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‘Pervasive Contamination’ Found At Indian Eye Drop Firm Linked To Antibiotic-Resistant Infections

by Malcolm Spicer

FDA also responds to sting OTC eye drop sector felt with warnings to Amazon after investigators purchased drops labeled with violative claims and a natural health care products firm with Amazon storefront offering drops with ingredient commonly used in joint health supplements and claims to “soften the membranes of the eye.”

US regulators apply a major dollop of balm to the black eye the OTC eye drop sector suffered in 2023 with a warning to an Indian firm making numerous products recalled due to contaminations and linked to antibiotic-resistant bacterial infections.

The Food and Drug Administration also responded to the sting the sector’s felt with warnings to e-commerce giant Amazon Inc. after investigators purchased OTC eye drops labeled with violative claims and to a natural health care products firm with an Amazon storefront offering eye drops, which contain an ingredient commonly used in joint health supplements, with claims to “soften the membranes of the eye.”

The FDA published warning letters on 14 November to Global Pharma Healthcare Private Ltd., in Thiruporur in southeast Indian state Tamil Nadu, and to Amazon at its headquarters in Seattle and a week earlier to Dexterity Health LLC in Austin, TX.

The agency’s *letter* to Global Pharma explains that prior to inspecting the firm’s plan in February and March and finding “pervasive contamination,” the FDA and the Centers for Disease Control and Prevention in December 2022 began investigating a multistate outbreak of infections with the antibiotic-resistant bacteria Pseudomonas aeruginosa which “ultimately affected more than 80 patients and led to 4 patient deaths and at least 14 cases of vision loss.”

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The warning submitted on 20 October by the FDA Center for Drug Evaluation and Research officials identifies the brands of artificial tears eye drop formulations made by Global Pharma and linked to the contamination, which CDC officials have said was previously not found in the US.

The firms marketing the products – EzriCare LLC's and Delsam Pharma LLC's artificial tears and Delsam's artificial eye ointment; all containing active ingredient carboxymethylcellulose sodium – face claims for damages from consumers alleging harm from using their products. Global Pharma recalled the artificial tear products in early February and the ointment later that month. (Also see "*Litigation Follows OTC Eye Drops Recall Due To Bacteria Strain Not Previously Seen In US*" - HBW Insight, 20 Feb, 2023.)

The CDER Manufacturing Quality and Compliance offices explain that because the products weren't made in a sterile facility, they are misbranded under section Food, Drug and Cosmetic Act Sec. 502(j) (*21 USC 352*(j)); Delsam's ointment also is misbranded under FD&C Act Sec. 502(a) (21 USC 352(a)); and sales of misbranded products also is prohibited under FD&C Act Sec. 301(a) (*21 USC. 331*(a)).

FDA analysis of samples "determined that these products were contaminated with microorganisms," the warning states.

Pseudomonas species bacteria was found in the EzriCare artificial tears sample, Bacillus species in the Delsam artificial tears sample and Burkholderia cepacia complex in the Delsam ointment sample

Pink Eye, 'More Permeable' Among Noncompliant Claims

As they have stated in previous warnings concerning eye drops marketed with claims rendering them unapproved drugs, CDER officials advised Amazon and Dexterity Health, dba Zazzee Naturals, that mis-labeled eye drops "are especially concerning from a public health perspective."

"Ophthalmic drug products, which are intended for administration into the eyes, in general pose a greater risk of harm to users because the route of administration for these products bypasses some of the body's natural defenses," stated the CDER's Office of Compliance in its letter to Amazon and Zazzee Naturals.

The six products FDA investigators purchased were labeled with claims to relieve pink eye – with two brands making the claim in their product's names as well as in labeling – or with claims to treat other ophthalmic conditions which aren't approved as indications for the products' formulations.

The manufacturers of all the products, in addition to two drug store chains offering store-brand products, were warned about the claims in warnings the CDER published in

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"There is a reasonable probability that instillation of a bacterially contaminated eye product into the eye may cause a range of ocular infections, from minor to serious, vision-threatening infections which could progress in some cases to life-threatening systemic bacterial infection," the CDER offices state.

Lengthy GMP Problem List From 'Insanitary Conditions'

Additionally, the lengthy and detailed list of good manufacturing practices deficiencies found at the plant put Global Pharma in violation of FD&C Act Secs. 501(a)(2)(A) and (B) (*21 USC 351*(a)(2)(A) and (B)).

Global Pharma, which the FDA in January added to its import alerts, committed to halting production of all drugs at its facility, according to the warning.

"Significantly, the pervasive contamination of your drug products, as indicated by FDA sample results, also demonstrates that all drugs made at your facility are adulterated under section 501(a)(2)(A) of the FD&C Act as they have been manufactured under insanitary conditions," the warning states.

Should the firm attempt to restart production at the facility, it would have to fulfill a list of FDA requirements to remediate its manufacturing procedures as lengthy and detailed as its list of GMP deficiencies.

The agency instructs Global Pharma, for instance, to conduct a comprehensive risk

September. (Also see "*All About Eye Drops: Warnings To Six Homeopathic And Two Allopathic Firms; Seven US, One Swiss*" - HBW Insight, 13 Sep, 2023.)

In addition to pink eye, the claims rendering the products unapproved as well as mis-labeled drugs included "designed to replace nutrients that diminish with age, disease, or trauma," and "temporarily relieves minor eye irritation such as dry, red, itchy, and burning eyes due to: •eyestrain and fatigue •light and glare •digital displays •airborne irritants (pollen and dust)," according to the *warning* to Amazon.

The CDER office also noted that five of the products are homeopathic formulations, which since 2019 have been subject to the same manufacturing and labeling regulations as other drugs available in the US. (Also see "*No Change To US FDA's Risk-Based Homeopathic Enforcement From Its OTC Monograph Overhaul*" - HBW Insight, 7 Dec, 2022.)

CDER officials inspected Zazzee Naturals' Amazon storefront in September, finding its Liquid MSM Drops for sale with the claim that "when applied directly to the eye ... shown to soften the membranes of the eye, allowing them to be more permeable, so that nutrients can pass through and provide nutrients to heal damage to the eyes."

A graphic on the site also states that Liquid MSM benefits "Include: Reduces Joint Pain . . .

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assessment of all contamination hazards with respect to its aseptic processes, equipment and facilities; provide a remediation plan that better assures ongoing management oversight throughout the manufacturing lifecycle of all drug products; and conduct a comprehensive, independent retrospective assessment of is cleaning effectiveness to evaluate the scope of cross-contamination hazards.

Lowers Inflammation," according to the *warning*.

The comprehensive remediation is necessary because FDA officials found problems including:

- The firm "failed to adequately clean the equipment used to aseptically produce Artificial Tears. Significantly, our investigators observed visible grease-like residue on product contact surfaces of your filling machine after they had been cleaned."

- "Cleanroom garments were not suitable for their intended use. ... garments indicated to be clean were observed to be stained, worn out, and stored improperly. ... re-used cleanroom garments for an unspecified number of times without tracking or validation."

- The firm's "quality system does not adequately ensure the accuracy and integrity of data to support the quality of the drugs you manufacture. ... permitted the unacceptable practice of using pre-filled batch release documents."

Responses Lacked Long List Of Details

The firm's responses to FDA officials' findings were uniformly inadequate, the warning explains.

The responses lacked "details of your internal investigation into the product contamination ... including but not limited to, a lack of descriptions of the activities performed and root cause analysis," according to the warning.

Global Pharma's response also lacked details "relating to future dynamic airflow pattern studies; heating, ventilation, and air conditioning (HVAC) system qualification; or media fill procedural revisions and "on procedural revisions to be made, including how you intend to establish and maintain assurance of the reliability of your supplier's certificate of analysis."

The FDA also warned two US firms manufacturing OTC eye drops in August about failing to maintain sanitary conditions. One of the firms, Pharmedica USA LLC in Phoenix, recalled OTC eye drops after FDA officials who inspected its facility in November recommended the action. (Also see "*US FDA Inspectors See Cloudy GMP Compliance At OTC Ophthalmic Drug Manufacturers*" - HBW Insight, 31 Aug, 2023.)

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The agency also reported problems with Illinois firm Sterling Pharmaceutical Services LLC in 2022 after it failed to convince FDA officials it was keeping contaminants away from a sterile processing line and was advised to conduct a comprehensive evaluation of the effectiveness of its environmental monitoring. (Also see "*Sloppy Sterility Seen At US OTC Ophthalmic Firm*" - HBW Insight, 12 Oct, 2022.)

The problems prompted the FDA to write a draft guidance published in October discussing quality considerations for ophthalmic drugs including recommendations for stability studies; approaches to evaluating visible particulate matter, extractables and leachables, and impurities and degradation products; and using in vitro drug release/dissolution testing as an optional quality control strategy for certain dosage forms. (Also see "*Eye Drop Manufacturers Get Advice On Seeing Quality Clearly In US FDA Draft Guidance*" - HBW Insight, 12 Oct, 2023.)

Comments on the draft – docket *FDA–2023–D–4177* – are accepted through 12 December. including solutions, suspensions, emulsions, gels, ointments and creams intended for delivery in and around the eye.

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