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Special Report

# Endotoxin Testing for Topical Ophthalmic Products No Longer Required

*Published by: James F. Cooper, PharmD, FAPhA*

Dr. John Metcalf, Senior Review Microbiologist for the FDA's Center for Drug Evaluation and Research (CDER), recently spoke at the PDA Micro 2014 in October. In his presentation, which addressed some of the myths surrounding microbiological requirements for drug manufacturing, he explained that the CDER will no longer require endotoxin limits for the approval of new drug applications for topical ophthalmic solutions and ointments[1].

This change in policy has long been under consideration. The agency's interest in endotoxin limits for eye medications began after an outbreak of TASS (toxic anterior segment syndrome), an acute inflammation of the eye following cataract or ocular lens-replacement surgery[2]. The incident, which occurred in 2005, involved at least 112 patients and prompted an investigation by the CDC, FDA and TASS Task Force. Together, this group of ophthalmic surgeons and other professionals sought the etiology of these adverse effects, exploring the medications, intraocular surgical tools and operating-room practices used in these procedures. A concern for endotoxin as a cause for this inflammation led CDER to consider endotoxin tests for topical eye medications. Adverse effects associated with eye surgery are not applicable to topical solutions.

Particular attention was paid to potential endotoxin contamination in a BSS (balanced salt solution) irrigating solution used in eye surgery as the cause of the TASS outbreak. However, a multi-facility outbreak continued unabated in 2006 (110 cases) *after* a recall of the suspected product. An investigation into the continuing outbreak by the TASS Task Force, led by Dr. Nick Mamalis[4], found no evidence supporting an association between a shared product and specific cases of TASS; that is, there was no product-related etiology. Their report listed many risk factors for TASS, including improper cleaning and/or sterilization of surgical instruments, and proper use, selection and mixing of medications (e.g., antibiotics, anesthetics, epinephrine and BSS). The task force urged use of preservative-free drugs and medications specifically intended for intracameral administration. Eye surgeons released a guide for recommended practices for sterilizing intraocular surgical instruments[5].

The claim that the TASS outbreak was caused by a specific BSS product (Cytosol) remains unsubstantiated. BSS is a simple physiological solution of calcium, magnesium, potassium and sodium salt that was terminally sterilized in 500-mL glass bottles. The out-of-specification (OOS) endotoxin results measured by the FDA and CDC could not be reproduced or verified. Kinetic chromogenic tests by microplate and LAL-cartridge methods, conducted by at least two contract test labs and this author, found that there was no test interference and no detectable endotoxin (<0.005 EU/mL). The report by the CDC lab was a false positive OOS result caused by testing under non-robust conditions[6]. That is, the non-interfering solution was diluted a thousand-fold and tested on a tube reader with a wide-range standard curve having a lambda value of 0.001 EU/mL. These test conditions prevented the discrimination of low-level signals from instrument noise.

Ophthalmic products have a pharmacopeial requirement for sterility. Historically, endotoxin testing was not considered for topical products because the surface of the eye itself is a natural barrier to endotoxin.

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The following points summarize a case against endotoxin testing of topical eye medications, presented at the PDA Micro meeting in 2009[3].

- **Safety:** The topical ophthalmic industry has a compelling safety record and no issues have emerged relative to endotoxin. Ophthalmic solutions are manufactured using aseptic processing; therefore, the control of bioburden removes the principal source of endotoxin.
- **Barrier:** The conjunctival and corneal epithelia serve as an endotoxin barrier. Additionally, mechanisms within tear film limit the adverse effects of endotoxin. Therefore, the proposed 0.5 EU/mL limit was unjustified for such a small dose (~50 $\mu$L) on the ocular surface.
- **BET interference:** Topical ophthalmic products are poorly suited for endotoxin tests because of considerable interference. The LAL-endotoxin reaction is an enzymatic cascade that requires specific conditions, such as neutral pH, to achieve optimum reaction. The stabilizers, preservatives, suspending agents and other excipients which yield microbiologically rugged topical solutions present significant interference mechanism to the BET. Moreover, glucans present in suspending agents cause false-positive results unless glucan blocking is applied. Therefore, end-product testing is clearly unrealistic for most of these medications.
- **Limiting endotoxin:** There are more cost-effective ways to assure low levels of endotoxin in topical eye solutions than requiring end-product testing. The drug industry has determined that endotoxin is primarily derived from water or materials of natural origin. Accordingly, the endotoxin concern for these drugs can best be addressed by formulating with water meeting a specification of $< 1$ EU/mL.

The FDA's policy change regarding topical products is welcome because the consequences of an endotoxin-limit requirement are not trivial. There would be great cost to retool the industry to depyrogenate plastic containers and to generate Water for Injection for formulation of non-pyrogenic topical products.

Since the outbreaks and subsequent investigations, the FDA has been proactive in addressing potential causes of TASS reactions. Accordingly, the Center for Devices and Radiological Health (CDRH) published a draft guidance in 2014 regarding endotoxin limits for the release of intraocular devices and single-use intraocular ophthalmic surgical instruments/accessories[7].

## Author Biography

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Dr. Cooper provides consultation and training to the parenteral drug industry regarding endotoxin analysis methods, investigation of endotoxin excursions and depyrogenation in aseptic processing. His experience includes founding an LAL (Limulus Amebocyte Lysate) production company, fifteen years of teaching nuclear pharmacy in medical universities, and nine years of Public Health Service at the National Institutes of Health and Food and Drug Administration. He is a faculty member for the Parenteral Drug Association for aseptic processing training and is a consultant to the FDA on endotoxin issues. Current research interests include development of methods for endotoxin testing of intraspinal compounded prescriptions and cyclotron-produced radioactive drugs.

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