Building a Better Sterility Assurance Application

Marla Stevens-Riley, Ph.D.
Master Microbiology Reviewer
Division of Microbiology Assessment
Office of Process and Facilities
Office of Pharmaceutical Quality
CDER/FDA

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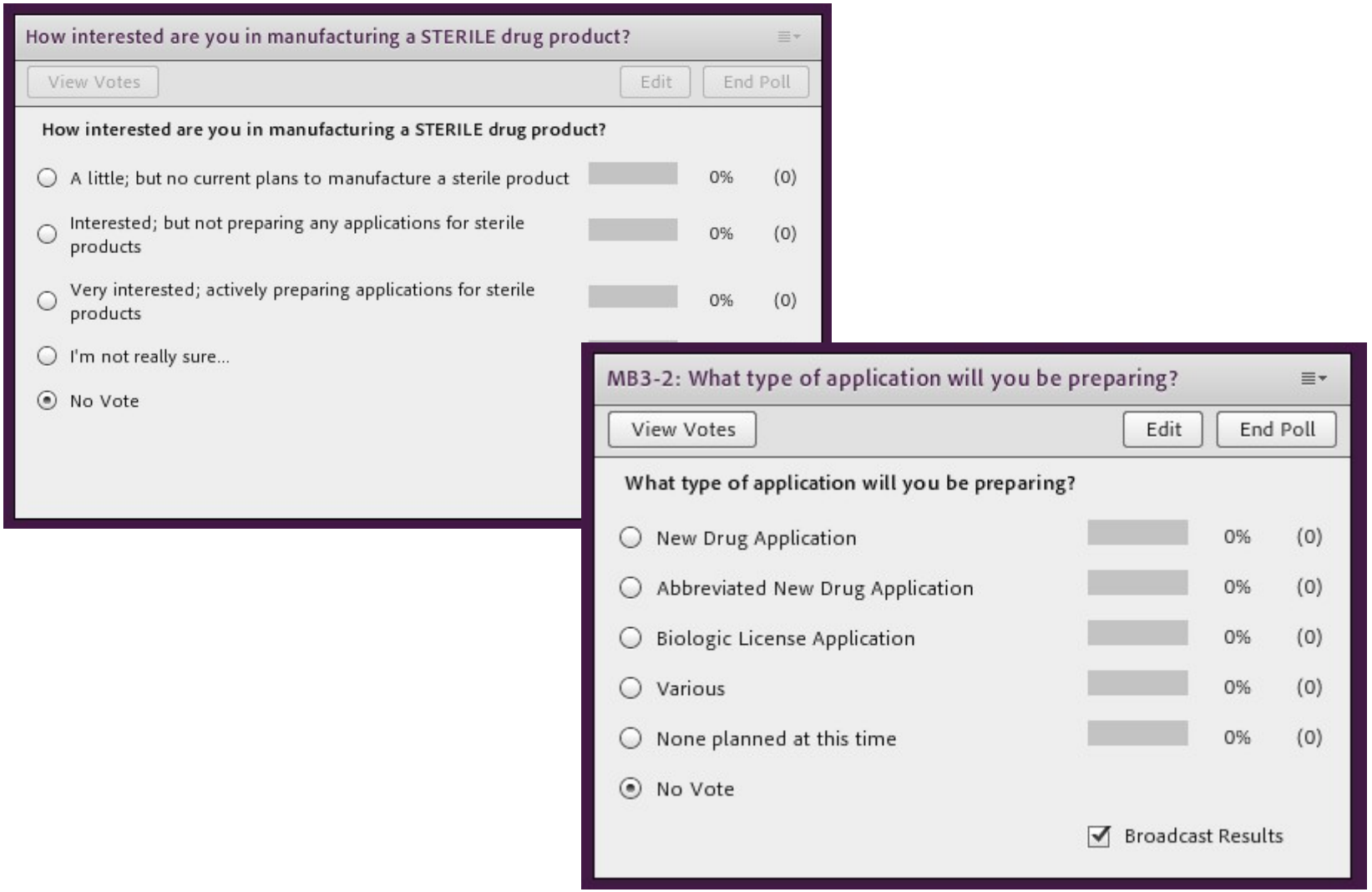
Overview

- Best practices
- Common deficiencies
- References

Two Polls


How interested are you in manufacturing a STERILE drug product?
View Votes
Edit
End Poll
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...
No Vote
MB3-2: What type of application will you be preparing?
View Votes
Edit
End Poll
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

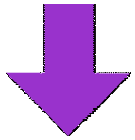
- **Absence of information for items received as sterile or depyrogenated or both**
  - Identify who performs the process
  - Describe the process
  - Indicate the location of validation information
  - Reference DMF if necessary and provide the LOA
  - Validation in the application, if possible

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 → hold → filter 1→ hold → filter 2→ 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
  - Explain. Explain. Explain.

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 that high levels in one unit will be diluted out

References

- **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

- **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

References

- **Guidance for Industry (2008): *Container and Closure System Integrity Testing* in Lieu *of Sterility Testing as a Component of the Stability Protocol for Sterile Products***
- **United States Pharmacopeia (USP) <1207> *Sterile Product Packaging***
- **Guidance for Industry (2012): *Pyrogen and Endotoxins Testing: Questions and Answers***

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

Marla Stevens-Riley, Ph.D.

Master Microbiology Reviewer

Division of Microbiology Assessment

CDER/OPQ/OPF

FDA