Microbiology Quality Assessment

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DMA Product Quality Microbiology

- Assessment of:
  - Manufacturing process
    - Sterility assurance supporting validation studies
  - Microbial process controls
    - Bioburden testing, filter integrity testing, environmental monitoring
  - Finished product quality attributes
    - Sterility, endotoxins, bioburden, container closure integrity, antimicrobial effectiveness

Efficient Assessment

An assessor's job is to assess the information provided to them.

If an assessor has to search for or request information, the assessor becomes a detective and assessment efficiency might be impacted.

Make it Easy to Understand

- Don’t leave out the basics:
  - Equipment name/ID, filling line name, room numbers
  - Validation and production parameters and loads
  - Validation approach, e.g., production loads/parameters, worst case loads/parameters, bracketing

Make it Logical

- Provide context in an introduction
  - Tell us how the validation supports commercial production
  - “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.”

Make it Simple

- Summarize relevant results
  - Long reports containing hand-written notebook pages and unrelated validation studies

    vs.

  - Summary tables with data for relevant loads: Min/max temperatures achieved, min/max F_0, BI results

Drug Master Files

- Problems with DMFs may cause confusion and potentially impact assessment efficiency

Drug Master Files

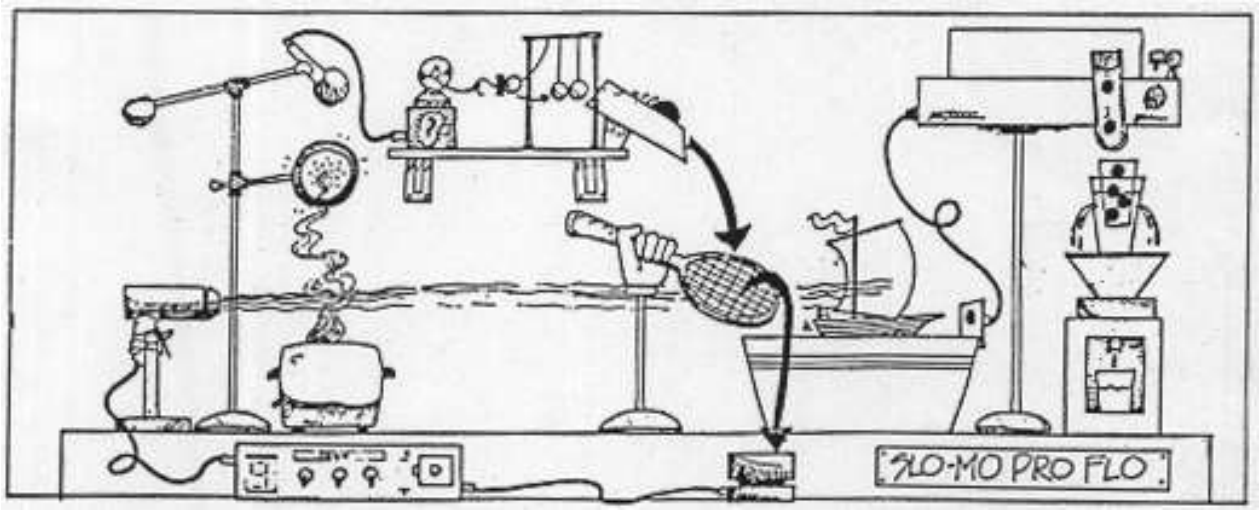
- Considerations:
  - Specify in LOA where ***relevant*** validation is (e.g., submission date, section and page numbers)
  - Electronic DMF submissions (May 5, 2018!)
  - Provide information directly in the marketing application

Common Deficiency Topics

1. Validation of pre-sterilized equipment
2. Media Fill Process Simulation
3. Drug Product Endotoxins Testing
4. Extended Storage Times Following Reconstitution / Dilution

Validation of pre-sterilized equipment

- Issue: Lack of sterilization validation for pre-sterilized, commercially available filling/filtration components (e.g. holding bags, filters)



Validation of Pre-sterilized Equipment

- Consideration: Clearly mention the use of pre-sterilized equipment in the application
  - Clearly indicate party responsible for sterilization of the system
  - If you are sterilizing it, too, tell us!
  - Reference DMF or provide sterilization validation in application

Validation of Pre-sterilized Equipment

- Why?
  - Avoid deficiencies concerning the content of equipment loads or which equipment is included in SIP validation
  - ‘Worst-case load’ isn’t descriptive enough

Media Fill Process Simulation

- Issue: Comparison of media fill simulation conditions to production conditions missing
- Consideration: Describe how media fill conditions simulate production/worst-case process

Media Fill Process Simulation

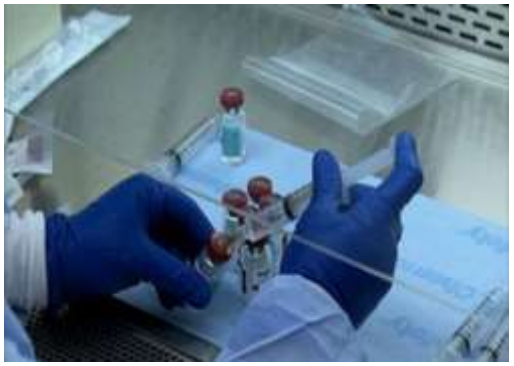
- Why?
  - Avoid simple deficiencies requesting:
    - Maximum filling duration
    - Filling speed
    - Routine/non-routine interventions
    - Container size/type

Drug Product Endotoxins Testing

- Issue: Pooling samples results in additional dilution equal to the number of pooled samples should only one sample exceed the endotoxins limit
- Considerations:
  - Pooling acceptable
  - MVD adjusted to proportional lower value
  - 'Adjusted MVD' = MVD/# of samples pooled

Drug Product Endotoxins Testing

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



Storage Post-Constitution / Post-Dilution

- Issue: Lack of microbiological studies in support of post-constitution / post-dilution storage time specified in package insert.
- Consideration: Provide risk assessment including microbiology challenge study data to support the post-penetration holding parameters to demonstrate that the final solution(s) do not support microbial growth during the storage period.

Storage Post-Constitution / Post-Dilution

- Potential study design
  - Inoculate final drug solution with minimum countable inoculum (≤ 100 CFU/mL) of challenge organisms
  - Incubate at specified storage temperature(s)
  - Sample at specified storage time(s) as well as intermediate and extended storage times
  - Growth generally accepted as population increases > 0.5 $\log_{10}$

Storage Post-Constitution / Post-Dilution

- Why?
  - Understand the risk associated with product labeling with regard to in-use stability and/or diluent compatibility claims

Reach the Approval Finish Line!

- Make the information easy to understand, logical, and simple to assess
- Avoid common deficiencies for basic information

Contact Information

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Technical Questions

- How to submit Controlled Correspondence

  https://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM411478.pdf

- Mail to: GenericDrugs@FDA.HHS.Gov

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: ANDA Submissions – Refuse-to-Receive Standards – 2013*

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

References

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

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

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

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

References

- *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf


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