Improving the Sterility Assurance Application to the FDA

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Admin / Organization

- Recommendation: Make it easy to read
  - Introduction and summaries
    - "Autoclave X was qualified by performing 3 empty chamber HD runs and 3 worst case HP/BI runs in 2016. The worst-case load covers all loads proposed for production – Results are provided on page 18…."
    - Provide summaries of results as well. Min/max temperatures achieved, min/max F_0, BI results.

Admin / Organization

- Make it easy to read
  - Give the simple things
    - Machine, autoclave, and filling line name, room numbers, etc.
    - i.e., Don't assume we know that only one filling line is in the building
  - English Translations

  - **Why?:** Faster and more efficient review

Sterilizing Filtration

- Increase in the use of pre-sterilized, commercially available filling/filtration trains.
- Pre-packaged and pre-sterilized sterilizing filter, tubing, large flexible bag, etc.

Sterilizing Filtration

- **Recommendation:** Clearly mention the use of this in the application
  - Reference DMF if necessary
- Clearly indicate responsible party for sterilization of system
- If you are sterilizing it too, tell us!

Sterilizing Filters

- **Why?:** Avoid deficiencies concerning the content of equipment loads or equipment included in SIP validations
- We do not know if it is covered by worst case or bracketed loading patterns

Sterilizing Filtration

- Re-use of sterilizing grade filters during production campaigns

Sterilizing Filtration

- **Recommendation**:
  - Avoid sterilizing filter re-use (when possible)
  - Indicate the maximum number of times filter may be re-used or re-sterilized
  - Utilize 'worst case' conditions during media fills and bacterial retention studies
- **Why?:**
  - Validate the filter's retentive capabilities after maximum number of proposed sterilizations and/or re-uses

Drug Master Files

- DMFs allow confidential information to be referenced from another party. However, when not appropriately referenced, DMFs tend to cause confusion and potentially decrease review and application approval efficiency

Drug Master Files

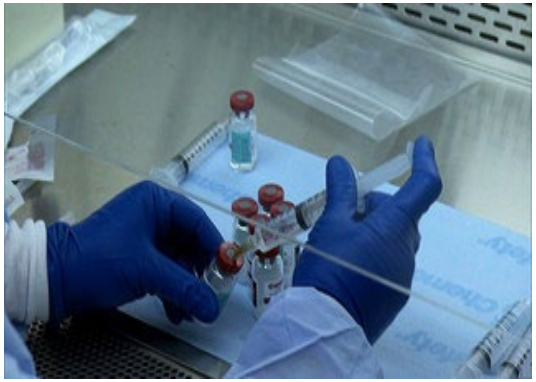
- **Recommendation:** Clearly indicate where ***appropriate*** validation information can be found (e.g., LOAs)
- Electronic DMF submissions
- If possible, provide information in application

- **Why?:** Avoid deficiencies concerning absent or confusing validation data
- Increase review efficiency and speed approval process

Nonsterile Powders

- Applications with PI instructions to reconstitute in an aqueous solution and hold

- Multidose or single dose with >7 days at 4ºC or 24 hours RT



Nonsterile Powders

- **Recommendation:**
  - Multidose
    - USP <51>, USP <60> at release (or risk assessment), an assessment of preservative content at the end of the storage time
  - Single dose (with PI storage times >7days at 4ºC or >24 hours RT)
    - A microbiological challenge study over the proposed storage time of the reconstituted solution, USP <60> at release (or risk assessment)
- **Why?:**
  - Improved risk assessment on nonsterile products with potentially long storage times

Bulk Bioburden Sampling

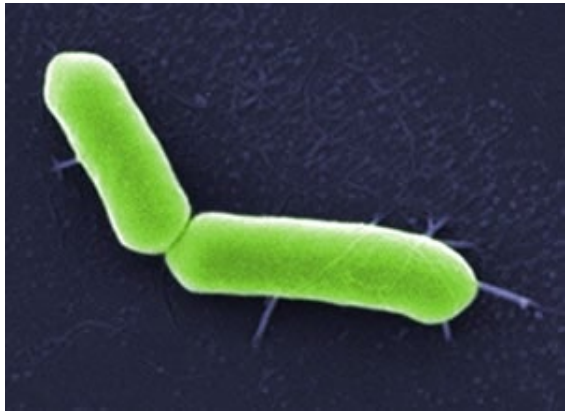
- **Recommendation:**
  - Understand the bulk solution bioburden load prior to *any* filtration (i.e., prior to 0.45μm or 0.2μm pre filters)
    - Sample, Measure & Monitor

- **Why?:** Sampling after filtration doesn't tell you how well controlled the bulk solution is. Can give a false impression. Microbial metabolites can pass through the filters.

Biological Indicators in Validation/Qualification

- Misinterpretation of BI incubation time for DP manufacturing facilities

- 7 day incubations vs incorrect 24 hour incubations



BIs in Validation/Qualification

- USP <55> (Biological Indicators)

  "Incubate each tube at the optimal recovery temperature specified by the manufacturer. Observe each inoculated medium-containing tube at appropriate intervals for a total of 7 days after inoculation."

- ISO 11138

  "An incubation period is commonly recognized to be 7 days for established sterilization processes, such as moist heat."

Guidance for Industry and FDA Staff

Biological Indicator (BI) Premarket Notification [510(k)] Submissions

1. Introduction

FDA regulates biological indicators (BI) intended to monitor sterilizers used in health care facilities as class II medical devices requiring premarket notification (510(k)). 21 CFR 880.2800(a). This guidance document provides information that will help manufacturers prepare 510(k)s for BIs used with conventional sterilization methods. FDA believes that providing this information will promote a consistent and efficient regulatory process.

Guidance issued by CDRH for healthcare facilities

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biological-indicator-bi-premarket-notification-510k-submissions

Attachment II. Examples of Validation of Biological Indicator Incubation Time

These recommendations are appropriate for all biological indicators, self contained or on a strip, which are intended to accompany products being sterilized through a sterilization procedure and to monitor adequacy of sterilization.

The incubation period for BIs may be reduced from the standard seven or more days, provided that the validation studies demonstrate that the revised numbers of days of incubation are sufficient according to appropriate methodology.

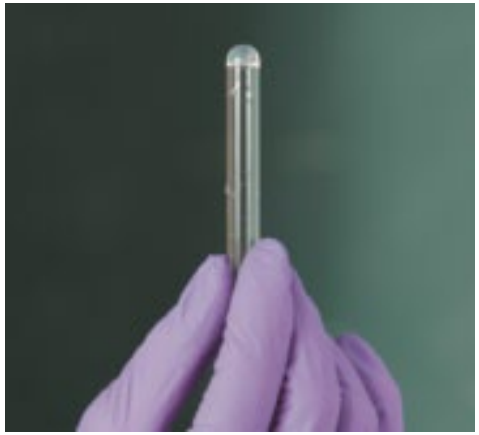
- Using the number of BIs that test positive on day 7 as the base of 100% grow out (denominator data), determine from the growth chart the number of BIs that have more than 97% of the base number of BIs (numerator) that test positive in each partial cycle for the proposed incubation time to be acceptable.

BI for Validation/Qualification

- **Recommendation:**
  - Incubate BIs used in validation studies for at least 7 days
- **Why?:**
  - Reduced incubation time clearance is for healthcare facilities – not drug product manufacturing sites.
    - The clearance for reduced time denotes that 97% of positive indicators show growth during the incubation period.
    - Is that acceptable for your facility?

Product Endotoxins Testing

- Pooling of samples, generally for small-volume parenterals (NMT 100 mL)



Product Endotoxins Testing

- **Recommendation:**
  - Pooling acceptable, NMT 3 units
  - Maximum Valid Dilution (MVD) adjusted to proportional, lower value
  - "Adjusted MVD" = MVD / # samples pooled

- **Why?:**
  - Ensure test method's ability to overcome potential product-related interference or enhancement

- Bonus – Make sure you understand the package insert maximum dose (pediatric?)

Media Fill Process Simulation

- **Recommendation:** Clearly indicate the maximum proposed time for filling during production

- **Why?:** We will routinely ask for the maximum proposed commercial filling duration and want to see that the process simulation studies can support it.

Media Fill Process Simulation

- **Recommendation:** Clearly indicate which lyophilizer was used.

- **Why?:** We see lyophilizers used in the media fill simulations that are not the lyophilizers proposed for commercial production.
  - This applies to all equipment used in the filling process.

Supplement Filing Tips

- Clear list of all changes up front (cover letter and intro pages of submission)
  - Change #1: New rubber stopper
  - Change #2: Increased filling duration
  - Change #3: Alternate autoclave load
- What are you changing from?
  - Don’t assume that we have all the prior reviews / submissions easily accessible. Might have been reviewed 10 years ago and not accessible.

Supplement Filing Tips

- If your proposed filing category is based on a prior approval:
  - When and what was approved in the past? What line #, what machine #, what ANDA #, date, copy of the approval (if not a confidential CMO issue)
- Make it logical:
  - "We propose CBE-30 because this filling line was previously approved in ANDA 12345 on Jan 1, 2020 *and nothing else is changing*"

Quiz

1. If your manufacturing plan includes purchasing a pre-sterilized filter but you also put the filter into an autoclave load, do you:

   A. Tell FDA you are also sterilizing it yourself and include data

   B. Tell FDA you are also sterilizing it yourself and do not include data

   C. Do not tell FDA about sterilizing it yourself since you purchased it sterile

Quiz

2. You are sampling the bioburden of the bulk solution and you are sampling it in between a 0.45μm pre filter and a 0.2μm sterilizing filter. Is this ok?

A. Yes

B. No

References

- *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf

- *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

References (2)

- *Guidance for Industry: Container and Closure System Integrity Testing* in Lieu *of Sterility Testing as a Component of the Stability Protocol for Sterile Products – 2008*

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/container-and-closure-system-integrity-testing-lieu-sterility-testing-component-stability-protocol

- *Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers - 2012*

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314718.htm

References (3)

- *Guidance for Industry: Comparability Protocols – Chemistry, Manufacturing, and Controls Information – Draft 2/03*
  https://www.fda.gov/media/70778/download
- *Guidance for Industry: Changes to an Approved NDA or ANDA – 2004*
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf
- *Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards – 2013*

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf

Contact Information

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Thank you!