Common Microbiology Deficiencies for Ophthalmic Suspension Drug Products

Arlene Chen, Ph.D.
Pharmaceutical Scientist

Division of Pharmaceutical Manufacturing Assessment III, Office of Pharmaceutical Manufacturing Assessment, Office of Pharmaceutical Quality
CDER | US FDA

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Overview

- Background:
  - Manufacturing of Ophthalmic Drug Products
- Top issues found during quality microbiology review

Background

- Manufacturing of ophthalmic suspensions is complex!
- Nearly all ophthalmic suspensions are filled using aseptic processing
- Manufacturing of drug products include a combination of different sterilization processes to account for soluble and insoluble phases that are later blended to create a sterile suspension
  - Filtration vs. steam sterilization vs. gamma irradiation
  - Sterile API powder requires additional care
- Containers, closures, and equipment contact parts sterilization
- Environmental monitoring and control (isolators)

Background

API

- **Insoluble**
  - Gamma irradiation
  - Ethylene oxide
- **Slurry (heat stable)**
  - Moist Heat Sterilization

Water for Injection (WFI), purified water, other soluble excipients

- Filtration
- Moist Heat Sterilization

Viscous Components

- Filtration at high temperatures
- Moist heat sterilization (autoclave or within a manufacturing vessel)

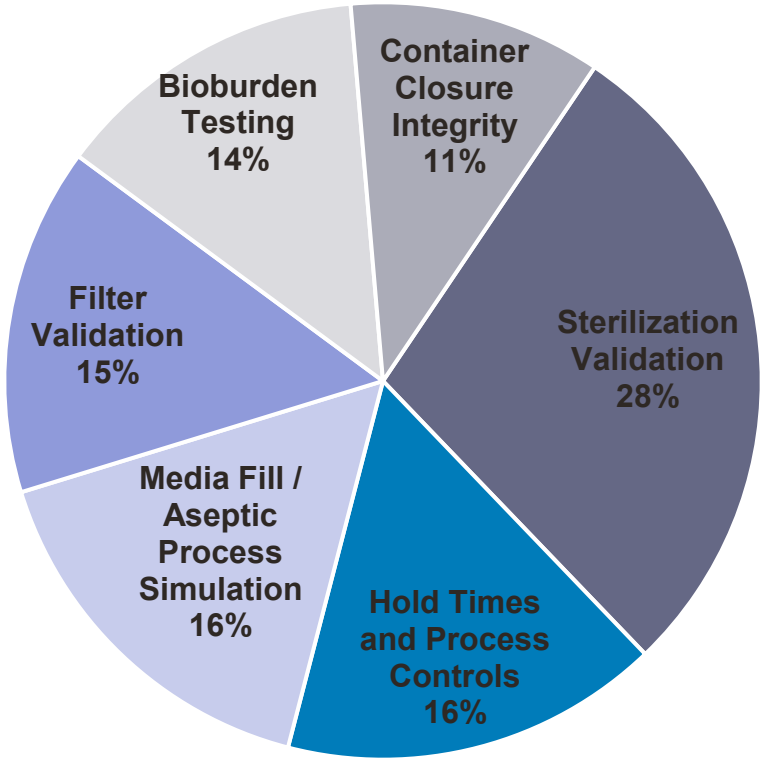
Container Closure System

- Gamma irradiation
- Ethylene oxide
- Moist Heat Sterilization

Sterility Assurance Information Requests

- Compiled Microbiology IRs issued from 2019 to 2025 for ophthalmic suspensions ANDAs
- Analysis of 108 IRs revealed critical sterility assurance gaps

Note, many of these information requests are common to all sterile product types



Container Closure Integrity Testing

- Gold standard
  - Microbial immersion method
- Dye Ingress
  - Subjective (visual) vs. objective (spectrophotometry)
- Other sensitive methods
  - High voltage leak detection
  - Helium leak detection
  - Vacuum decay leak detection

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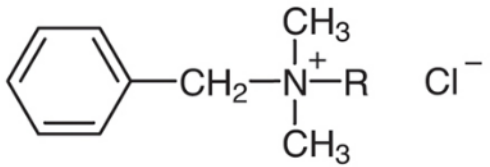
Thermo Scientific

Antimicrobial Effectiveness Testing (AET)

- Ophthalmic suspensions are typically multi-dose and contain a preservative
- Preservative content was not at or was below the minimum stability specification
- At least one primary stability batch should be tested for AET at expiry



benzalkonium chloride

Component Bioburden

- Pre-sterilization bioburden testing of all phases was not performed
- Excessive bioburden limits

Hold Times and Process Controls

Esteril

- Maximum hold times for each manufacturing stage were not described
- Microbiological study results in support of excessive hold times not provided

Sterilization of Container Closure System

- Sterilization by gamma irradiation or ethylene oxide
  - Studies performed did not follow the standards as recommended in ISO 11137 or 11135.
  - Recent requalification, dose audit and bioburden results not provided

Sterilization of manufacturing equipment

- Validation was not performed with an appropriate number of runs for all equipment (vessels holding sterile components, filling equipment)
- Recent requalification results were not provided

https://snowbellmachines.com/

Moist Heat Sterilization


Steris

- Moist heat sterilization may be used to sterilize heat-stable excipients or API (slurry)
- Validation was not performed with an appropriate number of runs
- Volume filled is not representative of commercial production
- Recent requalification results were not provided

Sterilization Validation

- Sterilization of API by gamma irradiation
  - Studies conducted per ISO 11137
  - Dose setting: Method 1 (average bioburden), Method 2A/B (fraction positive), VD_{max}^{25}
- Sterilization of API by ethylene oxide
  - Studies conducted per ISO 11135
  - Biological indicator/bioburden Approach (Annex A) vs. Overkill Approach (Annex B)

Sterilizing Filtration

Pall Corporation

- Vehicle (WFI) and other soluble excipients may be sterilized by filtration
- Drug product formulation and/or manufacturing conditions may impact filter effectiveness
- Viability study results not provided
- Product specific bubble point (BP) determination not provided
- At least one filter with pre-filtration BP at or near manufacturing minimum specification was not used

Decontamination of Isolators

- Biological indicator challenge studies did not use an appropriate number of runs
- Recent requalification results were not provided

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Media Fill/Aseptic Process Simulation

- An appropriate number of aseptic process simulations using the subject container closure system were not provided
- Maximum proposed filling duration proposed for production was not simulated
- All production operations not simulated (particularly aseptic powder fill)
- Recent requalification results were not provided

Summary

- Again, manufacturing of ophthalmic suspensions is complex!
- Submissions contain incomplete information to support various sterilization processes essential for demonstrating sterility assurance
- Common IRs include excessive hold times or acceptance criteria, studies not performed according to ISO standards, missing or inadequate validation and/or requalification data, and overall media fill insufficiencies
- Check current FDA guidance and references

References

- Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practices (2004)
- Guidance for Industry - Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994)
- USP <771> Ophthalmic Products
- USP <1207> Package Integrity Evalutions
- ISO 11135 - Sterilization of health care products - Ethylene oxide (2014)
- ISO 11137-1 - Sterilization of health care products - Radiation (2006)

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Email: arlene.chen@fda.hhs.gov

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