Endotoxin Testing Recommendations for Single-Use Intraocular Ophthalmic Devices

Guidance for Industry and Food and Drug Administration Staff

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Preface

Public Comment

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I. Introduction

This guidance document was developed to notify manufacturers of the recommended endotoxin limit for the release of intraocular devices and single-use intraocular ophthalmic surgical instruments/accessories in an effort to mitigate future Toxic Anterior Segment Syndrome (TASS) outbreaks. TASS is a sterile inflammatory condition localized to the anterior segment of the eye following intraocular surgery. It has been associated with significant decreases in vision and may require additional surgical procedures, including corneal transplants and glaucoma surgery, to resolve some of its sequelae.

National outbreaks of TASS have been associated with endotoxin. Devices used inside the eye, including intraocular devices and single-use intraocular ophthalmic surgical instruments/accessories, can potentially be contaminated with endotoxin as part of the manufacturing, sterilization, or packaging processes. This guidance document provides recommendations for endotoxin limits as well as endotoxin testing to manufacturers and other entities involved in submitting premarket applications (PMAs) or premarket notification submissions [510(k)s] for different categories of intraocular devices to aid in the prevention of future outbreaks of TASS.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Definitions

A. Intraocular Fluids: A nongaseous fluid intended to be introduced into the eye to aid performance of surgery such as to maintain anterior chamber depth, preserve tissue integrity, protect tissue from surgical trauma or function as a tamponade during retinal reattachment. 21 CFR 886.4275.

1. **Ophthalmic Viscosurgical Device (OVD):** Both viscous and viscoelastic intraocular fluids intended for use during surgery in the anterior chamber as a surgical aid to maintain space in the eye and protect ocular tissue from surgical trauma. They are usually intended for use in cataract surgery, corneal transplant surgery, and glaucoma filtration surgery. These devices are typically pre-packaged in a syringe and require PMA approval prior to being marketed. This term includes viscoelastic surgical aids.

B. Intraocular Lenses (IOLs): An artificial lens intended to be implanted to replace the natural lens of an eye. 21 CFR 886.3600. IOLs can be used to restore vision and replace the natural lens of the eye after it is removed during cataract surgery. IOLs can also be used in eyes where the natural lens is not removed but that require correction of refractive error. Examples of types of IOLs include monofocal, toric, multifocal, accommodative, iris reconstruction and phakic. Iris reconstruction lenses are used to cosmetically correct defects in the appearance of the eye, usually caused by the absence of an iris.

C. Capsular Tension Rings: A prosthetic device designed to stabilize the crystalline lens capsule in the presence of weak or partially absent zonules in patients undergoing cataract extraction with an intraocular lens.

D. Glaucoma Devices: A device used to treat glaucoma, a condition in which the pressure within the eye (i.e., intraocular pressure) is abnormally high, resulting in damage to the optic nerve. These devices are often partially implanted in the anterior segment of the eye with the other portion of the device residing on the eye. These devices include aqueous shunts (21 CFR 886.3920).

E. Phacofragmentation System: A phacofragmentation system is an AC-powered device with a fragmenting needle intended for use in cataract surgery to disrupt a cataract with ultrasound and extract the cataract. 21 CFR 886.4670. The hand piece is composed of a tip that delivers ultrasound energy which emulsifies the lens and aspirates lens material from its open end.

1. **Sleeves**: Surrounding the tip of the phacofragmentation handpiece is the sleeve, which is often of rubbery consistency and allows for irrigation around the tip as well as a barrier to tip penetration into lens material.
2. **Tubing**: Any lumened device that transmits fluid into or out of the eye.

F. Endotoxin: High molecular weight complex associated with the cell wall of Gram-negative bacteria that is pyrogenic in humans and specifically interacts with *Limulus* amebocyte lysate (LAL).[1]

G. Endotoxin unit (EU): Standard unit of measure for endotoxin activity initially established relative to the activity contained in 0.2 ng of the U.S. Reference Standard Endotoxin Lot EC-2 (USP standard reference material). Endotoxin is expressed in International Units (IU) and one EU is equal to one IU.[1]

H. Anterior segment: The front third of the eye including all structures located between the front surface of the cornea and vitreous.

I. **Anterior chamber:** The space in the eye that is behind the cornea and in front of the iris. It contains aqueous humor.
J. **Aqueous humor:** A transparent, watery fluid circulating in the anterior and posterior chamber of the eye. It maintains the intraocular pressure of the eye, provides amino acids and glucose to the avascular ocular tissues and plays a role in the immune response of the eye.
K. **Bacterial endotoxin test (BET)**: Assay for measuring active endotoxin by combining a liquid test sample with Limulus amebocyte lysate (LAL) reagent and measuring the resulting proportional reaction by gel-clot, turbidimetric, chromogenic, or other validated means of detection.[1]

III. Background

TASS has been increasing in frequency over the past decade from approximately 1 in 1,000 to about 2 in 100. [2-4] Some cases of TASS are severe enough to require secondary surgical interventions including glaucoma surgery and corneal transplantation.[5] The use of inadequately or improperly processed ophthalmic surgical instruments is one of many factors suggested as a potential cause of TASS.[6-9] In many TASS cases, bacterial endotoxin from medical devices is believed to cause the inflammation.[10,11] Endotoxin was found to be an intrinsic contaminant of a balanced salt solution used in cataract surgery that resulted in a TASS outbreak in 2005 involving 112 patients.[12]

Because bacteria thrive in media containing water, medical devices that are aqueous in nature, contain an aqueous component, or are otherwise exposed to water during the manufacturing process are vulnerable to bacterial proliferation and subsequent endotoxin contamination. Thus, ophthalmic viscosurgical devices (OVDs) that are commonly used in ophthalmic surgery are prone to endotoxin contamination. Further, the raw materials used in fabricating sodium hyaluronate (HA)-based OVDs, which are of biological origin, can also be a source of endotoxins. It has been shown that endotoxin in viscous materials such as OVDs incite more inflammation intraocularly than endotoxin in aqueous solution due to the prolonged contact with sensitive ocular tissue.[13]

The general principles of endotoxin testing, as described in the most recent FDA-recognized versions* of United States Pharmacopeia (USP) <85> Bacterial Endotoxin Test,[14] and the American National Standards Institute (ANSI)/Association for the Advancement of Medical Instrumentation (AAMI) ST72 Bacterial Endotoxins-Test Methodologies, Routine Monitoring and Alternatives to Batch Testing,[1] can be followed to test the endotoxin levels of these single-use intraocular ophthalmic devices.

The endotoxin limit for OVDs specified in International Organization for Standardization (ISO) 15798 (Ophthalmic implants-Ophthalmic viscosurgical devices) is 0.5 endotoxin units (EU) per milliliter (mL). During cataract surgery, the anterior segment of the eye can accommodate more than 0.3 ml of OVD after lens extraction and as much as 0.1 mL OVD may remain in the eye at

*A searchable database of FDA-recognized consensus standards is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

the end of the procedure. Hence, it is possible for 0.05 EU endotoxin to be left in the eye at the conclusion of the surgery, and this amount has been shown to cause inflammation.[13] This same study showed that inflammation can be elicited by as little as 0.02 EU endotoxin in an OVD. Therefore, FDA does not recognize the endotoxin levels in the ISO 15798 (Ophthalmic implants-Ophthalmic viscosurgical devices) standard.

In ISO 11979-8 (Ophthalmic implants-Intraocular lenses-part 8: Fundamental requirements Amendment 1), the endotoxin limit for IOLs is 0.5 EU per device or less. Any endotoxin present on an IOL or other solid ophthalmic devices goes into solution when placed in an aqueous medium such as the aqueous humor. Studies have shown that 0.08 EU endotoxin in a balanced salt solution can elicit inflammation in the eye.[13] Therefore, FDA does not recognize the endotoxin limit in ISO 11979-8 (Ophthalmic implants-Intraocular lenses-part 8: Fundamental requirements Amendment 1) or the limit in the ANSI series of standards for intraocular lenses.

IV. Scope

The recommendations made in this guidance are applicable to devices used within the eye, either as permanent implants or as single-use devices used in intraocular surgery. These include:

A. Intraocular Fluids (21 CFR 886.4275, Class III), specifically viscoelastic surgical aid (LZP)
B. Anterior Segment Solid Devices
    1. Intraocular lenses (21 CFR 886.3600, Class III), including
        a. Intraocular lenses (HQL)
        b. Multifocal intraocular lenses (MFK)
        c. Phakic intraocular lenses (MTA)
        d. Toric intraocular lenses (MJP)
        e. Accommodative intraocular lenses (NAA)
        f. Implantable miniature telescope (NCJ)
        g. Iris reconstruction lenses (NIZ)
    2. Capsular tension ring devices (Class III), including
        a. Endocapsular rings (MRJ)
    3. Glaucoma devices
        a. Aqueous shunts (21 CFR 886.3920, Class II), including
            i. Eye valve implant (KYF)
        b. Other glaucoma devices (Class III)
            i. Intraocular pressure lowering implants (OGO)
    4. Phacofragmentation systems (21 CFR 886.4670, Class II), specifically the accessories of irrigation/aspiration sleeves and tubing (HQC)

Endotoxin contamination of reusable manual ophthalmic surgical instruments is outside the scope of this guidance.

V. Recommendations

A. Intraocular Fluids

1. OVDs
   a. The recommended endotoxin limit for release testing is ≤0.2 EU/mL regardless of whether the intended site of use is the anterior or posterior segment.

   b. Endotoxin test method validation:
   The viscosity of OVDs can interfere with the BET. In addition to the general validation principles described in USP <85> and ANSI/AAMI ST72, the validation of the BET should include recovery of known amounts of endotoxin added/spiked to the OVD. For each OVD that is to be marketed, random samples from 3 lots of the OVD should each be spiked with endotoxin to final concentrations of 0.1, 0.2 and 0.5 EU/mL. Each test should be conducted in triplicate (i.e., each lot should be spiked and sampled three times for testing). The OVD should then be tested for endotoxin using the BET and the percentage endotoxin recovery should be calculated from the average of the values obtained from the three test samples from each lot. The detection limit may vary with the method used for testing (e.g., gel clot, turbidimetric and chromogenic) and, as such, it may be appropriate to experiment with different methods to ensure maximal recovery of endotoxin. For OVDs fabricated from HA of a high molecular weight, it may be appropriate to use an enzyme containing non-detectable levels of endotoxin to break down large molecules and make endotoxin more accessible for testing. The use of enzyme digestion will avoid the use of a high dilution factor to overcome interference, which may be appropriate for the OVD to meet the endotoxin limit.[13]

   c. If performed, animal testing for quality control and acceptance criteria with associated labeling claim:
   The phrase "non-inflammatory" in the labeling of an OVD should not be used since the OVD could elicit some inflammation but it may not be clinically significant. OVDs may be labeled as having "low inflammatory potential" if animal testing or another validated method for detecting inflammation is performed as a product release test.

   Although endotoxin in an OVD can be detected and quantified using a BET, the amount detected is only an approximation of the actual value due to the inherent limitations of the test. Furthermore, the amount of endotoxin detected can be affected by the unique properties of the individual OVD (e.g., the molecular weight), which could alter how the OVD binds to the ocular tissue and consequently the efficiency of enzyme digestion. Thus, the recommended method to assure that an OVD has low inflammatory potential is to test the product in the anterior segment of the eye with subsequent assessment of inflammation.

   Testing of an OVD in an animal model should be performed by injecting the OVD intracamerally.[15] The eyes should then be monitored for clinical signs of

inflammation using a slit lamp for at least three days (i.e., 72 hours). The test method should be validated by quantifying the inflammation elicited by injecting spiked OVD which results in intraocular doses of 0.01, 0.02 and 0.05 EU/eye, at a minimum.

We recommend that sponsors who intend to perform this testing submit a Pre-Submission to obtain feedback and recommendations from the Division of Ophthalmic and Ear, Nose, and Throat Devices on the animal testing validation, acceptance criteria for release testing, and any other methods of detecting inflammation. For more information on Pre-Submissions, please see "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf).

B. Anterior Segment Solid Devices

1. The recommended endotoxin limit for all anterior segment solid intraocular devices is ≤0.2 EU/device. This limit applies to implants that are placed entirely in the anterior segment such as IOLs, iris reconstruction lenses, and capsular tension rings. For glaucoma devices, this limit applies to the segment of the device placed in the anterior chamber and the segment(s) contacting the aqueous humor even though the main portion of the device may reside outside the eye. For single-use cannulated or lumened devices (e.g., irrigation/aspiration sleeves and tubing), this limit applies to the fluid path and the portion of the device with aqueous humor contact.

2. Test sample preparation:
   The standard 40 mL/device extraction ratio can be adjusted to accommodate the small size of solid intraocular devices in accordance with the recommendation in the "FDA Guidance for Industry Pyrogen and Endotoxin Testing: Questions and Answers" (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314718.htm). The volume of the extraction solution chosen should also take into consideration the endotoxin limit for the device and the sensitivity of the LAL lysate used in the testing. ANSI/AAMI ST72 specifies the minimum extraction time as 15 minutes at 37°-40°C or one hour at controlled room temperature (typically 18-25°C), or other demonstrated equivalent conditions.[1] Because of the extreme sensitivity of the eye to endotoxin, the FDA recommends that the extraction be performed at 37°-40°C with agitation for a minimum of 60 minutes to maximize the extraction efficiency. For cannulated or lumened devices, sample preparation should consist of filling the fluid pathway with the extracting medium that has been pre-warmed to 37°± 1°C and then held at 37°± 1°C for at least 60 minutes.

VI. References

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