Overview of a sterility assurance program for PET drugs

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Disclosures

• Employee of PETNET Solutions, a Siemens Company

• Will not discuss usages or indications for any approved and investigational agents
Objectives

• Explain the components of a sterility assurance program for PET drug manufacturing
Scope

• This presentation will be focused on the sterility assurance program for aseptic processing during drug manufacturing of F18 based products.

• Pharmacy applications and details from USP <797> requirements will not be addressed

• Will highlight FDA guidance released for PET drug manufacturing
Why is sterility testing important?

- Sterility testing is a retrospective analysis
- Must build a program that will provide confidence that the drug product is sterile since the testing is not complete prior to patient injection
Sterility Assurance Program

- Qualified materials
- Appropriate method validation
- Suitable environment for aseptic processing
- Environmental Monitoring
- Routine verification of manufacturing process
- People
Media Selection and Qualification

• Tryptic Soy Broth (TSB)
  – aerobic microorganisms
• Fluid Thioglycollate Medium (FTM)
  – aerobes, anaerobes and microaerophiles
• Tryptic Soy Agar (TSA)
  – Cultivation of bacterial strains
• Sadouraud Dextrose Agar
  – Dermatophytes (fungus)
Media Selection and Qualification

- Three commercially available lots of medium should be tested according to USP <71> or <61>
- Drug Manufacturer should qualify media by verifying accuracy of the certificate of analysis from the media manufacturer
- Tests include
  - Visual inspection
  - pH
  - Sterility
  - Growth Promotion
Routine verification of media

• A certificate of analysis should be inspected for each lot and shipment of media

• Certificate of analysis compared to local requirements for the material

• Periodically verify the full COA and growth promotion capability
  – Example:
    • Quarterly – single organism
    • Annual – full USP <71>/<61> verification on single lot of each media
Process materials qualification

• Filtration method validation
• Testing of the sterilizing filter with bubble point test
• Sterile components – perform incoming analysis of vendor COA for sterility and endotoxin free where applicable
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Sterility Test Method Suitability

• Methods
  – Membrane Filtration
  – Direct Inoculation

• Validation – USP <71>
  – Use known amount of microorganisms
  – Use drug product matrix
  – Inoculation volume
  – Positive and negative controls
Differences from USP<71>

- Volume tested
  - USP – half of the contents of the container for drug product that is 1-40 mL
  - Radiopharmaceuticals: typically less than 0.25 mL

<table>
<thead>
<tr>
<th>Quantity per Container</th>
<th>Minimum Quantity to be Used (unless otherwise justified and authorized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquids</td>
<td></td>
</tr>
<tr>
<td>Less than 1 mL</td>
<td>The whole contents of each container</td>
</tr>
<tr>
<td>1–40 mL</td>
<td>Half the contents of each container, but not less than 1 mL</td>
</tr>
<tr>
<td>Greater than 40 mL, and not greater than 100 mL</td>
<td>20 mL</td>
</tr>
<tr>
<td>Greater than 100 mL</td>
<td>10% of the contents of the container, but not less than 20 mL</td>
</tr>
</tbody>
</table>
Differences from USP<71> 

• Radioactivity 
  – Inoculation to occur within 30 hours of End of Synthesis 
  – Verify that the amount of radioactivity inoculated will not impact microbial growth 
  – Can be performed in the presence of raw isotope instead of Drug Product
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Environment

- Aseptic processing steps must be performed in a suitable environment
- ISO classification 5
- Minimize activity in controlled area

<table>
<thead>
<tr>
<th>Class Name</th>
<th>Particle Count</th>
</tr>
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<tbody>
<tr>
<td>ISO Class</td>
<td>U.S. FS 209E</td>
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<tr>
<td>3</td>
<td>Class 1</td>
</tr>
<tr>
<td>4</td>
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<td>7</td>
<td>Class 10,000</td>
</tr>
<tr>
<td>8</td>
<td>Class 100,000</td>
</tr>
</tbody>
</table>
Verification of Equipment

• At least Semi-annual verification of LFH:
  – Airflow velocity
  – HEPA filter leak test
  – Induction leak test/backstreaming test
  – Smoke pattern testing
  – Particle count
  – Additional tests for biological safety cabinet per NSF 49
  – Make sure you read the report to ensure that all required tests were performed
Cleaning Process

• Use sporicidal cleaning agent periodically (i.e. weekly)
• Document the cleaning process and validate that process
• Validation of cleaning process on materials that are to be cleaned (stainless steel, etc)
• Proves effectiveness of cleaning method
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Monitoring the Environment

• Routine environmental monitoring is important for monitoring the state of control of the facility and process
• Viable monitoring is performed for critical aseptic activities
• Settling plates used during the process
• Contact plates used to monitor the people performing the aseptic operation
Action/Alert limits

- Should be set for each location
- Based on historical data
- May be different for different sample locations
- Refer to USP <1116> for guidance
Trending EM Data

• EM data should be trended in two manners:
  – For each event
  – Monitor between different aseptic operations in the same ISO 5 area

• Example:
  – Trend growth of each aseptic event
  – Trend growth over time for that event
ID of growth

- Genotyping of RNA: bacterial, fungal
- Use qualified third party for identification
- ID can assist in finding the true root cause for an excursion or group of excursions
- Identify a Microbiologist to help interpret results
- Trend by class of microorganism
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Media Fill

• “A “media fill” (sometimes known as a “process simulation”) is the performance of an aseptic manufacturing procedure using a sterile microbiological growth medium in place of the drug solution. Microbiological growth medium is used in place of the drug solution during media fills to test whether the aseptic procedures are adequate to prevent contamination during actual drug production. A media fill is one part of the validation of an aseptic manufacturing process.”

1 Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs, April 2012
Media Fill

• Designed to evaluate:
  – Aseptic assembly of critical components
  – Qualify operator technique
  – Demonstrate the environmental controls are adequate
Media Fill Design

• Simulations employed site-specific, worst-case conditions, for all process steps downstream from the “sterilizing filter” up to product release including:
  – Maximum number of batches per day
  – Shelf life and expiration of components
  – Length of time the assembly is stored before filtration
  – Size of the vial
  – Maximum sample size
  – Sample handling and locations
  – Air and environmental conditions
Types of Media Fills

• Operator Qualification
  – Designed to test all processing steps that the operator normally performs during aseptic manufacturing should be simulated.
  – Separate qualifications for each aseptic process (i.e. final product vial assembly and sterility inoculations)

• Process Qualification
  – Designed to test all processing steps for the entire manufacturing process in one study
  – Can be designed to encompass both operator and process simulation for PET drug manufacturing
Media Fill Frequency

• Operator Qualification
  – Media Fill in triplicate for initial qualification
  – Each operator should participate in at least one media fill per year

• Process Qualification
  – Initial qualification in triplicate
  – The process at each manufacturing facility should have a media fill performed at least every 6 months
Media Fill Controls

• Negative control
  – To ensure the absence of false positive results, a negative control should be included to demonstrate that the medium was sterile to begin with.

• Positive control
  – Media fill positive control shows that the medium in the drug product container will support growth after exposure to the filling process.
  – Single organism control is allowed.
  – 10 to 100 CFU
  – Should be performed in area separate from critical manufacturing area.
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Personnel Training

• Only trained, authorized personnel may perform aseptic operations
• Effectiveness of training should be confirmed with written tests and practical evaluation (i.e. media fill and observation by other personnel)
• Personnel that fail tests should be re-instructed and re-evaluated by qualified personnel to ensure correct aseptic processing practices
• Training should be documented
Mindset

• Operators should understand why they are cleaning and understand the proper cleaning processes.

• Be aware of aseptic techniques (i.e. first air for critical processing steps).

• Pay attention to gowning. People are the largest source of microbes during aseptic processing.

• Pay attention to health. Sick employees or excessive sweating should be monitored during aseptic techniques.
Summary

• We rely on a system of sterility assurance

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