



U.S. Food and Drug Administration

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Microbiology/Sterility Assurance Information for PET Applications – NDAs & ANDAs

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Microbiology Review

- Part of CMC
- Separate Discipline from Chemistry
- Focus on Sterility and Pyrogenicity
- Review of New Applications (INDs, NDAs & ANDAs) and Supplements
- INDs and NDAs reviewed by OPS Microbiology Group
- ANDAs reviewed by OGD Microbiology Group

Product Information

- **Description of the Final Dosage Form**
 - Solution (approximate volume range in mL)
 - Composition of the solution for injection
 - Container and Closure System
 - Are container-closure systems provided from commercial vendor?
 - Sterile, sealed, pyrogen-free?
 - Submit DMF reference or Certificate of Analysis
- **Manufacturing Methods**
 - General description of the manufacturing process
- **Sterilization Validation**
 - If components or equipment are sterilized and/or depyrogenated at the PET facility, describe sterilization/depyrogenation processes and provide validation study reports

Facility Description

- Manufacturing Site: Name & facility address
- Floor Plan
 - Process Flow, Room Numbers & Critical Environments
 - e.g., Laminar air flow workstations, biosafety cabinets, isolators
 - Critical Environment Specifications
 - Equipment

Description of Manufacturing Processes

- Fluid Path through Processing Equipment into Final Container
- Preparation of Bulk Solution (Carrier & Solvent) including Storage
- Product Solution Sterilization (generally filtration)
- Sample collection and product distribution
- Transfer of Solution into Product Container

Filtration Process Validation

- Specify the Filter
 - Vendor and product identification (e.g., catalog number)
 - Manufacturer Certificate?
- Specify the Filtration Conditions
 - Filtration Time, Pressure, Flow Rate & Volume
 - Identified in the batch records
- Specify the Integrity Test
 - Batch record should indicate that filter integrity is tested after filtration prior to product release
 - Test Method & Acceptance Criteria
- Validation of the Membrane
 - Who did the validation (usually done by vendor)?
 - Test Method & Acceptance Criteria

In-Process Sterilization

(if critical items are not provided sterile)

- Sterilization Process Parameters
 - Validation Studies
 - Manufacturing
- Solution Components (certificates, filtration, etc.)
- Vials, Syringes, Stoppers
- Tubing, Mixing Vessels, Columns, Filters

Filling Process Validation: Media Fills

- Simulated Manufacturing
- Methods: Describe the manipulations, growth medium, incubation parameters & test frequency
- Describe the Acceptance Criteria
- Data Summary
 - 3 runs to qualify each new operator and process
- Requalification Frequency
 - 1 run/operator annually or after procedural changes
- Actions Following Failures

Microbiology Monitoring

- Routine Monitoring of Personnel, Surfaces, Air & Materials
 - Sampling Methods & Frequency
 - Cultivation: Media and Incubation Parameters
 - Special Tests (i.e., Yeast, Molds & Anaerobes)
- Acceptance Levels (Alert and Action)
- Actions Following Exceeded Levels

Container Closure Integrity

- Validate Integrity of Final Product Dosage Form (usually done by vendor if commercially supplied)
- Assay
 - Challenge Methods
 - Detection Methods
 - Acceptance criteria

Microbiology Release Tests

- Sterility
- Endotoxins
- Testing is required: 21 CFR 212.70(e)
- Product may be Released Before the Test is Finished: 21 CFR 212.70(c)

Sterility Test

- Identify the Testing Laboratory
- Sample Type, Size, Time & Storage
 - Method
 - Reference USP or SOP
 - Growth Media, Incubation Parameters and Examination Time Points
 - Actions Following a Test Failure
 - Notifications, Investigation and Corrective Action Plans

Endotoxins Test

- Testing Laboratories
- Methods: Include Materials, Controls & Validation
 - Modified Gel-Clot or Rapid Photometric
 - Reference USP or SOP
- Product Specification
 - NMT 175 EU/V per USP in which V is the maximum patient's dose per hour (refer to USP <85>)
 - Express criterion as EU/mL of the injection at the product expiration time
- Actions Following a Test Failure

Formal Written Procedures

- List, Reference or Provide SOPs

Maintenance of Product Quality: Stability

- No Microbiology Requirements

Summary (1)

- Describe the Dosage Form
- Identify Where Product is Made
- Describe the Steps in its Manufacture
- Specify and Validate Sterilization of Components & Equipment, or
- Qualify Vendors of Components and Equipment

Summary (2)

- Validate the Aseptic Process
- Describe the Microbiological Environmental Monitoring
- Microbiological Release Tests
 - Describe and Validate Methods
 - Specify Acceptance Criteria
 - Define Actions Following a Failed Result

References

- *Guidance for Industry: PET Drug Applications – Content and Format for NDAs and ANDAs*
 - *Fludeoxyglucose F 18 Injection*
 - *Ammonia N 13 Injection*
 - *Sodium Fluoride F18 Injection*
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078738.pdf>
- *Attachment I* for sample submission formats
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078740.pdf>
- *Guidance: PET Drugs – Current Good Manufacturing Practice (CGMP)*
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070306.pdf>

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Growth Promotion Testing of Media

- Media Prepared In-House
 - Growth promotion test EACH Batch
- Commercially Purchased Media
 - Initial Growth Promotion Testing
 - FIRST 3 batches (part of vendor qualification)
 - Subsequent Growth Promotion Testing
 - Sterility Test or Environmental Monitoring Media
 - If used within label's shelf life & stored according to label's recommendations → test one batch PERIODICALLY (e.g., quarterly)
 - Media Fills (process simulation studies)
 - Inoculate a separate vial from the same batch of medium (serves as positive control & growth promotion test)