Question-based Review (QbR) for Sterility Assurance of Aseptically Processed Products: Quality Overall Summary Outline

Module 2.3: Quality Overall Summary

2.3.S DRUG SUBSTANCE

Is the drug substance sterile? If so, what is the design space for the manufacture of the sterile drug substance and have all of the relevant processes been validated? (Note: Please see below in "2.3.P Drug Product", as needed, regarding detailed questions to be addressed in this section which may be applicable to the manufacture of a sterile drug substance.)

2.3.P DRUG PRODUCT

2.3.P.1 Description of the Composition of the Drug Product

- **Description of drug product**
  What is the final dosage form and route(s) of administration?
- **Drug product composition**
  What is the composition of all drug product configurations?
- **Description of container/closure system**
  What is/are the primary container/closure system(s) for all drug product configurations?

2.3.P.2 Pharmaceutical Development

2.3.P.2.5 Microbiological Attributes

- **Container/Closure and Package integrity**
  How was the container/closure system for the drug product validated to function as a barrier to microbial ingress?
- **Preservative Effectiveness**
  If the drug product (whether preserved or inherently antimicrobial) is intended for multi-dose administration, how was the antimicrobial effectiveness demonstrated for the drug product?
- **Reconstitution, Dilution and Storage**
  Is the drug product packaged as single-use/dose, multi-dose, and/or pharmacy bulk?
  What are the labeling instructions for reconstitution and further product dilution with regard to diluents used and storage conditions?
  If the drug product is reconstituted (or further diluted) and stored prior to administration, what studies were conducted to demonstrate that the drug product does not support microbial growth over the storage periods/conditions described in labeling?
  If the drug product is a pharmacy bulk product, what are the labeling instructions for product entry and dispensing?
  If the drug product is a pharmacy bulk package and the labeling indicates that the drug product may be dispensed over a time period

greater than four hours after initial closure entry, what studies were conducted to support the extended dispensing period?

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturers

Where is the drug product manufactured and where will finished product release and stability testing be performed?

2.3.P.3.3 Description of the Manufacturing Process and Process Controls

How will the drug product manufacturing process be designed for commercial production?

ASEPTIC FILL MANUFACTURING PROCESS

- **Building and facilities**

  Where is the drug product manufactured within the proposed facility and specifically where does aseptic processing occur?

  How are the areas specifically used for the manufacture of the drug product designed so as to reduce the risk of product contamination?

  What major equipment will be used for commercial production of the drug product and where is the equipment located?

- **Overall manufacturing operation**

  What is the scientific justification for selecting aseptic processing for this drug product?

  What is the overall design for the manufacturing process for the drug product? What are the critical operations during which the sterile bulk drug solution or equipment contact surfaces are exposed to the manufacturing environment?

- **Sterilization/Depyrogenation of containers, closures, equipment and components**

  COMPONENT DEPYROGENATION

  What is the design space of the container/closure depyrogenation processes for commercial production and what are the critical parameters for each container/closure depyrogenation process?

  How will the critical parameters of each depyrogenation process be monitored and controlled during commercial production?

  What is the requalification/ revalidation program for each container/ closure component depyrogenation process?

  COMPONENT STERILIZATION

  What is the design space of container/closure sterilization processes for commercial production and what are the critical parameters for each container/closure sterilization process?

  How will the critical parameters of each container/closure sterilization process be monitored and controlled for commercial production?

  What is the requalification/revalidation program for each container/closure sterilization process?

  EQUIPMENT STERILIZATION

  What is the design space of each relevant bulk drug or product contact equipment sterilization process for commercial production and what are the critical parameters for these processes? How will the critical

parameters of each sterilization process for all relevant product contact equipment be monitored and controlled for commercial production? What is the requalification/revalidation program for the sterile bulk drug or product contact equipment sterilization process(es)?

- **Environmental monitoring**
  How is the environmental monitoring program designed to detect microbiological quality of critical manufacturing areas, processes, equipment, components, raw materials, bulk drug, and personnel? What is the action plan implemented in the event that any alert and/or action level is exceeded?

2.3.P.3.5 Process Validation and/or Evaluation

ASEPTIC FILL MANUFACTURING PROCESS

- **Drug product solution filtration**
  What is the design space of how each drug product solution/fluid stream is subjected to sterilizing filtration during commercial production to ensure the removal of microorganisms without adversely affecting product quality?
  How was the design space for each sterilizing-grade filter and associated drug product solution/fluid stream validated to demonstrate bacterial retention under simulated process conditions?
- **Holding periods**
  What holding periods and conditions are included in the design space of the manufacturing process during commercial production which are intended to minimize the risk of microbial contamination?
  What studies were performed to demonstrate that extended holding periods of the bulk drug solution, either after compounding and before filtration or after filtration and before aseptic filling, do not promote microbial growth?
- **Sterilization/Depyrogenation of containers, closures, equipment and components**
  COMPONENT DEPYROGENATION
  How was the design space of each component depyrogenation process validated to demonstrate thermal reproducibility, uniformity and endotoxins removal and how does it support the conditions proposed for commercial production? What is the container/closure component depyrogenation change control program in terms of validation and design space? What is the requalification program for each container/closure component depyrogenation process?
  COMPONENT STERILIZATION
  How was the design space of each component sterilization process validated to demonstrate reproducibility, uniformity and microbiological efficacy and how does it support the conditions proposed for commercial production?

What is the component sterilization change control program in terms of validation and design space? What is the requalification program for each component sterilization process?

EQUIPMENT STERILIZATION

How was the design space of each sterile bulk drug or product contact equipment sterilization process validated to demonstrate thermal reproducibility, uniformity and microbiological efficacy and how does it support the conditions proposed for commercial production?

What is the equipment sterilization change control program in terms of validation and design space? What is the requalification program for each equipment sterilization process?

- **Media fill procedures and specification**
  How has the design space for the overall commercial aseptic manufacturing process and filling for the drug product been validated?
- **Actions concerning product when media fills fail**
  What investigative activities and product disposition actions are taken when results from a media fill do not meet acceptance criteria that have been established?

2.3.P.5 Control of Drug Product

2.3.P.5.1 Specifications

What are the relevant microbiological tests, test methods, and acceptance criteria necessary for release of the finished drug product, and what were the corresponding results for the exhibit batches?

If the drug product release specification includes a test for bacterial endotoxins, how was the acceptance criterion established and calculated?

2.3.P.5.2 Analytical Procedures - See Section 2.3.P.5.1

2.3.P.5.3 Validation of Analytical Procedures

For each microbiological release test for the finished drug product, how was the analytical method validated?

2.3.P.7 Container Closure System - See Section P.1

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusion

What is the proposed drug product expiry?

2.3.P.8.2 Post-Approval Stability Protocol and Stability Commitment

What are the microbiological tests, test methods, acceptance criteria, and testing schedule in the post-approval stability protocol?

What are the post-approval commitments for the finished drug product in the stability program?

2.3.P.8.3 Stability Data

What microbiological results are available for the exhibit batch(es) placed in the current stability program?

2.3.A APPENDICES

2.3.A.2 Adventitious Agents Safety Evaluation

2.3.A.2.1 Materials of Biological Origin

Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources?

If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of prion contamination (causative agent of TSE)?

2.3.A.2.4 Viral Clearance Studies

If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

2.3.R REGIONAL INFORMATION

2.3.R.1 Executed Batch Record

How does the batch size (number of units) for the executed batch(es) compare with the batch size(s) proposed for commercial production? For each sterilization or depyrogenation process, what cycle parameters and equipment were used for the executed batch(es)? How do these compare with those proposed for commercial production?

2.3.R.2 Comparability Protocol

Is a Comparability Protocol included in the application for post approval changes that might affect sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?