Aseptic Controls in PET Manufacturing

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EXPECTATIONS FOR ASEPTIC CONTROLS IN PET DRUG MANUFACTURING

There is no difference between academic and commercial manufacturing in 21 CFR 212
PET DRUG MANUFACTURING IS LOW RISK

Characteristics that define the risk profile of PET drugs

Primary
- Use of closed containers during the automated synthesis process for a typical PET drug
- Short shelf-life
- Small volume batches in one product vial and quality control testing of the whole batch

Secondary
- Use of microbiologically hostile and often lethal synthesis steps
- Synthesis is often completed in minutes
- Pre-sterilized components, aseptic component assemblies and manipulations, and the use of closed containers during the automated synthesis process for a typical PET drug
- Characteristics result in an extremely low – typically zero – bioburden process stream before sterile membrane filtration in the final production step

SURVEY RESULTS OF PET DRUG MANUFACTURERS
2020 AND 2023 SURVEYS

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</thead>
<tbody>
<tr>
<td>FDA Approved PET Drug batches produced</td>
<td>51,603</td>
<td>50,771</td>
<td>50,658</td>
<td>52,925</td>
<td>51,973</td>
<td>59,194</td>
<td>58,550*</td>
<td>57,676*</td>
<td>61,880*</td>
<td>66,193*</td>
<td>69,655*</td>
</tr>
<tr>
<td>Number of out-of-specification (OOS) sterility test results</td>
<td>4</td>
<td>2</td>
<td>9</td>
<td>12</td>
<td>5</td>
<td>13</td>
<td>2</td>
<td>7</td>
<td>13</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Number of FARs filed for the OOS sterility test results</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>11</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Number of confirmed/presumed product sterility failure</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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*Data based on 2023 survey results as of 10-Oct-2023
**Data not available
SURVEY RESULTS OF PET DRUG MANUFACTURERS
2020 AND 2023 SURVEYS

• Sterility OOS rate is 0.014 % for 11 years (2013 and 2023)
• No confirmed/presumed product sterility failures for at least 6 years (373,148 batches)
• Controls for PET Drug manufacturing should be set based on the risk

Comments from the Community

Controls based on risk management
• Inspectors have expressed concerns about longstanding processes for which firms have substantial in-house performance and safety records.
• Can FDA discuss the need for additional controls that increase regulatory burden and cost in light of historical documented evidence for substantial safety and compliance?
• What can PET manufacturers do to help the FDA recognize such evidence as part of a Sponsor risk management program?

FACILITY EXPECTATIONS

• Clean room not required
• ISO Class 5 PECs required to be in a segregated area
• ISO Class 5 PEC certifications every 6 months
• Dynamic smoke studies
  • No requirement in 21 CFR 212 to video record smoke study testing

Comments from the Community

Facility
• What standards does FDA enforce regarding rooms that contain laminar flow hood/cabinet, especially regarding ISO 5 LAFW positively pressured inside a controlled room?
• Can FDA specifically point to applicable Guidance and reference standards (such as USP) that apply to room classification and recommended minimum standards?
FACILITY EXAMPLE

ISO Class 5 PECs located in a segregated area

ISO Class 5 PECs located in ISO Class 7 area

CLEANING OF ISO 5 AREAS

- Sterile 70% IPA required
- Sterile sporicidal not required
- Sterile wipes required
- Validating hold time of cleaning agents not required
  - Manufacturer's hold time can be followed

Comment from the Community

Validation for Cleaning
- What are FDA’s expectations around Disinfectant Efficacy Studies (DES) and cleaning validation studies for PET manufacturers?
ENVIRONMENTAL MONITORING

- Action vs alert levels
  - Alert levels not required in 21 CFR 212
  - No guidance in 21 CFR 212 regarding action level limit
    ○ FDA Aseptic Processing guidance references 21 CFR 210 and 211
  - Multi-use facilities may benefit from using USP 825 action limits
    ○ USP 825 compendially applicable November 1, 2023
- Active air sampling not required for routine monitoring in 21 CFR 212

### Viable Air and Surface Sampling (USP Chapter <825>)

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Air Sampling Action Levels (cfu/m³ of air per plate)</th>
<th>Surface Sampling Action Levels (cfu/device or swab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&gt;1</td>
<td>&gt;3</td>
</tr>
<tr>
<td>7</td>
<td>&gt;10</td>
<td>&gt;5</td>
</tr>
<tr>
<td>8</td>
<td>&gt;100</td>
<td>&gt;50</td>
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ENVIRONMENTAL MONITORING

**Comments from the Community**

- What are the FDA’s expectations of house flora testing given the low risk of PET manufacturing compared to the cost of these tests?
- Identification of EM results
  ○ What benefit has FDA seen from this?
  ○ Costs associated with this
  ○ Quarterly EM trend reports not required in 21 CFR 212 but frequently expected/requested in inspections
- Qualification of materials
  ○ What is the expectation for growth promotion of plates/tubes if growth promotion is included on the CoA?
2023 SURVEY RESULTS
EM DURING FPV ASSEMBLY

14. Please identify the areas typically sampled for environment microbial monitoring as part of the
assembly of the final product vial in an ISO 5 area. If you select "other," please describe.
16 responses

- Passive air settling plate: 13 (81.3%)
- Active air sampling plate: 4 (25%)
- Operator finger touch plate (left): 13 (81.3%)
- Operator finger touch plate (right): 14 (87.5%)
- Work surface: 12 (75%)
- None: 0 (0%)
- Particle counts: 1 (6.3%)
- N/A: 1 (6.3%)

2023 SURVEY RESULTS
EM DURING STERILITY TESTING

15. Please identify the areas typically sampled for environment microbial monitoring as part of the
sterility test inoculation in an ISO 5 area. If you select "other," please describe.
16 responses

- Passive air settling plate: 12 (75%)
- Active air sampling plate: 3 (18.8%)
- Operator finger touch plate (left): 11 (68.8%)
- Operator finger touch plate (right): 12 (75%)
- Work surface: 11 (68.8%)
- None: 2 (12.5%)
- Particle counts: 1 (6.3%)
- N/A: 1 (6.3%)
- Clean room and Ant-room areas: 1 (6.3%)

11/18/2023
What is the **alert level** for the number of microbial CFUs in ISO 5 areas?

What is the **action level** for the number of microbial CFUs in ISO 5 areas?

**MEDIA FILL EXPECTATIONS**

**Comments from the Community**

- PET manufacturers often encompass multiple products/processes into one media fill to justify worst-case scenario
- What are the expectations for MF in each room and ISO 5 area vs risk-based approach?
- What are FDA’s expectations regarding the MF for product vs for operators?
- Product vial assembly hold time should be tested
  - Can hold time be tested separately from other MF?
**COMMENTS FROM COMMUNITY**

**Guidance Documents**

- Will the FDA be updating and/or issuing new media fill guidance for PET drug manufacturers?
- When will the PET guidance document be updated and when will sterility assurance guidance for PET, as discussed in the last PET Drug Workshop with FDA, be released?
- Inspectors have recently referenced “the new 212” when making justifications for new standards/expectations. When were inspectors trained on new expectations? Can the industry have a copy of this training?

**REFERENCES**

- 21 CFR 212-Current Good Manufacturing Practice For Positron Emission Tomography Drugs
- Guidance, PET Drugs – Current Good Manufacturing Practice (CGMP), FDA, December 2009
- Guidance, PET Drugs – Current Good Manufacturing Practice (CGMP) (Small Entity Compliance Guide), FDA, August 2011
- Guidance, Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs, FDA, April 2012
- Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, FDA, September 2004
- USP Chapter <825> Radiopharmaceuticals-Preparation, Compounding, Dispensing, and Repackaging, Official as of 01-Dec-2020
- PET Drug Manufacures Survey Results, conducted by Coalition of PET Drug Manufactures in 2023
- PET Drug Manufacures Survey Results, conducted by Coalition of PET Drug Manufactures in 2020