FDA Concerns Regarding Microbiological Quality of Topical Ophthalmic Products: A CDER Microbiologist's Perspective

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Disclaimer

- The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA


Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

CDER/OPQ/Office of Pharmaceutical Manufacturing Assessment/Division III

OPMA Role within CDER:

1. Submission Assessment
   - NDA/ANDAs/BLAs, Supplements, INDs, DMFs, Mtg Pkgs
   - Microbiology/Facility/Manufacturing Process
2. Subject Matter Expertise
   - Facility Inspections
   - Incidents (drug contamination, infection outbreaks)
   - CDER Policy (guidance/inquiries, outside organizations)
   - Input to CDER re: inspectional findings & assessments

Presentation Outline

- Regulations/Compendial Requirements & Microbiological Critical Quality Attributes (CQAs): Topical Ophthalmic Drug Products
- Recent FDA Concerns
  - Adverse events
  - Recalls
  - Warning Letters
- Relevant Guidance & Technical Reports for Industry
- Expectations re: Non-preserved Topical Ophthalmic Presentations & Multidose Units

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Microbiological Critical Quality Attributes for Topical Ophthalmics

- Sterility
- Antimicrobial Effectiveness for multiple dose units
  - Provides microbiological quality during drug in-use time
- Container Closure Integrity

CFR and Topical Ophthalmic Sterility Requirement: Link

21CFR200.50(a)(1)

§ 200.50 Ophthalmic preparations and dispensers.

(a)

(1) Informed medical opinion is in agreement that all preparations offered or intended for ophthalmic use, including preparations for cleansing the eyes, should be sterile. It is further evident that such preparations purport to be of such purity and quality as to be suitable for safe use in the eye.

(2) The Food and Drug Administration concludes that all such preparations, if they are not sterile, fall below their professed standard of purity or quality and may be unsafe. In a statement of policy issued on September 1, 1964, the Food and Drug Administration ruled that liquid preparations offered or intended for ophthalmic use that are not sterile may be regarded as adulterated within the meaning of section 501(c) of the Federal Food, Drug, and Cosmetic Act (the act), and, further, may be deemed misbranded within the meaning of section 502(j) of the act. This ruling is extended to affect all preparations for ophthalmic use. By this regulation, this ruling is applicable to ophthalmic preparations that are regulated as drugs. By the regulation in § 800.10 of this chapter, this ruling is applicable to ophthalmic preparations that are regulated as medical devices.

CFR and Topical Ophthalmic Sterility Requirement: Link

21CFR200.50(b)

(b) Liquid ophthalmic preparations packed in multiple-dose containers should:

(1) Contain one or more suitable and harmless substances that will inhibit the growth of microorganisms; 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.

Microbiological CQAs for Topical Ophthalmics: USP Chapters

- USP<51> Antimicrobial Effectiveness Testing
  - For multiple dose units
  - See table 3 for acceptance criteria

PRODUCT CATEGORIES

For the purpose of testing, compendial articles have been divided into four categories (see *Table 1*). The criteria of antimicrobial effectiveness for these products are a function of the route of administration. It is expected that formulations containing preservatives will meet minimal efficacy standards, whether packaged as multidoses or unit doses.

Table 1. Compendial Product Categories

Category	Product Description
1	Injections; other parenterals including emulsions, otic products, sterile nasal products, and ophthalmic products made with aqueous bases or vehicles
2	Topically used products made with aqueous bases or vehicles; nonsterile nasal products and emulsions, including those applied to mucous membranes
3	Oral products other than antacids, made with aqueous bases or vehicles
4	Antacids made with an aqueous base

Microbiological CQAs for Topical Ophthalmics: USP Chapters

- USP<771> Ophthalmic Products-Quality Tests
  - Section: Drug Product Quality

STERILITY

Ophthalmic dosage forms must meet the requirements of *Sterility Tests* ⟨71⟩. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described in ⟨71⟩, along with aseptic manufacture, may be used. The immediate container for ophthalmic products shall be sterile at the time of filling and closing. See also *Universal Tests, Container–Closure Integrity*.

ANTIMICROBIAL PRESERVATIVES

Antimicrobial agents must be added to products that are packaged in containers that allow for the withdrawal or administration of multiple doses, unless one of the following conditions prevails: 1) there are different directions in the individual monograph; 2) the ▲radiopharmaceutical drug product▲ (USP 1-Dec-2022) contains a radionuclide with a physical half-life of <24 h; ▲▲ (USP 1-Dec-2022) 3) the drug product, without additional agents, is sufficiently microbicidal to meet the requirements of *Antimicrobial Effectiveness Testing* ⟨51⟩, ▲or 4) the container–closure system is capable of maintaining sterility of the product throughout its shelf life until opened or accessed. Once opened or accessed, it must maintain antimicrobial effectiveness during the intended use period. Antimicrobial agents▲ (USP 1-Dec-2022) must meet the requirements of ⟨51⟩ and *Antimicrobial Agents—Content* ⟨341⟩. Acceptance criteria for antimicrobial preservative content in ▲multi-dose▲ (USP 1-Dec-2022) products should be established.

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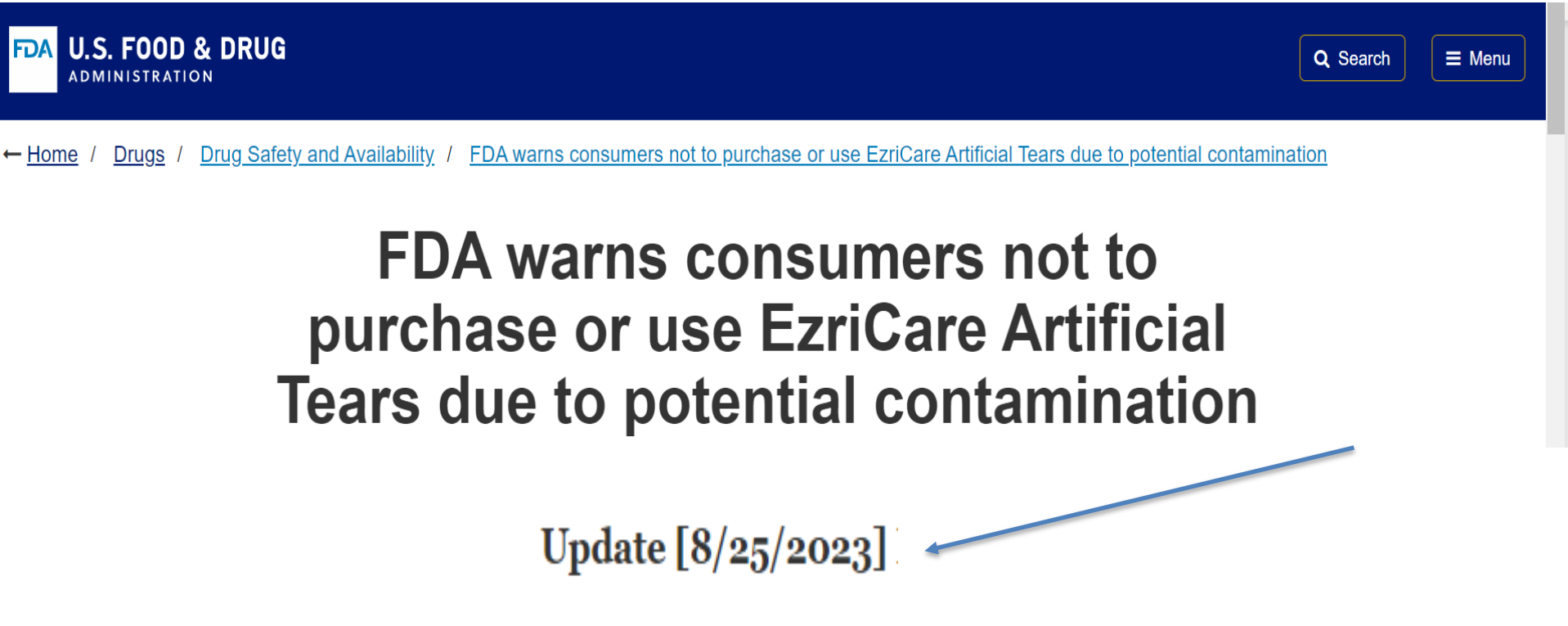
Case #1: EzriCare Artificial Tears Adverse Events & Recall : Link



Case #1: EzriCare Artificial Tears Adverse Events & Recall : Link

Update [8/25/2023] FDA is reminding the public that these recalled products should not be used, including off-label use in animals. FDA does not have direct knowledge of veterinary use of these products or of animal adverse events that are linked to the products; however, on August 14, 2023, the New Jersey Department of Health issued a Health Alert Network message calling for animal caretakers to immediately discontinue using EzriCare Artificial Tears, Delsam Pharma Artificial Tears, and Delsam Pharma Artificial Ointment on animal patients.

If you suspect that an animal under your care contracted an infection or serious side effects from these products, please report it to FDA: How to Report Animal Drug and Device Side Effects and Product Problems.

Update [2/22/2023] FDA recommended that Global Pharma recall Delsam Pharma's Artificial Eye Ointment, and the firm agreed to initiate a recall.

Case #1: EzriCare Artificial Tears Adverse Events & Recall : Link

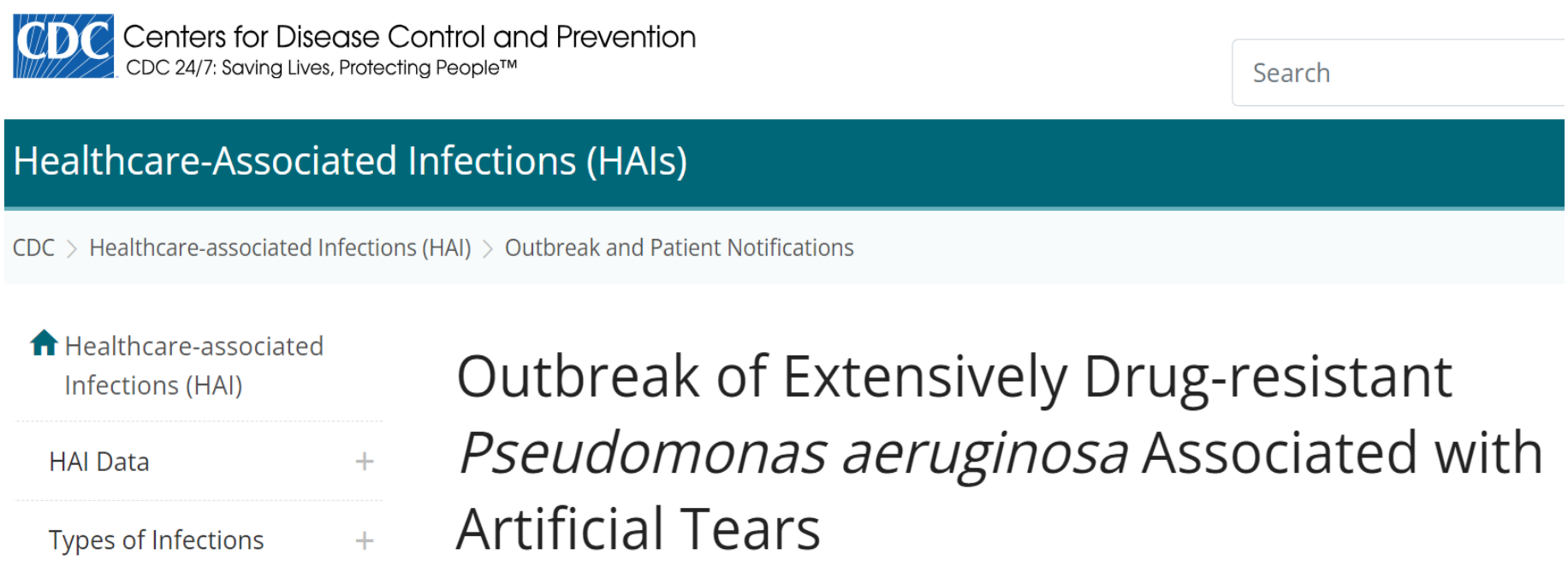
[2/2/2023]

Global Pharma initiated a voluntary recall at the consumer level of all unexpired lots of EzriCare Artificial Tears and Delsam Pharma's Artificial Tears. FDA recommended this recall due to the company's current good manufacturing practice (CGMP) violations, including lack of appropriate microbial testing, formulation issues (the company manufactures and distributes ophthalmic drugs in multi-use bottles, without an adequate preservative), and lack of proper controls concerning tamper-evident packaging.

FDA is collaborating with the Centers for Disease Control and Prevention (CDC) and state and local health departments to investigate a multistate outbreak involving a rare, extensively drug-resistant strain of *Pseudomonas aeruginosa* bacteria. As of January 31, 2023, CDC identified 55 patients in 12 states with infections that have been linked by epidemiologic and laboratory evidence to use of EzriCare Artificial Tears. Associated adverse events include hospitalization, one death with bloodstream infection, and permanent vision loss from eye infections. CDC issued an alert recommending consumers stop using EzriCare Artificial Tears pending additional guidance from CDC and FDA.

FDA also placed Global Pharma Healthcare Private Limited on import alert for providing an inadequate response to a records request and for not complying with CGMP requirements. The import alert prevents these products from entering the United States.

Case #1: CDC- *P. aeruginosa* and Artificial Tears Outbreak: Link



Case #1: CDC- *P. aeruginosa* and Artificial Tears Outbreak: Link

CDC is collaborating with the Food and Drug Administration (FDA) and state and local health departments to investigate a multistate outbreak of an extensively drug-resistant strain of *Pseudomonas aeruginosa*. The outbreak strain, carbapenem-resistant *Pseudomonas aeruginosa* with Verona integron-mediated metallo-β-lactamase and Guiana extended-spectrum-β-lactamase (VIM-GES-CRPA), had never been reported in the United States prior to this outbreak. The outbreak is associated with multiple types of infections, including eye infections. The investigation has identified EzriCare artificial tears as a common exposure for many patients. CDC and FDA recommend clinicians and patients **stop using and discard EzriCare Artificial Tears and two additional products made by the same manufacturer, Delsam Pharma's Artificial Tears, and Delsam Pharma's Artificial Ointment.**

Case #1: CDC- *P. aeruginosa* and Artificial Tears Outbreak: Link

Current Update

As of May 15, 2023, CDC, in partnership with state and local health departments, identified 81 patients in 18 states (CA, CO, CT, DE, FL, IL, NC, NJ, NM, NV, NY, OH, PA, SD, TX, UT, WA, WI) with VIM-GES-CRPA, a rare strain of extensively drug-resistant *P. aeruginosa.* This represents an increase of 13 patients since the last update. Among these 13 patients, 6 (46%) had specimens collected prior to the February 2, 2023, manufacturer recall of products associated with this outbreak. These cases were confirmed after the recall date due to the time it takes for testing to confirm the outbreak strain and because of retrospective reporting of infections. Of the 7 patients who had specimens collected after the recall, most either resided in long-term care facilities with other known cases or reported use of a recalled brand of artificial tears.

Dates of specimen collection were from May 2022 to April 2023. Patients were initially identified from cultures of sputum, bronchial wash, or tracheal aspirate (14); sites related to the eye (e.g., cornea, vitreous; 21); urine (13); other nonsterile sources (3); blood (3); and ear (1); and from rectal swabs (26) collected for surveillance. Adverse outcomes that were associated with clinical (non-surveillance) cultures and reported to public health include 14 patients with vision loss, an additional 4 patients with enucleation (surgical removal of eyeball), and 4 deaths within 30 days of VIM-GES-CRPA clinical culture collection.

Case #1: CDC- *P. aeruginosa* and Artificial Tears Outbreak: Link

Most patients reported using artificial tears. Patients reported over 10 different brands of artificial tears, and some patients used multiple brands. EzriCare Artificial Tears, a preservative-free, over-the-counter product packaged in multidose bottles, was the brand most commonly reported. This was the only common artificial tears product identified across the four healthcare facility clusters. Laboratory testing by CDC identified the presence of VIM-GES-CRPA in opened EzriCare bottles from multiple lots; these bottles were collected from patients with and without eye infections and from two states. VIM-GES-CRPA recovered from opened products match the outbreak strain. Testing of unopened bottles of EzriCare Artificial Tears by FDA identified bacterial contamination; further characterization of the contaminants is ongoing.

Three products have been voluntarily recalled by their manufacturer, Global Pharma (Chennai, India), in association with this outbreak: EzriCare Artificial Tears, Delsam Pharma Artificial Tears, and Delsam Pharma Artificial Ointment. No other products have been linked to this outbreak. Patients and healthcare providers should immediately stop using and discard EzriCare Artificial Tears, Delsam Pharma Artificial Tears, and Delsam Pharma Artificial Ointment.

FDA encourages health care professionals and patients to report adverse events or quality problems with any medicine to FDA's MedWatch Adverse Event Reporting program . Consumers may also report adverse reactions by contacting FDA's Consumer Complaint Coordinators .

Case #1: Global Pharma Healthcare Private Limited WL: Link

Case #1: Global Pharma Healthcare Private Limited WL: Link

***Pseudomonas aeruginosa* Outbreak and FDA Testing of Samples**

In December 2022, FDA began collaborating with the Center for Disease Control and Prevention (CDC) on an investigation into the multistate outbreak of antibiotic-resistant *Pseudomonas aeruginosa* infections that ultimately affected more than 80 patients and led to 4 patient deaths and at least 14 cases of vision loss. As part of this investigation, FDA collected finished product samples of Artificial Tears and Artificial Eye Ointment batches that were manufactured by your facility, and we sent the samples for sterility testing at FDA laboratories. Our analysis of intact (unopened) units found that 18 batches of Artificial Tears were non-sterile. In addition, we also sampled a batch of your Artificial Eye Ointment product, and this batch was also found to be non-sterile. The testing of these intact units revealed that your ophthalmic drug products were intrinsically contaminated with microorganisms. Microbiological isolates from the non-sterile samples were further characterized using whole genome sequencing and compared to isolates in a national database.[2] *Pseudomonas aeruginosa* isolates from three different batches of intact Artificial Tears samples collected by FDA were found to be close genetic matches to more than 85 clinical isolates associated with this outbreak. These test results demonstrate that these lots are adulterated under section 501(a)(1) of the FD&C Act, in that they have been contaminated with filth, and rendered injurious to health.

Case #1: Global Pharma Healthcare Private Limited WL: Link

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Inadequate Equipment and Processes

A. You lacked adequate scientific evidence that the aseptic filling machine used for manufacture of Artificial Tears was suitable for its intended use. Your qualification report was inadequate, including a lack of data on any batches filled as part of the qualification study. Further, all batches of Artificial Tears distributed to the U.S. market were manufactured using filling machine parameters that were outside the design specifications of the equipment.

Case #1: Global Pharma Healthcare Private Limited WL: Link

B. You lacked validation of the processes used to manufacture your aseptically filled Artificial Tears, for example:

• You failed to validate methods that were intended to render your ophthalmic drug products sterile. Specifically, you lacked a study to show the **(b)(4)** performed on your Artificial Tears product using a **(b)(4)** can reliably achieve sterilization.

• Your media fill program lacked assurance that aseptic processing operations are appropriately performed to prevent microbial contamination. Our inspection found that you failed to perform appropriate and sufficient media fills studies, for example:

o Your media fills failed to adequately simulate the commercial aseptic manufacturing operation. Interventions were not simulated sufficiently or accurately. In addition, you have a manually intensive line with minimal barrier protection where the possibility of contamination is greater. Despite this, you filled **(b)(4)**-**(b)(4)**% of the production batch size during media fills.

o Manufacturing lines used to produce the Artificial Tears and Artificial Eye Ointment products were not qualified by three successful media fills.

o You removed integral units (i.e., units with intact container-closure systems) from media fills without adequate justification and failed to incubate all integral units for the full **(b)(4)** period.

o The personnel responsible for visual inspection of media-filled units lacked appropriate training and qualification.

Case #1: Global Pharma Healthcare Private Limited WL: Link

Lack of Container Closure Integrity

You lacked evidence of reliable container closure integrity for your multi-use ophthalmic products that purport to be sterile. While visual inspections revealed leakers during batch manufacture, there was no assurance that your visual inspection procedure was adequate.

Your product distributors received complaints of leaking Artificial Tears and Artificial Eye Ointment units. FDA's laboratory performed container closure integrity testing of Artificial Eye Ointment, batch H29, manufactured at your facility. FDA tested 20 units, and 1 unit was found to allow microbiological ingress, which further confirmed that your container-closure system lacks integrity and is insufficient for maintaining sterility. Notably, batch H29 was also found to be non-sterile through FDA testing.

All sterile drugs must be packaged using a container-closure system that protects product integrity for the duration of its shelf-life. Maintenance of product integrity throughout stresses of its manufacture, storage, distribution, and consumer use is critical to product quality and safety. Loss of container-closure integrity is a direct cause of non-sterility of medicines.

Case #1: Global Pharma Healthcare Private Limited WL: Link

Inadequate Formulation for Artificial Tears and Artificial Eye Ointment

You manufactured multi-dose, over-the-counter (OTC) ophthalmic drug products for the product owners, EzriCare LLC, and Delsam Pharma LLC. These products lacked antimicrobial properties to preserve the formulation. Significantly, your firm also marketed this multi-dose product without performing antimicrobial effectiveness studies. It is essential that multi-dose ophthalmic drug products contain one or more suitable substances that will preserve the product and minimize the hazard of injury resulting from incidental contamination during use.

In your response, you state that antimicrobial effectiveness testing (AET) will be initiated for your Artificial Tears product, and you will use these studies to determine if a suitable preservative will be added to the formulation. Your response is inadequate because you do not explain why you failed to perform AET studies prior to launch of your drug product, and how you will correct such fundamental flaws in your product development program. You also make no commitment to conduct AET for the Artificial Eye Ointment formulation. In addition, although your protocol indicates that you follow the United States Pharmacopeia (USP), the acceptance criteria in the Artificial Tears protocol is less stringent and not in alignment with USP <51> *Antimicrobial Effectiveness Testing*.

Case #1: Additional WLs Associated with Infection Outbreak

- US Distributors of DP manufactured at Global Pharma Healthcare Private Limited
  - EzriCare LLC: Link
  - Delsam Pharma LLC: Link

The inspection of your facility revealed that you operate as a distributor of [redacted]. Your receipt in interstate commerce of adulterated drugs, and the delivery or proffered delivery thereof, is a violation of section 301(c) of the FD&C Act, 21 U.S.C. 331(c), and your distribution of adulterated drugs violates section 301(a) of the FD&C Act, 21 U.S.C. 331(a).

Case #2: Recalls & Adverse Events

- Multiple Recalls
  - DP manufacturer not clear in recall announcements
  - DP Distributed in US by Velocity Pharma LLC
    - The Velocity Pharma website states, “We specialize in developing a product that does not contain a harmful preservative or harmful ingredients”.
- The Harvard Drug Group, LLC (Nov 01 ,2023) Link
- Cardinal Health, Inc. (Nov 01, 2023) Link

Case #2: Recalls & Adverse Events

- Common language in these recall announcements:
  - "(Recalling firm) received information from FDA indicating investigators found insanitary conditions in the manufacturing facility and positive bacterial test results from environmental sampling of critical drug production areas in the facility."
  - "The (recalling firm) has received three (3) reports of adverse events related to these products including reports of vision blurriness, vision loss, and burning eyes. The reports of adverse events were shared with our supplier, Velocity Pharma, LLC."

Case #3: Kilitch Healthcare India Limited WL: Link

Case #3: Kilitch Healthcare India Limited WL: Link

Insanitary Conditions

Your drug products are adulterated under section 501(a)(2)(A) of the FD&C Act because they were prepared, packed, or held under insanitary conditions. FDA investigators observed your facility to be in a state of disrepair, poorly cleaned and maintained as evidenced by:

- **(b)(4)** residue on the **(b)(4)** adjacent to the HEPA filters in the ISO 5 area.
- Multiple barefoot employees in an ISO 8 area, without required gowning, including gloves, while handling materials being transferred into the ISO 7 manufacturing area.
- Operators used visibly dirty restricted access barrier system (RABS) **(b)(4)** for interventions on the filling line.

Your response is not adequate. While you commit to replacing the **(b)(4)** that surround the HEPA filtration system, your response does not include an evaluation of the residue on the **(b)(4)** to determine its identity or investigate the source. You also commit to perform re-training of personnel for gowning requirements and implement a procedure for sterilization of RABS **(b)(4)**, however, you do not evaluate the microbiological impact that lack of proper gowning and unclean RABS **(b)(4)** has on your classified areas, such as ISO 5, ISO 7, and ISO 8. The potential impact to sterile drug products produced under these insanitary conditions is also not addressed.

Case #3: Kilitch Healthcare India Limited WL: Link

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Poor Practices in the Aseptic Processing Areas

In addition to the insanitary conditions described above, during the inspection of your facility, we observed poor practices and behaviors in ISO 5 areas during the manufacturing of sterile drug products. These poor practices included, but are not limited to:

- Operators performing interventions on the filling line in ISO 5 areas using a cloth to wipe the **(b)(4)** of the filling **(b)(4)** and the conveyor.
- Operators leaning over the filling line, including open and filled eye drop bottles, blocking unidirectional airflow.
- Operators in the ISO 5 area not wearing goggles and therefore had exposed skin during line set-up and aseptic processing.
- Operators observed placing bags of components that made contact with the walls in the ISO 7 area into the ISO 5 area without the bags being disinfected.

Case #3: Kilitch Healthcare India Limited WL: Link

Inadequate Media Fill Program

Your media fills failed to accurately simulate commercial operations. Our inspection found the aseptic operations simulated during your media fills were not sufficiently representative of commercial aseptic manufacturing operations. It is your routine practice not to document interventions of the filling line in the manufacturing batch record during production. Because of this, your program lacks reliable data to determine the quantity and duration of interventions to simulate during media fills. In addition, during the inspection there were numerous interventions performed during routine manufacturing that were either not simulated as part of a media fill, or lacking in quantity and duration in the media fills compared to what was observed during production.

Case #3: Kilitch Healthcare India Limited WL: Link

2. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards (21 CFR 211.194(a)).

Your firm failed to collect the required amount of environmental and personnel monitoring samples required by your procedures to support the manufacture of sterile drug products. During the inspection, a reconciliation of samples that should have been taken during manufacturing activities and those that were actually taken did not match. Interviews with microbiology laboratory staff and management confirmed that it is your routine practice to fabricate results for samples that were never taken or to alter results for samples that would otherwise fail to meet established specifications.

Case #3: Kilitch Healthcare India Limited WL: Link

3. Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.42(c)(10)).

Environmental Monitoring Deficiencies

Your environmental monitoring (EM) program is deficient. Locations selected for EM in critical areas such as the ISO 5 aseptic processing line, do not have scientific justification to support the chosen locations. For example, standard operating procedure (SOP) KHIL/RB/QC/036 "Swab Testing" describes locations such as "**(b)(4)**" without providing details to ensure samples are taken from the same location each time. When asked to provide justification for sampling locations, no documentation was provided.

Additionally, the materials used to perform environmental and personnel monitoring are inadequate. The media used does not contain a neutralizing agent and operators were observed spraying **(b)(4)** near open plates. The plates themselves were observed numerous times to have desiccated media pulling away from the sides of the plates and cracking.

Case #3: Kilitch Healthcare India Limited WL: Link

Delay in Drug Product Recall

FDA held a teleconference with your firm and your U.S. Agent on October 25, 2023, to discuss our concerns regarding your sterile ophthalmic drug products. During this call, we recommended that you recall all drug products within expiry due to the insanitary conditions at your facility and other egregious violations, as described in this letter.

Due to the potential public health risks associated with the situation at your facility, the Agency released their own announcement on October 27, 2023 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-purchase-or-use-certain-eye-drops-several-major-brands-due-risk-eye). Despite numerous attempts by the Agency to obtain your recall decision, your firm did not initiate a recall until November 15, 2023 (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/kilitch-healthcare-india-limited-issues-voluntary-nationwide-recall-various-eye-drops-potential), approximately three weeks after the initial discussion.

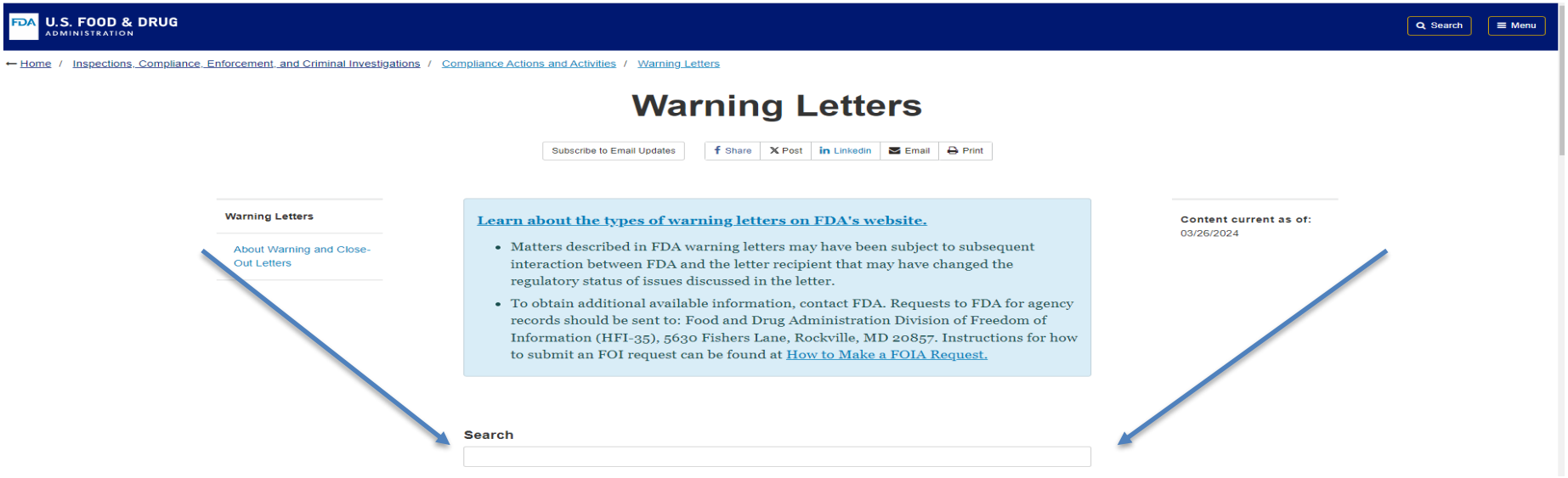
Result of Infection Outbreaks

- Increased FDA scrutiny of companies that MANUFACTURE, DISTRIBUTE or SELL topical ophthalmic DPs

- Increased number of inspections and WLs

Result of Infection Outbreaks

- FDA Warning Letter Search: Link

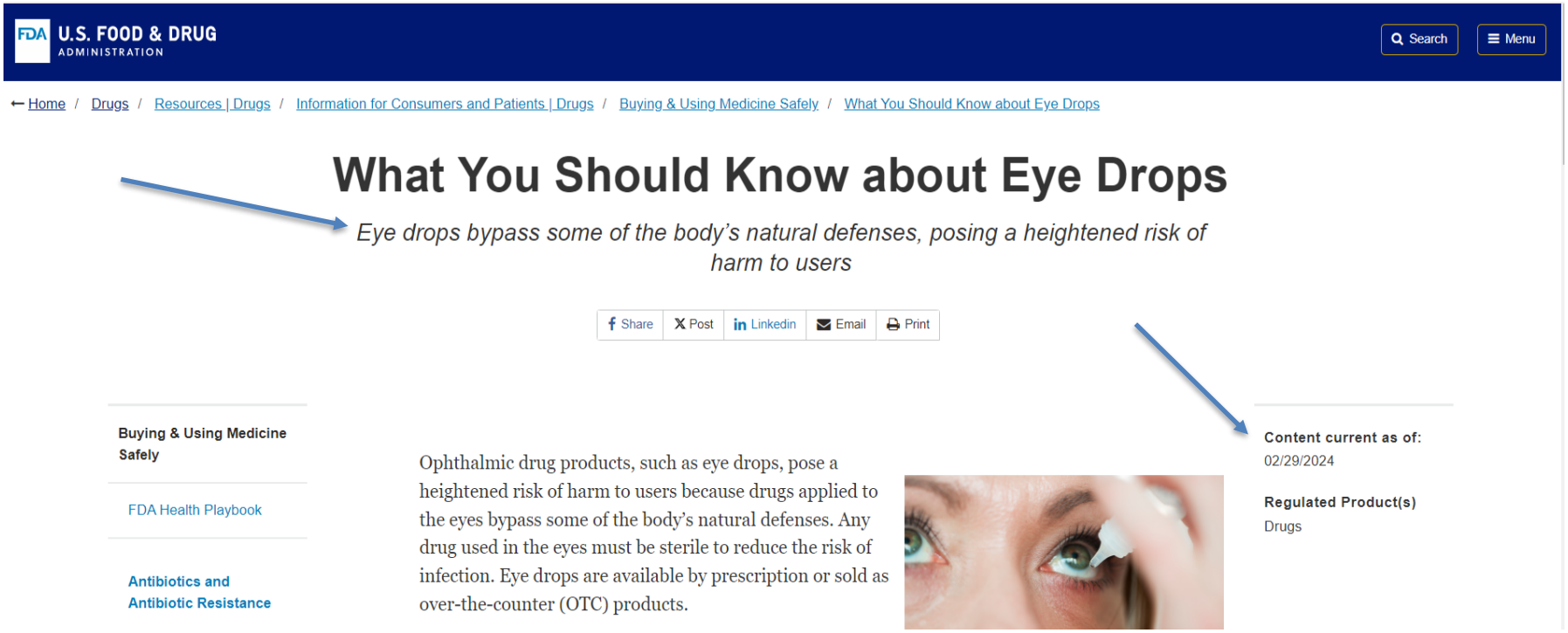


- Search Word: “ophthalmic”
- 56 total Warning Letters
- 20 from August 2023-present

Result of Infection Outbreaks

- FDA Warning Letter Search
  - Manufacturers and insanitary conditions
  - Testing of unopened units that demonstrate microbiological contamination
  - Websites that advertise unapproved drugs making unsupported clinical claims
  - On-line sales of adulterated drugs (those manufactured in a facility with insanitary conditions) or drugs that are not FDA approved

FDA Advisory-Information for Consumers & Patients: Link



- See advisory for a list of consumer tips & links to FDA announcements

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Relevant Guidance for the Manufacture of Sterile Drugs

- Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice: Link
- Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products: Link
- Guidance for Industry: Quality Considerations for Topical Ophthalmic Drug Products: Link
- Guidance for Industry: Insanitary Conditions at Compounding Facilities: Link

Relevant Technical Reports for the Manufacture of Sterile Drugs

- Parenteral Drug Association Technical Report No. 1 (TR 1) , Revised 2007, Validation of Moist Heat Sterilization Processes Cycle Design, Development, Qualification and Ongoing Control: Link
- Parenteral Drug Association Technical Report No. 26 (TR26) Revised 2008, Sterilizing Filtration of Liquids: Link
- Parenteral Drug Association Technical Report No. 13 (TR 13), Revised 2022, Fundamentals of an Environmental Monitoring Program: Link
- Parenteral Drug Association Technical Report No. 22 (TR22), Revised 2011, Process Simulation for Aseptically Filled Products: Link

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Expectations: Non-preserved Topical Ophthalmic Presentations

- Single Dose Presentation (no micro in-use concerns)

OR

- If a multiple dose presentation: the container closure system prevents microbial ingress during use
  - These are very specialized devices
  - For application products: the drug is approved for use with the device after review of the NDA/ANDA/BLA with supporting data
  - OTC manufacturers should have the data on-site for inspection
  - Caution: each device may not be compatible with every drug
  - For guidance on product specific studies to support use of a multi-dose container that does not allow microbial ingress during use, contact CDER-OPQ-inquiries@fda.hhs.gov

In Conclusion

- Drugs intended to be sterile with inadequate microbiological quality present real and significant safety risks to patients
- It is critical that manufacturing processes for drugs intended to be sterile be properly validated and performed according to CGMP
- It is critical that manufacturers of drugs intended to be sterile demonstrate through scientific studies that the container closure system and drug formulation are appropriate for the intended use of the drug

THANK YOU!

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301-796-1576

For General Micro Drug Quality Questions:

CDER-OPQ-inquiries@fda.hhs.gov