Building a Better Sterility Assurance Application

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Overview/Learning Objectives

- Best practices
- Common issues→ common deficiencies
- References

Best Practices

- **Best practices benefit:**
  - Application holder: less information requests
  - Application reviewer: review efficiency
  - Patients: necessary drug products to market

Best Practices: Tip 1

- **Write informative narrative summaries**
  - Describe the general programs and the specific processes for the drug product
  - Provide adequate details
  - Describe the “what,” “why,” “how” of studies
  - Ensure information is consistent with reports
  - Provide rationale

Best Practices: Tip 2

- **References to Drug Master Files (DMFs)**
  - Proprietary information is placed in DMFs
  - DMF(s) reference placed at all relevant locations
  - Provide a current Letter of Authorization (LOA)
    - Module 1
    - Details for location of information in the DMF

Common Issues

- **Conflicting information**
  - Between narratives in different modules
  - Between narratives in different sections
  - Between summaries of documents and the details in those documents

Example:

P.3.3-Line 4 and Filling machine Z

P.3.5-Line 10 and Filling machine X

Common Issues

- **Absence of rationale or justification**
  - Validation should support the commercial production
  - Explain how validation supports commercial production
  - Provide justification for alternative validation schemes

Example:

P.3.3 and P.7-10 mL vial for commercial production

P.3.5-Depyrogenation validation using 2 mL vial

Common Issues

- **No information about items received as sterile or depyrogenated**
  - Applicant is responsible for:
    - Describing the items affected and the specific process
    - Identifying the entity performing the process(es)
    - Identify the location of the validation information
      - Application
      - DMF reference and LOA

Common Issues

- **Sterilizing filter not identified in autoclave loads**
  - Which “filter” is in the equipment load?
    - Air filters, bioburden reduction filters, product filters
  - “Filter” does not adequate describe the function

Example:

Equipment load #4: filter, filter housings, scoops, manifolds, bowls

Common Issues

- **Bioburden monitoring is not described**
  - Bulk solution should be monitored for bioburden
  - Routine monitoring is not described
  - Point(s) of monitoring is not described
  - Monitoring location during the process not adequate

Common Issues

- **Bioburden monitoring location not adequate**
  - **Monitor before any filtration**

Compound → hold → filter 1→ hold → filter 2→ filling

Common Issues

- **No pressure and vacuum conditions used for container closure integrity testing**
  - For microbial ingress and dye ingress testing
  - These conditions remove air bubbles, particulates, dried product
  - Both conditions ensure a fluid pathway through the breach to allow ingress
  - Justify alternative parameters

Common Issues

- **Unacceptable incubation conditions for Biological Indicators (BIs)**
  - *G. stearothermophilus* incubation is 7 days
  - Commercial BIs available with reduced incubation times of 24-48 hours
  - Certificate of analysis refers to FDA guidance pertaining to health care facilities
  - Concern is sub-lethally injured spores

Common Issues

- **Media fills are not representative of maximum production conditions**
  - Container closure system
  - Duration
  - Interventions
  - Environmental monitoring and growth promotion
  - Rejected or discarded units
  - Provide rationale for use of alternatives

Common Issues

- **Incorrect use of pooling for endotoxins testing**
  - Pooling allowed for units of 100 mL or less
  - Pool no more than 3 units
  - Must divide the maximum valid dilution (MVD) by the maximum number of pooled units
  - High levels of endotoxin in one unit can potentially be diluted out

Common Issues

- **Incorrect endotoxin limit for product release**
  - Monographs may not reflect current labeling
  - Acceptable endotoxin exposure is based on the maximum adult dose in 1 hour
  - Maximum dosing and route of administration in current package insert
  - Perform the calculations and follow USP <85>

References: Organization

- **Guidance for Industry (1994): *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products***

- **Guidance for Industry (2004) : *Sterile Drugs Products Produced by Aseptic Processing-Current Good Manufacturing Practice***

References: Organization

- **Question-Based Review (QbR) for Sterility Assurance Evaluation (Product Quality Microbiology Review) of an ANDAs**
  - ***QbR for Sterility Assurance of Aseptically Processed Products***
  - ***Quality Overall Summary (SA-QOS) Outline for Terminally Sterilized Products***
  - ***QbR for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions***

https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/abbreviated-new-drug-application-anda-forms-and-submission-requirements

Summary

- Summarize information clearly and consistently
- Provide validation data or reference a DMF for it
- Review the common deficiencies of this presentation
- Use the references on Slides 18 and 19

Challenge Questions

- 1. True or False

If an application has an associated DMF, then the application should container both a letter of authorization from the DMF holder and a reference to the DMF in the relevant sections of the application.

Challenge Questions

- 2. Fill in the blank

The FDA recommends that pooling for endotoxins testing use no more than _____ total units.

a. 2
b. 3
c. 4
d. No pooling of units is allowed.

Thank you

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