Sterility Assurance and Risk Management: A CDER Microbiologist’s Perspective

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Disclaimer

• The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA
Presentation Outline

- Div. Microbiology Assessment: Role in CDER
- Risk management themes/ICH Q9
- Manufacturing processes and microbiological risk of drug to patient
- Case studies: application review/inspectional observations
CDER/OPQ/Office of Process and Facilities/Division of Microbiology Assessment

Functions:

1. Submission Review
   • NDA/BLA/ANDAs, Supplements, INDs, DMFs, Mtg Pkgs

2. Subject Matter Expertise
   • Facility Inspections
   • Incidents (drug contamination, infection outbreaks)
   • CDER Policy (guidance/inquiries, outside organizations)
   • Input to CDER re: inspectional findings & assessments
Risk Assessment and Risk Management

• To manage risk, one first needs to understand risk (RISK ASSESSMENT)

• May 2016: ISPE/FDA workshop
  – Industry shared examples of how firms perform formal risk assessment
Risk Assessment and Risk Management

• Do all pharma firms perform a formal assessment of risk?
  – Yes/No

• Does your firm perform a formal assessment of risk?
  – Yes/No
Guidance for Industry

Q9 Quality Risk Management
Q9 Quality Risk Management

Themes:

• “In relation to pharmaceuticals…, the protection of the patient by managing the risk to quality should be considered of prime importance”
Q9 Quality Risk Management

• “Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company’s ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.”
"Two primary principles of quality risk management are:

• The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and

• The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk."
Drugs and Microbiological Risk

• Q: How is patient microbiological risk from drugs mitigated?

• A: The drug manufacturing process is key to acceptable microbiological quality.
Manufacturing Processes & Quality

• Drug microbiological quality is built into the manufacturing process, not generated by end product testing
  – Sterilization validation & Quality by Design vs
  – Sterility/pyrogen/bacterial endotoxins testing of finished product which are required in the CFR
§211.113-Control of Microbiological Contamination

b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.
Manufacturing Process and Sterilization Validation Guidance

- Sterilization Process Validation Guidance
- Aseptic Processing Guidance
- PDA TR #1: Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control
- PDA TR #26: Sterilizing Filtration of Liquids
Quality by Design for Pharmaceutical Microbiology

Stephen Langille, Ph.D., Lynne Ensor, Ph.D., & David Hussong, Ph.D.

FDA

American Pharmaceutical Review
October 2009
Quality By Design and Microbiological Quality

• Drug Product: **Critical Quality Attributes**

  – Sterile products:
    • absence of viable microbes
    • non-pyrogenic (most/not all sterile dosage forms)

  – Nonsterile products: free from objectionable microbes
Quality By Design and Microbiological Quality

• Drug Product: **Critical Quality Attributes**
  a function of:

• Critical Process Parameters & Critical Control Points
  – Sterilization process, equipment depyrogenation process, bulk solution holding time limits, exposure of aseptic process steps to environment, …and others
Quality By Design and Microbiological Quality

• Each manufacturing process uses DIFFERENT process parameters & critical control points
• Lesser manufacturing processes may introduce micro risk to product quality
• Relationship: level of regulatory review scrutiny with manufacturing process
Sterile Manufacturing Process

1. Sterile Filtration/Aseptic Fill Combined with TS Overkill Cycle
2. TS Overkill Cycle
3. TS with < Overkill Cycle (bioburden based or product specific cycles)
4. Sterile Filtration/Aseptic Fill

TS=Terminal Sterilization
Terminal Sterilization, Sterility Assurance and Risk Management

- Overkill vs Product Specific/Bioburden based
- Definition of Overkill

A sterilization design approach where minimal information is required about the product bioburden. A worst-case bioburden assumption is used to determine the delivered lethality needed to achieve a PNSU of $10^{-6}$ on or in the items being sterilized. When using this approach, the qualification program must demonstrate that both the $F_{\text{BIO}}$ and $F_{\text{PHY}}$ are greater than 12 minutes. (PDA TR #1)
Terminal Sterilization, Sterility Assurance and Risk Management

• Case Study #1: Application Review
• Applicant: $F_0$ of NLT 10.5 minutes
• No discussion of bioburden monitoring in application
Case Study #1

Reference is made to PDA Technical Report No. 1 Rev. 2007 (Validation of Moist Heat Sterilization Processes) which states on page 28 that “ongoing bioburden monitoring is then conducted to assure that the specified cycle continues to be appropriate” when describing the product specific terminal sterilization process.
Case Study #1

Reference is also made to your information request response dated __ which states that a product-specific design approach is used for terminal sterilization of the drug product. However, it is unclear if every batch will be monitored for bacterial spores (see PDA TR#1; page 26) to demonstrate that the product (after filling into the bag) does not contain spores that are more heat resistant than those used during validation of the sterilization process.
Case Study #1

• Provide a commitment to include spore testing for every batch, and provide the test method.

• Follow up Comment/Information Request

  It is acknowledged that the methods for monitoring of bacterial spores will be provided at a future date. These test methods must be submitted prior to approval.
Terminal Sterilization, Sterility Assurance and Risk Management

• Case Study #2: Application Review
• Application: Overkill TS Cycle
• The application lacked verification that the units used in CCI study were exposed to the sterilization cycle
Case Study #2

Confirm that the vials used for container closure integrity testing were subjected to terminal sterilization using the production parameters of 121 to 124 °C for 20 minutes. If not, provide the results of container closure integrity tests on units subjected to production sterilization conditions.
Terminal Sterilization, Sterility Assurance and Risk Management

- Case Study #3: Application Review
- Applicant: Use of short BI incubation times
Case Study #3

We note that the Biological Indicator (BI) ____ ampoule used in the sterilization validation of the ____ has an associated Certificate of Analysis and incubation instructions that state, “The 48 hour incubation meets the criteria established in the FDA protocol for validation of reduced incubation time (RIT).” Please note that existing FDA CDRH guidance on reduced incubation times for BIs as derived from the draft Guidance for Industry Biological Indicator Premarket Notification [510(k)] Submissions (2001) is specifically directed towards BIs used to monitor sterilization processes in healthcare facilities and specifically not directed towards “BIs intended for use in a manufacturing setting.”
Case Study #3

**CDER does not generally recognize the acceptance criterion that the minimum incubation time is the greatest number of days to obtain more than 97% positive BIs subjected to a partial cycle (as indicated in the guidance) to justify a reduced incubation period of 48 hours compared to the commonly recognized incubation period of 7 days for BIs used to validate sterilization processes for the manufacture of sterile drug products (ANSI 11138-1:2006/(R) 2010). Therefore, please consider the use of more suitable BIs and/or incubation conditions for future sterilization validation studies.**
Terminal Sterilization, Sterility Assurance and Risk Management

• Case Study #4: Application Review
• Application: Overkill Terminal Sterilization
  – Only validated maximum loads
Case Study #4

We acknowledge the data provided to validate the terminal sterilization of maximum 20 mL and 50 mL vial loads using the ___ sterilizer. If load patterns other than the maximum load patterns described will be used for terminal sterilization of the drug product during commercial production, provide data summaries from three consecutive runs of minimum, maximum (if different from the load patterns used for the validation studies in the submission) or worst case loads that will be used in commercial production of the drug product.
Aseptic Processing, Sterility Assurance and Risk Management

• Case Study #5: Application Review
• Process: Sterile filtration/aseptic processing
• Filter validation study lacks information about how the sterilizing filter was sterilized
Case Study #5

Provide the sterilization parameters used for sterilizing the test filters used in the study and compare these to the sterilization parameters used for sterilizing the product filters used in commercial production.
Aseptic Processing, Sterility Assurance and Risk Management

- Case Study #6: Application Review
- Process: Sterile filtration/aseptic processing
- Filter validation study parameters do not represent commercial process
  - Filter validation: flow rate of 600 mL/min
  - Proposed production parameter: $\leq 100$ RPM
Case Study #6

Reference is made to the filter retention validation report which states that the process conditions include a maximum process flow rate of 600 mL/min. Reference is also made to table X which provides the production filtration flow rate specification of ≤ 100 RPM. Finally, reference is also made to table Y which provides three different filtration flow rates (872 mL/min, 702 mL/min and 740 mL/min) for the process validation lots using a filter pump speed of 100 RPM.
Case Study #6

• The filtration flow rates for the process validation lots are outside of the process parameters that were validated by __.

• Amend the application with a maximum filtration flow rate using units of mL/min.

• If the maximum filtration flow rate is greater than 600 mL/min, then provide an updated filter retention study using filtration process parameters representative of your drug product manufacturing process. Alternatively, provide a rationale as to how the existing filter retention validation report is supportive of your drug product manufacturing process.
Aseptic Processing, Sterility Assurance and Risk Management

• Case Study #7: Inspectional Observation
• Process: Sterile filtration/aseptic processing
• No process for replacement of RABS gloves
Case Study #7

RABS gloves are only replaced after they have failed a visual or automated integrity test. For example, a review of the RABS glove integrity log book for the RABS in _____, covering the previous six integrity testing results from 17 September 2015 to 18 January 2016, revealed that at least two and up to eight gloves failed integrity testing during each testing time point. No investigations or deviations were initiated following the detection of glove failures to determine the potential impact on batches produced during the period prior to glove integrity failure detection.
Aseptic Processing, Sterility Assurance and Risk Management

• Case Study #8: Inspectional Observation
• Process: Sterile filtration/aseptic processing
• Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.
Case Study #8

1. Integral units are rejected during media fills without adequate justification.

   a. During media fill batch ___ on the ___ line, there were a total of 35,469 vials processed. The machine data report identified 10 vials rejected for vial tare weight out of range, 325 vials rejected for net weight out of range, 3830 rejected for vials without gas, and 57 good vials rejected. This is a total of 4222 (11.9%) of the filled vials. These rejected vials included units that were filled with media and were integral.
Aseptic Processing, Sterility Assurance and Risk Management

- Case Study #9: Inspectional Observation
- Process: Sterile filtration/aseptic processing
- Activities performed during media fills are not also performed during production
Case Study #9

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

The following investigations identified operator behavior as the likely root cause of contaminated vials during media fills:
- 4 Media fills with 31, 17, 1 and 1 turbid units
Case Study #9

In each case these root causes were identified with the aid of video recordings from the facility surveillance system. The investigations failed to evaluate and document review of video recordings from previously manufactured commercial batches to determine if similar operator behavior existed. They also failed to evaluate videos of subsequent commercial batches to verify that deficiencies in operator behavior had been corrected.
TS or AP, Sterility Assurance and Risk Management

• Case Study #10: Application Review
• Application:
  – Sterilization cycle uses a filtration step prior to moist heat terminal sterilization
  – No demonstration that the pre-filtration holding step is acceptable
  – Note that this deficiency may apply to either TS or AP
Case Study #10

Provide a validation study for the proposed 6 day holding period between compounding and the start of filtration.

Summarize the solution holding conditions and bioburden sampling of the solution over the maximum and ‘worst case’ durations.
TS or AP, Sterility Assurance and Risk Management

• Case Study #11: Application Review

• Application:
  – Terminal sterilization or aseptic processing
  – Bioburden sampling occurs after filtration of sample
Case Study #11

We note that the “pre-filtration” bioburden sample is taken after the bulk drug solution has been passed through a 0.45 μm filter (Figure X). The determination of the concentration of the bulk solution bioburden after the solution has already been filtered does not provide you with an accurate understanding of the microbiological quality of your manufacturing process prior to 0.45 μm filtration. Provide a commitment to perform bioburden sampling prior to passage of the bulk drug solution through a 0.45 μm filter. It is acceptable to continue to perform the bioburden sampling step after filtration of the solution through a 0.45 μm filter (in addition to prior to), if you wish.
TS or AP, Sterility Assurance and Risk Management

• Case Study #12: Application Review
• Application:
  – CCI test to be used in stability program instead of sterility test
Case Study #12

We note that the stability protocol specification indicates that container closure integrity testing may be performed in lieu of sterility testing, as allowed in the Guidance for Industry “Container and Closure System Integrity Testing as a Component of the Stability Protocol for Sterile Products”; however the proposed container closure integrity test method has not been described, nor has validation data been provided for the method.
Case Study #12

If container closure integrity testing is to be performed in lieu of sterility testing for stability batches, provide a description of the method, including method sensitivity and method validation data. Alternatively, please commit to test stability batches using only the currently approved sterility test method, and to provide the information requested above in a future supplement if container closure integrity testing in lieu of sterility testing is to be implemented for the stability protocol.
Summary

• The drug product manufacturing process is directly proportional to its sterility assurance.

• Sterility & apyrogenicity are Critical Quality Attributes assured by adequate Critical Process Parameters & Critical Control Points.

• Industry & regulators should remember: **CPPs and CCPs = patient safety**
Thank You

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