Hot Topics in Drug Product Process Validation: A Reviewer’s Perspective

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Presentation Outline

• Quality microbiology content of BLA submissions
  – Guidance documents and regulations

• Process validation: common deficiencies and case studies
  – Sterilizing filtration
  – Post-reconstitution and post-dilution storage
  – Media fills

• Conclusions and reference slides
  – Drug product quality micro content for CDER BLAs
Laws and Regulations

• Public Health Service Act
  – Section 351 (a)(2)(C) -- Licensure of biological establishments and products
    • The **biological product** must be safe, pure and potent
    • The **facility** in which the biological product is manufactured, processed, packed, or held **must meet standards designed to assure that the biological product continues to be safe, pure and potent**

  – Interprets that “biological products” are also “drugs”
    • The FFD&C Act applies to a biological product, except no application required under section 505
    • Inspection under both the provisions of both the PHS Act and the FD&C Act

• Both the PHS and FD&C Acts require that biological products must be manufactured under CGMP as described in 21 CFR 210 and 211 and 600-680
Laws and Regulations (cont.)

• Validation of aseptic and sterilization processes:
  – 21 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.

  – Addresses the validation of aseptic and sterilization processes

• Refer to 21 CFR Part 211 for additional regulations applicable to sterile drug products.
BLA Content:
Guidance for Sterile Drugs

  – Outlines the sterilization process validation information that should be provided in an application.
  – Referenced for BLAs in the following guidance:
    • Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use (1996)
BLA Content: Guidance for Sterile Drugs (cont.)

  - Provides guidance on how to comply with CGMP regulations.
  - Use in conjunction with other compliance programs and guidance.

- Established Conditions: Reportable CMC Changes for Approved Drug and Biologics Products (2015 draft)
Common Deficiencies and Case Studies

• Sterilizing filtration
  – Refer to PDA Technical Report 26 (Sterilizing Filtration of Liquids) for general guidance.
  – Topics:
    • Integrity testing
    • Process parameters
    • Microbial retention validation

• Post-reconstitution and post-dilution storage

• Media fills
Sterilizing Filter Integrity Testing: Common Deficiencies

- No information or insufficient information for product bubble point determination.
- Test description missing or insufficient.
- Acceptance criterion listed only as “pass.”
  - Wetting agent not specified.
  - Numerical value for “pass” not provided.
- Sterilizing filter integrity test results from process validation lots not provided.
Sterilizing Filtration Parameters: Common Deficiencies

• Filtration time limit (product contact time):
  – Time limit was not included in parameters.
  – Proposed time limit was significantly longer than required for the production process and was not appropriately validated by the microbial retention study.
Sterilizing Filtration Parameters: Common Deficiencies (cont.)

• Pressure or flow rate limit:
  – Peristaltic pump speed range provided *in lieu* of pressure or flow rate limit. Pump speed should be correlated to a parameter validated by the microbial retention study (flow rate or pressure).
  – Controls should be in place to ensure that the pressure or flow rate limit validated by the microbial retention study is not exceeded during production.
Sterilizing Filtration Parameters: Case Study

• Issue:
  – The microbial retention study modeled flow rate and pressure limits for the filtration process, but the production process parameters included peristaltic pump speed range *in lieu* of flow rate or pressure.

• Information request:
  – The sterile filtration parameters should include flow rate as validated by the microbial retention study. Peristaltic pump speed is only one factor that contributes to filtration flow rate. Please amend section 3.2.P.3.4 to include the operating range for flow rate. In addition, please provide the maximum flow rates for sterile filtration of the process validation lots.
Sterilizing Filtration Parameters: Case Study (cont.)

• Result:
  – The calculated flow rates for the process validation lots were provided. The calculated flow rates were well below the maximum flow rate validated by the microbial retention study.
  – The sponsor agreed to implement pressure monitoring of the sterile filtration process and to set a maximum pressure limit.
    • Current expectations for monitoring and control of sterilizing filtration processes in such cases are being developed.
Microbial Retention Validation: Common Deficiencies

• Retention study report and viability data not provided in addition to the summary data, or the study report was not legible.

• Scaled-down study parameters were not compared to production parameters, or the scaled-down study did not support the worst-case production parameters.
  – Product contact time, flow rate or pressure, product volume per unit of membrane surface area, temperature.
Microbial Retention Validation: Common Deficiencies (cont.)

• Inadequate justification for not performing the study as a single-stage direct challenge with unmodified product under worst-case conditions.
  – The drug product formulation was bactericidal to the challenge organism under the conditions of the study, so water was used as a surrogate solution.
  – The study design was modified to accommodate an unnecessarily long filtration time limit.
Microbial Retention Validation: Case Study 1

• Issue:
  – The microbial retention study was performed as a two-stage test: product conditioning followed by bacterial challenge. The challenge organism (*B. diminuta*) was suspended in water because the drug product formulation was bactericidal to *B. diminuta*.

  • In this case, the proposed time limit for production filtration was reasonable.
  
  • The challenge organism was not viable in the drug product formulation for the full duration of the proposed time limit.
  
  • Performance of a two-stage test was justified.

– However:

  • In general, water is not a suitable surrogate solution for BLA products.
  
  • Studies were not performed to identify the bactericidal component of the product or process, which would allow for a more suitable study design.
Microbial Retention Validation: Case Study 1 (cont.)

• PMC:
  • The microbial retention study was done with purified water as a surrogate solution for the drug product. **Perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution.** Product attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) **should model the drug product as closely as possible while preserving viability of the challenge organism.** Alternatively, a reduced exposure time approach may be appropriate.
Microbial Retention Validation: Case Study 2

• Issue:
  – The microbial retention study was performed as a two-stage test: product conditioning followed by bacterial challenge with *B. diminuta* suspended in unmodified product.
    • The proposed time limit for filtration was 7 days. The maximum filtration time for the process validation lots was ~2 days.
    • The proposed filtration time limit was much longer than that needed for production.
      – The risk of microbial penetration of the filter increases with time.

• Result:
  – The time limit for filtration was lowered to ~3.5 days based on the bacterial challenge stage of the microbial retention study.
Common Deficiencies and Case Studies

• Sterilizing filtration
• Post-reconstitution and post-dilution storage
  – Microbial challenge studies
• Media fills
Post-Reconstitution and Post-Dilution Storage

• Lyophilized products are reconstituted prior to administration, as directed in the label.

• Proposed post-reconstitution storage time should be supported by microbial challenge studies to demonstrate that the product does not support microbial growth under the proposed storage conditions.
  – This requirement also applies to post-dilution storage times for liquid or reconstituted products.
Post-Reconstitution and Post-Dilution Storage Studies

• To support a post-reconstitution or post-dilution storage time:
  – Challenge studies should be conducted using a panel of microorganism provided in the USP<51> (Antimicrobial Effectiveness Testing) plus typical skin flora or species associated with hospital-borne infections.
    • Challenge levels should be less than 100 CFU/mL.
    • Temperature(s) described in the proposed product’s labeling should be tested.
    • Test should be conducted for twice the recommended storage period and use the label-recommended diluent(s).
    • No increase from the initial counts is defined as less than 0.5 log\(_{10}\) unit higher than the initial inoculum.
Post-Dilution Storage: Case Study 1

• Initial labeling:
  – “Product A” is diluted in 0.9% NaCl prior to administration.
  – Proposed post-dilution storage conditions: up to 24 hours at 2-8°C or up to 12 hours at 23-27°C.

• Growth promotion study results:
  – Growth-promoting for *P. aeruginosa*:
    • By 32 hours at 2-8°C
    • By 24 hours at 23-27°C
  – Growth-promoting for *E. coli*:
    • By 16 hours at 23-27°C
      – Two-fold increase in CFU at the 12 hour time point (duplicate samples)

• Labeling revision:
  – Storage at 23-27°C was removed from the labeling.
Post-Dilution Storage: Case Study 2

• Initial labeling:
  – “Product B” is diluted in 0.9% NaCl prior to administration. The infusion time, which is based on patient tolerance of the drug, is 10-20 hours.
  – Labeling stated that room temperature diluted solution should be used within 24 hours of preparation.

• The sponsor was asked to include the 10-20 hour infusion time in the growth promotion study design.

• Study results: product was growth-promoting for *P. aeruginosa* and *E. coli*.
  – Both were TNTC at the first time point (24 hours) at 25°C and 30°C

• Review actions:
  – Labeling revision: post-dilution storage for not more than 4 hours at 2-8°C prior to administration.
  – Risk was communicated to clinical reviewers.
Common Deficiencies and Case Studies

- Sterilizing filtration
- Post-reconstitution and post-dilution storage
- Media fills
  - Media fill program information
  - Media fill data
Media Fills: Common Deficiencies

• Relevance of media fill information and data to the “Product X” manufacturing process was not clearly explained.

• Insufficient detail and justification regarding the media fill conditions (e.g., line speed, number of vials filled, inspected, rejected or discarded and incubated).

• Maximum hold times were not validated.

• Summaries of environmental and personnel monitoring data from the media fills were not provided.

• Growth promotion studies were incomplete or not provided.

• Contaminating microorganisms were not identified

• Acceptance criteria for media fills were not provided.

• No plans for action to be taken following a media fill failure.
Media Fills: Case Study

• Media fill information provided in the original BLA submission:
  – “The [“Product X”] manufacturing process is covered by [the drug product manufacturer’s] routine bracketed media fill process, which is regularly validated”.
  – Minimal information about the media fill program.
  – Minimal data from only one media fill.
    • Data from the three most recent fills or from the initial qualification + more recent fills should be provided.
Media Fills: Case Study (cont.)

- **Media fill program** information that was provided in the BLA is **underlined**:
  
  - Requalification frequency
  
  - Requalification strategy
    - Matrix approach, bracketing approach, etc.
    - How does the requalification strategy apply to “Product X” manufacturing?
  
  - Procedures used to simulate any steps of a normal production fill
    - Lyophilization, hold times, etc.
    - Are the manufacturing process steps for “Product X” covered?
Media Fills: Case Study (cont.)

• **Media fill program** information that was provided in the BLA is *underlined* (cont):

  - How do media fills provide a worst-case challenge for aseptic processing operations?
    * Interventions, *duration*, number of personnel, etc.
    * How are the media fill parameters worst-case compared to the production parameters for “Product X” manufacturing?

  - Acceptance criteria for media fills

  - Actions taken when media fills fail
    * Investigations and microbial ID
    * Product disposition
Media Fills: Case Study (cont.)

• Data provided in the BLA for one media fill is underlined:
  • Identification of aseptic filling area and fill line
  • Identification of container-closure system (type, size, etc.)
  • Type of medium and fill volume
  • Date of the fill, total time for the fill, number of units filled, and number of units incubated
  • Number of units filled but not incubated (and reasons for exclusion)
  • Number of positive units
  • Media fill process parameters (compare to production parameters for the BLA product)
  • Production steps simulated and interventions performed
  • Incubation parameters for filled units (time, temperature, container orientation)
  • Growth promotion test procedures and test results for the medium
  • Environmental and personnel monitoring results (number of samples, excursions, microbial ID)
  • In addition to the data above, the media fill reports may also be requested
Media Fills: Case Study (cont.)

• Filing deficiency:
  – Insufficient relevant information provided on the media fill program, including media fill acceptance criteria and action taken in the event of a failure.
  – Insufficient information on the aseptic processing operations relevant to “Product X” to enable a substantive and meaningful review.
Conclusions

• Sterilizing filtration:
  – Integrity testing information and data should be provided.
  – Filtration parameters should be supported by the microbial retention study.
  – Modifications to the microbial retention study design should be made only when necessary and should be supported by viability study data.

• Post-reconstitution and post-dilution storage conditions indicated in the labeling should be supported by growth promotion study data.
Conclusions (2)

• Media fill data should be explained in the context of the product under review, and sufficient information should be provided.

• Refer to the guidance documents and pre-meeting comments for the drug product information that should be included in your BLA.
  
  – **FDA review timelines are based on the expectation** that applications are complete at the time of submission.
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Reference: Drug Product Micro Content for CDER BLAs

- Provide the following information in section 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:
  - Description of the manufacturing areas and fill line, including air classifications.
  - Description of the environmental and personnel monitoring programs.
  - Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.
  - Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.), the pressure limit or flow rate limit for sterilizing filtration, and the acceptance criterion for post-use integrity testing.
  - Parameters for filling, stoppering, and capping.
  - Processing and hold time limits, including the time limit for sterilizing filtration.
  - Bioburden and endotoxin limits.
• Provide protocols and reports with validation data in section 3.2.P.3.5:
  – Bacterial filter retention study for the sterilizing filter.
  – Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
  – Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program.

  • Note that this requirement includes disposable filtration/filling assemblies and storage bags which are supplied “ready to use.”

  • For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.

(continued on the next slide)
Reference: Drug Product Micro Content for CDER BLAs

• Provide protocols and reports with validation data in section 3.2.P.3.5:

(continued from the previous slide)

– Three successful consecutive media fill runs, including summary environmental and personnel monitoring data obtained during the runs.

– Isolator decontamination, if applicable.

– Maintenance of container closure integrity during production (vial capping, syringe or autoinjector assembly, etc.).

– Summary of shipping validation studies and data.

  • For pre-filled syringes, the effects of varying air pressure on plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data that demonstrate that plunger movement during air transportation does not impact product sterility.
Reference: Drug Product Micro Content for CDER BLAs

• Provide drug product testing information and data in the appropriate sections of Module 3:
  
  – Verification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. In addition, the test methods should be described.
  
  – Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).
  
  – Low endotoxin recovery studies. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin standard (CSE or RSE) into undiluted drug product and testing for recoverable endotoxin over time.
  
  – Container closure integrity testing information and data. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) and at expiry.