

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

Questions to be completed by ANDA Sponsors for the preparation of a Sterility Assurance-Quality Overall Summary (SA-QOS):

Module 2.3: Quality Overall Summary

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?
What is the container/closure design space and change control program in terms of validation?
- **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 (Package insert and product labeling)**
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?

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?

Is parametric release in lieu of sterility testing being requested for the finished drug product?

TERMINAL MOIST HEAT STERILIZATION

- **Autoclave process and performance specifications**
What is the design space of the terminal sterilization process for commercial production and what are the critical parameters of the production terminal sterilization cycle?
- **Autoclave loading patterns**
What loading patterns are included in the sterilization process design space for the commercial terminal sterilization of the finished drug product?
- **Methods and controls to monitor production cycles**
How will the critical parameters of the terminal sterilization cycle/process be monitored and controlled during commercial production?
- **Requalification of production autoclaves**
What is the sterilization process requalification/revalidation program?
- **Reprocessing**
Will the drug product be re-processed or re-sterilized and how has the impact of any reprocessing/ re-sterilization procedure been assessed?
- **Environmental monitoring including product bioburden**
What are the in-process microbiological controls in place for monitoring the manufacturing environment and product prior to sterilization?

COMPONENT DEPYROGENATION

What is the design space of the container/closure depyrogenation process 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 loading patterns are included in the design space for each depyrogenation process for container/closure components of the finished drug product used for commercial production?

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

COMPONENT STERILIZATION

If components require individual sterilization prior to assembly and terminal sterilization of the filled drug product, what is the design space of each component sterilization process for commercial production and what are the critical parameters for each component sterilization process?

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

What loading patterns are included in the design space for each sterilization process for container/closure components of the finished drug product used for commercial production?

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

2.3.P.3.5 Process Validation and/or Evaluation

TERMINAL MOIST HEAT STERILIZATION

Has the validation data for the terminal sterilization process provided in the subject application been previously submitted and approved in another ANDA/NDA?

- **Heat distribution and penetration (including thermal monitors and effects loading)**

How was the design space of the terminal sterilization process validated to demonstrate uniformity and reproducibility of heat distribution and heat penetration and how does it support the conditions and loading patterns proposed for commercial production?

- **Microbiological efficacy of the cycle (including identification and characterization of bioburden, characterization of biological indicators)**

How was the microbial efficacy of the terminal sterilization cycle design space demonstrated to show at least a sterility assurance level (SAL) of 1×10^{-6} ? How were these validation studies designed?

What is the terminal sterilization change control program in terms of validation and design space?

- **Hold time prior to terminal sterilization**

Are there validation studies that support holding periods of the bulk solution after compounding or of the finished drug product after filling, but prior to terminal sterilization?

How were pre-sterilized bulk holding periods/conditions validated?

COMPONENT DEPYROGENATION

Has the validation data for the container/closure component depyrogenation processes provided in the subject application been previously submitted and approved in another ANDA/NDA?

How was the design space of each component depyrogenation process validated to demonstrate thermal reproducibility and uniformity and endotoxin removal and how does it support the conditions proposed for commercial production?

What is the component depyrogenation change control program in terms of validation and design space?

COMPONENT STERILIZATION

Has the validation data for the component sterilization processes provided in the subject application been previously submitted and approved in another ANDA/NDA?

If components require individual sterilization prior to assembly and terminal sterilization of the filled drug product, how was the design space of the component sterilization process validated to demonstrate thermal

reproducibility and uniformity and microbial 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?

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?

- **Sterility**
- **Pyrogen or Endotoxin**

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 - N/A for terminally sterilized products

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?