Production Technologies: Aseptic Processing

Zhihao Peter Qiu, Ph.D.

External Advocacy Lead China, Roche Genentech, Washington DC, USA
(Former Director of Division of Biotechnology Manufacturing, OPQ, CDER, US FDA)

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Aseptic Processing

- The use of appropriate technologies, process and detection methods to increase the protection of the product from potential extraneous sources of contamination
  - Restricted Access Barriers Systems (RABS), isolators, robotic systems,
  - Rapid/alternative methods

- The effectiveness of the aseptic processing should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data.
  - Personnel training and qualification program
  - Environmental monitoring Program

Aseptic Processing

The major variable in the control of aseptic processing arises not from the sterilization processes, the cleanroom, or the filtration processes that are so often the subject of technical papers and regulatory guidelines, but rather from the workforce itself ”
– PDA.

Personnel Training and Qualification

- A well-designed, maintained, and operated aseptic process should minimize personnel interventions.
  - Human-borne contamination is the most critical risk factor in aseptic processing
- Personnel should have adequate qualifications and regular training on aseptic techniques, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards.
  - Qualification to enter Grade A/B areas. Aseptic gowning and aseptic behaviors should be confirmed and assessed at least annually using visual and microbial sampling.
  - The requirement to change socks to facility socks for entry to Grade C and above
  - Electronic devices used in cleanrooms (e.g. mobile phones and tablets) should be designed to permit cleaning and disinfection.
  - The requirement for clean room garments used in Grade A/B areas.

Personnel Training and Qualification

- Aseptic techniques
  - Contact sterile materials only with sterile instruments
  - Sterile gloves should be regularly sanitized or changed, as appropriate, to minimize the risk of contamination
  - The principle of slow, careful movement should be followed throughout the cleanroom
  - Keep the entire body out of the path of unidirectional airflow
  - Proper aseptic manipulations should be conducted in a manner that does not compromise sterility of the product

Environmental Monitoring

- Provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness
- Risk assessments should be performed in order to establish a comprehensive environmental monitoring program
  - knowledge of the process and product, the facility, equipment, historical monitoring data, air visualization studies
  - sampling locations, frequency of monitoring, monitoring methods
- Appropriate alert and action limits for viable and total particle monitoring
- Procedures for investigation of exceeding alert and action limits, periodic EM trending and assessment of risk to product quality.

Aseptic Processing

- Contamination Control Strategy (CCS)
  - Preparation Controls
  - Processing Controls
  - Protection Controls

Contamination Control Strategy (CCS)

- Identify, assess and control the risks associated with aseptic processing
  - The understanding of the entire manufacturing process and the product
    - aseptic environment preparation
    - aseptic filling stages
  - All critical control points
    - raw materials or intermediates
    - containers and closures
    - Other supporting areas
  - Facility, HVAC, utility and equipment design
  - Personnel

Preparation Controls

In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together.

- It is critical that containers should be filled and sealed in an extremely high-quality environment.
- All product and component contact equipment should be sterilized prior to use.
- All raw materials or intermediates should be sterilized and aseptically added.
- Bulk solutions or intermediates should be sterilized.
- Validation studies should be conducted to demonstrate the efficacy of the sterilization cycle.

Preparation Controls

- Processes should be performed aseptically in Grade A with an appropriate background
  - The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items with direct or indirect product contact
  - The filling line set-up and filling of the sterile product
- There should be adequate environmental monitoring conducted during those operations.
- The Aseptic Process Simulation studies should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps and interventions.

Processing Controls

- Aseptic manipulations should be minimized through the use of engineering design solutions such as preassembled and sterilized equipment.
  - Knowledge of the product and process
  - Risks to product sterility
- There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production.
  - Should be assessed during the “Smoke Study” and APS based on risks posed to the product sterility
  - Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition
  - APS should not be used to justify practices that pose unnecessary risks to product sterility

Processing Controls

- The duration of each aspect of aseptic preparation and processing should be limited to a defined and validated maximum time
  - A risk based validation of Hold Times for equipment, components, and containers.
- There should be a validated maximum permissible time for each product between the start of the preparation to the end of the aseptic filling process
  - The holding time prior to filling.
  - The aseptic processing time.
  - The filling time.
- Maximum permitted holding times for sterile product and equipment exposed during the aseptic process should be verified during APS.

Protection Controls

- The use of advanced aseptic processing technologies, such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions and to minimize the risk of contamination.
  - Appropriately designed for its intended use
  - Validation of decontamination procedures
- Robotics and automation of processes can also be considered to eliminate direct human critical interventions
  - Establish an adequate environmental monitoring program to meet the regulatory requirements and expectations.

Protection Controls

- Transfer of sterilized materials, equipment, components and ancillary items into grade A should be done using appropriate validated methods with accompanying disinfection of the exterior of the sealed packaging.
  - Suitable protection after sterilization
  - Establish sterile hold times
  - The effectiveness of disinfection procedures should be validated
- It is critical that all transfer steps be carefully controlled and evaluated in the CCS to maintain sterility of the product.

Protection Controls

- Procedures that expose a product or product contact surfaces should be performed under unidirectional airflow in a Grade A environment
  - Open primary packaging containers should be maintained under grade A conditions (under the protection of first air)
  - The maintenance of unidirectional airflow should be demonstrated and qualified
  - Vial capping should be performed under at least Grade A air supply
    - Detection of improperly seated stoppers
    - Non-integral vials should be rejected prior to capping
- Critical surfaces, areas and operations should be monitored to ensure the quality of the aseptic processing environment as defined in the CCS.

Closing Discussions

- CCS implementation
  - What manufacturers should prepare to implement the CCS?
  - Whether manufacturers should have a formalized CCS document?
- The adoption of innovative technologies to increase the protection of products
  - Whether manufacturers should retrofit their existing equipment with new technologies, or build entirely new lines with these technologies?
    - Compliance status and regulatory requirements
    - Impact on process and product quality
  - How to implement rapid detection methods?
    - Full validation of non-compendial methods
    - What are the regulatory expectations?

Closing Discussions

- Implementation of Annex 1 in the US
  - Annex 1 is largely aligned with FDA's guidance for sterile drug manufacturing
  - Will the FDA enforce EU's GMPs Annex 1 in the US?
    - Have their own national laws and guidances
    - Are not obligated to comply with Annex 1
  - For similar reasons, FDA will not be enforcing PUPSIT
    - PUPSIT continues to be a challenge.
    - FDA's guidance provides risk based approaches to filter integrity testing
- How should manufacturers be prepared for inspections by different HAs?

Contact Information

Zhihao Peter Qiu
Roche/Genentech
600 Massachusetts Avenue, #300
Washington, D.C.
Phone: 240-672-8890
qiu.zhihao@gene.com