Building a Better Sterility Assurance Application

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Overview

• Best practices
• Common deficiencies
• References
Two Polls

**How interested are you in manufacturing a STERILE drug product?**

- A little, but no current plans to manufacture a sterile product: 0% (0)
- Interested; but not preparing any applications for sterile products: 0% (0)
- Very interested; actively preparing applications for sterile products: 0% (0)
- I'm not really sure...: 0% (0)
- No Vote: 0% (0)

**MB3-2: What type of application will you be preparing?**

- New Drug Application: 0% (0)
- Abbreviated New Drug Application: 0% (0)
- Biologic License Application: 0% (0)
- Various: 0% (0)
- None planned at this time: 0% (0)
- No Vote

**Broadcast Results**
Best Practices

• Best practices benefit:
  – Application holder: less deficiencies
  – Application reviewers: review efficiency
  – Public: necessary drug products to market
Best Practices

• Write good narrative summaries
  – Describe the general programs and specific processes for the drug product
  – Provide adequate details
  – Describe the “what,” “why,” “how” of studies
  – No conflicting information with reports
  – Provide rationale
Best Practices

• **Reference Drug Master Files (DMFs)**
  – Proprietary information placed in DMFs
  – Provide a reference to the DMF
  – Provide current Letter of Authorization (LOA)
Common Deficiencies

• Conflicting information identified
  – Between narratives in different modules
  – Between narratives in different sections
  – Between summaries of documents and the details in those documents
Common Deficiencies

• Absence of rationale or justification
  – Validation supports the specific commercial production process
  – Validation is not always identical to production
  – Explain how validation study supports the commercial production process
Common Deficiencies

• Absence of information for items received as sterile or depyrogenated or both
  – Identify who performs the process
  – Describe the process
  – Indicate the location of validation information
  – Reference DMF if necessary and provide the LOA
  – Validation in the application, if possible
Common Deficiencies

• Failure to mention the sterilization method of the product filter
  – Filters can be sterilized by autoclave
  – Filters can be sterilized by steam in place
  – Filters can be purchased as sterile
  – Describe the commercial sterilization process
  – Provide data to validate the sterilization process
Common Deficiencies

- Bioburden monitoring is not described
  - Routine performance is not described
  - Point(s) of monitoring is not described
  - Monitoring location is not adequate

Compound $\rightarrow$ hold $\rightarrow$ filter 1 $\rightarrow$ hold $\rightarrow$ filter 2 $\rightarrow$ filling
Common Deficiencies

• No pressure or vacuum conditions for container closure integrity testing
  – For microbial ingress and dye ingress testing
  – These conditions remove air bubbles, particulates, dried product
  – These conditions “simulate” shipping conditions
Common Deficiencies

• Unacceptable incubation conditions for Biological Indicators
  – *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 Deficiencies

• Media fills are not representative of maximum production conditions
  – Container closure system
  – Duration
  – Interventions
  – Environmental monitoring
  – Rejected or discarded units
Common Deficiencies

• 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
  – Concern that high levels in one unit will be diluted out
References


References

• Question-Based Review (QbR) for Sterility Assurance Evaluation of an ANDA (2011)
  – *QbR for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions*
  ➔ Detailed product quality microbiology information begins on page 6

• United States Pharmacopeia (USP) <1207> Sterile Product Packaging

References

• Guidance for Industry and FDA Staff (2007): *Biological Indicator (BI) Premarket Notification [510(k)] Submissions*

• International Organization of Standardization (ISO) *Sterilization of health care products-biological indicators-Part 1: General Requirements 11138-1:2006/(R)2010*
Thank you

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