on the bottle except where the location may alter the storage temperature of the bottle. The strength, quality, purity of an ophthalmic drug product may be affected by the storage conditions in which the bottle is stored, most notably the temperature. For that reason, the storage conditions upon which the expiration date is based are included in the drug product's labeling. Storage of the ophthalmic bottle under temperature conditions which differ from the drug product's labeling may alter the period of time that the product can be expected to maintain its strength, quality and purity. If an alternative temperature condition can be used for a limited time without affecting the strength, quality and purity of the ophthalmic product, the alternative temperature conditions will be included in the labeling of the product. Other factors, such as use in the operating room, use in a hospital room, use in an examination room or use in a patient's home should not be expected to alter the strength, quality or purity of the ophthalmic drug product.

For some topical ophthalmic drug products, the orientation of the bottle (upright, sideways or upside down) may affect the duration of time which the ophthalmic drug product's strength, quality and purity are maintained. In recognition of this factor, during the development of an ophthalmic drug product, a variety of different storage orientations are tested. If a difference is noted between these orientation positions, the worst case position is selected to establish the shelf life and the labeling of the ophthalmic drug product may include specific instructions on storing the bottle in a particular orientation. It remains the case, that if special conditions exist for an ophthalmic drug product to maintain its strength, quality and purity, the conditions will be explicitly described in the drug products labeling.

The Joint Commission (TJC) is a US accrediting agency focusing on improvement strategies that help health care organizations continuously improve patient's safety and their quality of care. Dr. Robert Campbell, PharmD, BCSCP, Director, Clinical Standards Interpretation Group and Director, Medication Management of The Joint Commission has requested that any questions regarding their position on drug product expiration dating or limitations on the use of drug products be directed to him.

In summary, the FDA determines as part of the review leading to the approval of topical ophthalmic new drug products, an expiration date which is included on each bottle. This expiration date is based on extensive formal testing of the drug product in the marketed container closure system and includes sterility assurance. The antimicrobial preservative included in multidose topical ophthalmic drug products is intended to minimize the hazard of injury that might result from contamination of the bottle during use. The FDA expects that the strength, quality, and purity of the topical ophthalmic drug product will be maintained during the entire period of its use if stored as described in the labeling and used by the date listed on the bottle as the expiration date. Topical ophthalmic drug products are not limited to use by a single individual or a duration of use shorter than the expiration date included on the bottle unless specific statements to that effect are included in the labeling of the product.

If you have any additional questions, please feel free to contact me at (301) 796-0690.

Sincerely,

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov