FDA Perspective on Aseptic Process Simulation for Cell Therapy Product Manufacturing

Lily Y. Koo
Division of Manufacturing and Product Quality
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
US Food and Drug Administration

Overview

- Define aseptic boundary for cell/tissue processing
- Open vs. closed processing steps
- Cryopreserved product vs. fresh product
- Process scale-up and scale-out
- Aseptic process simulation (APS) study design considerations
- Case studies

Applicable Regulatory Requirements

- Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (statutory CGMP)
- Title 21 Code of Federal Regulations
  - Parts 210s -211s – CGMP for Finished Pharmaceuticals
  - Parts 600 - 610s – Additional biological products standards
- Guidance
  - **Guidance for Industry: Sterile Drug Products Produced By Aseptic Processing - Current Good Manufacturing Practice (Sept. 2004)**

Cell Therapy Products – Unique Considerations

- Highly product-specific manufacturing processes with inherent variability
  - Allogeneic vs. autologous therapies
  - Cryopreserved vs. fresh final product
  - Centralized vs. near-patient manufacturing
- Final product consists of viable cells or cell-derived matrices and not amenable to final sterilization/filtration
- Aseptic techniques often required throughout manufacture
- Full test results may not be available before final release

Aseptic Processing

- **Aseptic Processing Definition**. "Handling **sterile** materials in a controlled environment, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels." (**PDA**, TR# 22, 2011 revision)
- Critical elements to successful aseptic processing:
  - Personnel performance (gowning and aseptic techniques)
  - Environmental quality and control
  - Validated cleaning and sterilization of container/closures, equipment, utensils, and product-contact surfaces
  - Aseptic process simulation (APS) – challenges the overall process with worst-case microbial contamination risks/conditions to evaluate aseptic process robustness and to comply with CGMP requirements

Where does it begin… end?

- Define aseptic boundaries for the manufacturing process
  - Initial aseptic cell/tissue harvest? Transport to bedside?
  - Know your process – aseptic processing begins when you need to maintain sterility from that point forward and ends when the container closure system containing the final product is closed (Not just “media fill”!)
  - APS should be performed for aseptically produced vectors, biological matrices, or cell culture media which are not amenable to terminal sterilization/filtration

Manual/Open Aseptic Processing

- Detailed step-by-step instructions should be in place for consistent, repeatable manual operations
- All open manipulations, any direct/indirect (e.g., fluid path) operator/equipment contact with the product should be simulated as closely as possible
- Include representative or worst-case operations, conditions, and interventions to challenge routine manufacturing operations
- Glove/sleeve change requirements should be based on operation risk assessments and a simple “change as necessary” may not be sufficient

Manual/Open Aseptic Processing – cont.

- Equipment/material layout during processing should be as defined as possible to avoid crowding and interference with airflow (MINIMIZE clutter!)
- When tissue is used to obtain cells, a suitable tissue surrogate based on attributes and availability may be used to facilitate process simulation
- Duration of process simulation may be shorter duration than your process based on risk assessments to ensure the shortened time will be representative of the actual duration in terms of interventions, shift changes etc.

Automated/Closed Aseptic Processing

- Closed processing using closed aseptic transfer technology
- Less stringent environmental requirements (ISO 7/8) and reduced human interventions
- Validation of closed systems and process steps – functionally "closed"
  - Demonstrate integrity of closed production and aseptic interfaces between the unit systems throughout lifecycle of use and under full range of operating conditions
  - Recommend performing APS as part of the initial validation of closed systems

Cryopreserved Product vs. Fresh Product

- Cryopreserved drug product
  - Generally a long product shelf life, but may require additional processing steps
  - May facilitate distribution, but requires cold-chain shipping logistics
  - Final container closure suitability and integrity must be demonstrated after exposure to cryo-conditions
- Fresh product
  - Generally a short product shelf-life
  - Final product may be sensitive to shipping conditions
  - Full test results may not be available before release
  - Demonstration of asepsis during product transportation (e.g., leak-proof) can be part of the validation strategy

Aseptic Process Scale-up/Scale-out - Considerations

- Does the quality system have the capacity to support process scale-up/scale-out for the manufacturing process: where is the bottle-neck?
  - Scalability by size/volume (scale-up)
    - Have the aseptic connections changed?
    - Has the mass transfer frequency increased?
    - APS may be required along with PPQ and media hold studies
  - Scalability by adding parallel processing culture systems (scale-out)
    - Simulation to demonstrate capacity is dependent on the risks of cross-contamination (e.g., facility design, HVAC coverage, etc.)
    - Define and test at maximum capacity
- APS requirements and strategies during process scale-up/scale-out will be highly dependent on process-specific, facility-specific risk assessments

General Considerations for APS Study Design

- What is the number of concurrently processed lots/campaigns?
- What is the worst-case usage of BSCs?
  - Number of initial APS runs per qualified BSC based on risk assessment (e.g., equivalence, processing activities, location with environmental considerations)
  - Requalification runs may validate BSCs on a rotational basis
- What is the process volume of cell culture?
- What are the types and frequency of aseptic connections/disconnections and equipment assembly/disassembly?
- What is the duration of exposure for the open steps?
- What are the operator specific tasks and worst-case operator occupancy?
- Any operator changes during breaks or shifts?

General Considerations for APS Study Design – cont.

- Perform smoke studies under dynamic conditions for ISO 5 areas
- Appropriate controls/surrogates should be uniquely considered and identified for each product/process
- Use of microbial growth supportive medium and include growth promotion testing using the appropriate challenge medium and microorganisms
- APS sample incubation for not less than 14 days at 20-35°C
- If one or more positive units in the simulated final product containers and/or failed control units, the failure(s) should be investigated and the APS runs should be repeated
- Aseptic processes and operator proficiency should be requalified at a frequency determined based on risk assessment
- Requalification may be required after aseptic process changes based on risk

Case Study #1

Allogeneic tissue for immediate post-release transplantation

- **Open manufacturing process:** Aseptic tissue collection, transport to manufacturing facility, tissue sectioning, multi-day tissue feeding/culturing using sterile cell culture plates, transfer to final container closure system, packaging, hand delivery to surgery room. Open manipulations performed inside ISO 5 BSCs. Sterility testing results are not available before transplantation.
- **Batch definition:** Single donor sourced tissue intended for a single recipient
- **Proposed APS Study Design:** The sponsor proposed to simulate the entire aseptic process in real time and simulate the tissue processing steps without including the tissue or a tissue surrogate
- **FDA feedback:** 1) FDA requested a detailed SOP and side-by-side description of the actual aseptic manufacturing steps and the respective activities simulated during APS. 2) Use of tissue surrogate to simulate tissue processing steps and contact with equipment and identify appropriate APS study controls. 3) Condense closed incubation time. 4) Simulate final product transport (e.g., motion, container orientation) to assess asepsis maintenance/container closure integrity during transport (media hold study) to the surgery room.

Case Study #2

Autologous cells subject to ex-vivo transduction and expansion prior to reintroduction

- **Open/closed manufacturing process:**
  - Aseptic cell collection by leukapheresis, transport to manufacturing facility, magnetic-bead based cell selection/expansion/viral transduction/formulation/filling/ cryopreservation, transport to patient bedside
  - Cell bags are aseptically connected between closed operation steps. Aseptic connections and disconnections are performed in ISO 5 BSC.
  - Open operations performed in ISO 5 BSC or isolator
  - Cell culture media and vector are not sterile filtered
- **Batch definition:** Single patient sourced blood cells intended for the same patient
- **Proposed APS Study Design:** Three APS modules: cell product manufacturing process, vector production and filling, preparation of cell culture media
- **FDA feedback**
  - Include antibody-coated beads during simulation of the cell selection step
  - Identify critical steps and collect samples at those steps during APS for final incubation to determine potential points of contamination
  - Change of workstation and operator between steps or shifts needs to be incorporated in APS at representative frequencies and using maximum number of operators

Case Study #3

"Allogeneic virus specific T cells

- **Open/closed manufacturing process:** Aseptic cell collection from seropositive donors, transport to manufacturing facility, cell co-incubation/stimulation, manual formulation, automated filling using a closed system, cryopreservation, shipping to clinical centers
- **Batch definition:** Multi-donors to multi-recipients (HLA-matched)
- **Proposed APS Study Design:** APS would simulate filling only
- **FDA feedback:**
  - All open manipulations need to be simulated, including any addition
  - Perform aseptic process simulation as part of the initial validation to demonstrate that the filling system is functionally closed
  - Demonstrate cryovial integrity during and after exposure to cryo-conditions

Acknowledgment

- Randa Melhem
- Ellen Huang
- Anthony Lorenzo
- Qiao Bobo
- Laurie Norwood
- John Eltermann


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Environmental Control and Monitoring

- The extent of environmental control depends on the manufacturing process and the working conditions:
  - Less stringent when adopting automated closed manufacturing systems or environment (e.g., isolator)
  - More stringent when performing manual open processing inside a ISO 5/Class A Biological Safety Cabinets (BSC)
  - EM should be performed during setup activities
- A routine EM program with established methods, frequencies, and sampling locations should be in place to demonstrate control over environment
- EM during APS should include non-viable air, viable air, viable surface, viable personnel, if applicable