



Aseptic Processing of Biological Products: Current Regulatory Issues

“Facing the Challenges of Drug Product Manufacturing”

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Series

CDER Microbiology Issues: A Deeper Dive

Presentation Outline

- Quality microbiology content of BLA submissions
 - Guidance documents and regulations
- Process validation: common deficiencies
 - Sterilizing filtration
 - Post-reconstitution and post-dilution storage
 - Container Closure Integrity
- 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**
- Federal Food, Drug, and Cosmetic (FD&C) Act (1938, 1962, 1997, 2007)
 - 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

- Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994)
 - Describes sterilization process validation information that should be included in an application
- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)
 - Provides guidance on how to comply with CGMP regulations
 - Use in conjunction with other compliance programs and guidance

BLA Content: Guidance for Sterile Drugs (cont.)

- Container Closure System Integrity Testing *in lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products (2008)
- Established Conditions: Reportable CMC Changes for Approved Drug and Biologics Products (2015 draft)

Common Deficiencies

- **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
- Container Closure Integrity

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 is not included in parameters
 - Proposed time limit is significantly longer than what is required for the production process and is 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

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

- 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*
- 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 (cont.)

- The following post-marketing commitment was agreed upon:

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.

Common Deficiencies

- Sterilizing filtration
- **Post-reconstitution and post-dilution storage**
 - Microbial challenge studies
- Container Closure Integrity

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

- 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.

Post-Reconstitution and Post-Dilution Storage Studies (cont.)

- Test duration should be 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

- 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

Common Deficiencies

- Sterilizing filtration
- Post-reconstitution and post-dilution storage
- **Container closure integrity**

FDA 1994 Guidance: Container Closure Integrity Tests

“.....sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container-closure system. Documentation of the sensitivity of the container-closure integrity test should be provided.”

FDA 2008 Guidance: Container Closure Integrity Tests

- Sterility tests are **not recommended** as a component of a stability program for confirming the continued sterility throughout a product's shelf-life or dating period
- Alternatives to sterility testing ...might include any **properly validated physical or chemical container and closure system integrity testor microbiological container and closure system integrity tests** (e.g., microbial challenge or immersion tests)

FDA 2008 Guidance: Container Closure Integrity Tests (cont.)

- A test method is adequately validated if it has been proven through **scientifically accepted studies** to be capable of detecting a breach in container and closure system integrity
- An appropriate container and closure system integrity test **should be conducted annually and at expiration** or as otherwise required by applicable regulations

Common Deficiencies

- Container closure integrity test (CCIT) not included in the stability program
- Inadequate qualification of the container closure system for integrity
 - Inadequate description of the CCIT methods
 - Sensitivity of method not known or described
 - Lack of appropriate controls
- Vial capping parameters not described
 - Worst case capping parameters not validated
- CCI of syringes
 - Shipping of syringes

Example: Container-closure integrity test with an inadequate positive control

- Applicant proposed to use a CCIT capable of detecting defects as small as 160 microns
 - Positive control used during method validation was a container prepared with a 160 micron defect.
- Current CCIT methods are capable of detecting leaks \leq 20 microns
- System suitability controls with a smaller defect size should be used for routine testing..

Resolution

- The following information request was sent to the applicant:

The system suitability controls for container closure integrity testing of syringes and pens are prepared with a relatively large defect size (removing the needle shield). System suitability controls with a smaller defect size should be used for routine testing. The study performed by [XXXYY contract lab] showed that the method is capable of detecting 5, 10, and 30 micron defects.

- The applicant committed to implementing a system suitability control with a smaller defect size (≤ 20 microns).

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 (cont.)

- CCIT should be used in lieu of sterility for drug product on stability (annually and at expiry)
- CCIT method validation studies should demonstrate adequate sensitivity using appropriate controls
- 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.

Reference: Drug Product Micro Content for CDER BLAs

- 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.

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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.