Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions

Disclaimer: These are general answers and may not be applicable to every product. Each application is reviewed individually. Each application may have unique product-specific or process-specific review issues. This document represents the Office of Generic Drugs' (OGD's) current thinking on these topics.

Submission and Format:

Q: How can the Question-based Review approach be applied to a Quality Overall Summary for an application that contains sterility assurance information?

A: The Chemistry Question-based Review (QbR) approach was designed with the expectation that applications would be organized according to the Common Technical Document (CTD) format, a submission format adopted by multiple regulatory bodies including the FDA. Firms are strongly encouraged to submit their applications in the CTD format (either eCTD or paper).

Like the Chemistry QbR-QOS, we believe the QBR approach can be used to address sterility assurance aspects of an application, and that a summary of the sterility assurance information from Module 3 may be provided in a Sterility Assurance Quality Overall Summary (SA-QOS). By answering QbR questions according to a SA-QOS outline (in Module 2, Section 2.3), firms are more likely to provide a complete summary of the sterility assurance information and facilitate a more efficient review process.

Q: Is a SA-QOS necessary for sterile product applications?

A: No, the SA-QOS is not a requirement for sterile product applications.

Q: Should separate chemistry and sterility assurance QOS documents be submitted?

A: Yes, separate QOS pdf and Word files should be submitted for both chemistry and sterility assurance sections.

Q: What should be included in the SA-QOS?

A: The SA-QOS in Module 2 (Section 2.3) is a summary of the sterility assurance information provided in Module 3. Supporting information such as validation data reports, SOPs, protocols, and batch records should <u>not</u> be included in Module 2.

Q: Should the SA-QOS be submitted electronically?

A: Yes, all QBR applications, both eCTD and paper submissions, should include an electronic SA-QOS. Do not provide separate files for each section or question. For paper submissions, it is recommended that both the electronic SA-QOS and a paper SA-QOS be included.

Q: What file format should be used for the SA-QOS?

A: For OGD QbR submissions, the electronic SA-QOS should be provided as both a pdf and a Microsoft Word file.

Q: What fonts should be used in the SA-QOS?

A: Because of FDA's internal data management systems, please only use these True Type fonts: Times New Roman, Arial, Courier New. Times New Roman is recommended as the main text font.

Q: Can color be used in the SA-QOS?

A: Yes, but applicants should ensure that the SA-QOS is legible when printed in black and white.

Q: Should the applicable QbR question be presented for each section of the QOS, followed by the applicant's answer?

A: Yes, include all the QbR questions without deletion in the SA-QOS. If a question is not applicable, answer as not applicable, with a brief justification. This also applies to multi-part questions.

Q: For amendments to applications, should the documentation consist of a revision of the SA-QOS?

A: The SA-QOS does not have to be updated after submission of the original application. However, if substantial changes are made to Module 3, then a revised SA-QOS is recommended with the changes indicated.

Q: Can the SA-QOS be submitted for both ANDAs and NDAs?

A: Yes, the SA-QOS outline is appropriate for both NDAs and ANDAs.

Q: May the SA-QOS information presented in Module 2 be submitted in lieu of the traditional Module 3 information?

A: No, the Module 2, Section 2.3 SA-QOS information may be considered an overview of the detailed data, study reports, protocols, SOPs, batch records, etc. typically submitted in Module 3.

Q: Can the SA-QOS FAQ information be used for supplemental applications?

A: Yes, the relevant QBR and FAQ information can be used for supplements.

Q: Can a DMF submission be organized according to the SA-QOS outline?

A: Yes, the relevant section headings and details as described in this SA-QOS can be used for organizing sterility assurance information in DMF submissions. CTD formats for DMFs are recommended.

Content:

Q: How is "design space" defined in terms of production and validation for a terminally sterilized drug product?

A: "Design space" as defined by ICH Q8(R1) Pharmaceutical Development is "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval."

For example, in terms of container/closure systems, the design space may include materials (container and closure type and composition), dimensions and tolerances, production assembly process parameters, and production sterilization/depyrogenation conditions (parameters and limits).

For example, in terms of sterilization and depyrogenation processes, the design space may include process parameters (both validation and commercial production), sterilization and depyrogenation equipment, process limits and acceptance criteria, load sizes, and load composition.

Q: How should DMFs be referenced?

A: If the information for a particular section is contained within a DMF and not available to the applicant, then reference the appropriate DMF for the specific process at that location in the SA-QOS. The reference should include a description of the type of information in the DMF, the DMF holder's name, the DMF number, and the submission date and page numbers/sections in the DMF containing the appropriate information. Note that LOAs should contain similar identifying information.

Q: How should studies be correctly identified in SA-QOS?

A: Any type of study that is provided in the SA-QOS should be identified with a title, report number, and date, if available.

Q: Is the current SA-QOS Outline applicable for applications for products manufactured by a terminal sterilization process other than moist heat?

A: This document only applies to products terminally sterilized by moist heat and was designed with this type of terminal sterilization process in mind. However, some of the same principles and details can apply to other processes.

Q: Will a SA-QOS Outline be made available for products manufactured by aseptic processing and not by terminal sterilization?

A: Yes, it is currently being developed and will be made available at a later date.

SUGGESTED READING

ANSI/AAMI/ISO 11135-1:2007 "Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices"

ANSI/AAMI/ISO 11137-1:2006 "Sterilization of health products – Radiation – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices"

ANSI/AAMI/ISO 11137-2:2006 "Sterilization of health products – Radiation – Part 2: Establishing the sterilization dose"

ANSI/AAMI/ISO 11137-3:2006 "Sterilization of health products – Radiation – Part 3: Guidance on dosimetric aspects"

Food and Drug Administration. "Guidance for Industry: Comparability Protocols – Chemistry, Manufacturing, and Controls Information" (Draft Guidance) February 2003

Food and Drug Administration. "Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products" February 2008

Food and Drug Administration. "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" November 1994

Food and Drug Administration. "Guidance for Industry: Q8(R2) Pharmaceutical Development" (Revision 2) November 2009

Food and Drug Administration. "Guidance for Industry: Q9 Quality Risk Management" June 2006

Food and Drug Administration. "Guidance for Industry: Q10 Pharmaceutical Quality System" April 2009

Food and Drug Administration. "Guidance for Industry: Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes" February 2010

Food and Drug Administration. "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" December 1987

Langille, S., Ensor, L., and Hussong, D. "Quality by Design for Pharmaceutical Microbiology" American Pharmaceutical Review, Volume 12 (Issue 6), pages 80-85, September/October 2009

Metcalfe, J. "Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration" American Pharmaceutical Review, Volume 12 (Issue 1), pages 84-89, January/February 2009

USP Chapters:

<1> Injections
<51> Antimicrobial Effectiveness Testing
<71> Sterility Tests
<85> Bacterial Endotoxins Test
<151> Pyrogen Test

QUALITY OVERALL SUMMARY CONTENT QUESTIONS

Review of Common Technical Document-Quality (CTD-Q) 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?

Q: What information should be presented in this section?

A: Indicate the dosage form and route(s) of administration.

Examples of dosage forms include:
Injection, solution
Injection, emulsion
Injection, suspension
Injection, powder (for solution or for suspension)
Injection, powder, lyophilized (for solution or for suspension)
Solution
Suspension
Irrigant
Ointment

Examples of routes of administration include:
Intravenous
Intramuscular
Subcutaneous
Intrathecal
Epidural
Otic
Ophthalmic
Inhalation
Irrigation
Topical

- Drug product composition

What is the composition of all drug product configurations?

Q: What information should be presented in this section?

A: For each drug product configuration, provide the quantitative composition per unit of measurement, e.g. per mL.

Include the function of each ingredient of the drug product, e.g. API, preservative, pH adjuster, solvent, etc.

Example:

Ingredient	Function	Content per mL
Total volume	--	

- Description of container/closure system

What is/are the primary container/closure system(s) for all drug product configurations?

Q: What information should be presented in this section?

A: For each drug product configuration, list each container/closure component and include description* and manufacturer. Include both primary and secondary packaging components, such as shroud, dust cover, foil overwrap, etc. Packaging components such as cartons need not be described here.

Include all the proposed manufacturers for each container/closure component to be used in commercial production. For example, if vials are acquired from two different manufacturers, then these should both be included.

Example for vial/stopper container/closure system:

Product Configuration (Strength & Fill volume/ container)	Component	Description*	Manufacturer
	Vial		
	Stopper		
	Seal		
	Vial		
	Stopper		
	Seal		

* Include product name, manufacturer's product code or part number, and features such as type, size, rubber formulation, color, etc.

Alternatively, a table listing components (formatted as above) may be used for other container/closure systems:

- Large volume parenteral (LVP): e.g. flexible bag, administration port, injection port, overwrap, etc.
- Pre-filled syringe: e.g. barrel, plunger/stopper, plunger rod, cap, needle shield, etc. Non-product contact parts should be identified.
- Ophthalmic: e.g. ophthalmic bottle, dropper, and cap
- Blow/fill/seal or form/fill/seal: resin

For complex container/closure systems, describe the components that constitute the fluid pathway, i.e. those that are in or will be in direct contact with the dosage form.

For components that are received ready for sterilization or ready for use and that are not re-processed prior to filling/commercial release, provide the name and address of the facility that performs the depyrogenation and/or sterilization process and, if applicable, cite the DMF that contains a description and validation of the depyrogenation and/or sterilization process.

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?

Q: What information should be presented in this section?

A: Provide a brief description of the method, materials and container/ closure components used for the study, controls performed, acceptance criteria, results, and conclusions. The description of the method should include:

- How the test and control units were prepared
- Number of units tested
- Nature and duration of the challenge
- Any conditions applied (e.g. vacuum, pressure)
- Method of detection and sensitivity of the test

- How positive controls were prepared and challenged

The study design should address any interface that functions as a sterile barrier and ensure that the entire fluid pathway of the drug product is assessed.

Acceptable test methods may include chemical, physical, and microbiological methods such as microbial immersion challenge, dye ingress and egress methods, yttrium ingress, helium leak testing, pressure decay leak detection, and high voltage leak detection.

Ideally, all container/closure systems proposed for commercial production should be represented in the validation study. If the container/closure components used in the study differ from those proposed for commercial production, then provide a comparative table and the rationale for their use in the study. For example, if two different vials with identical neck dimensions are used with the same stopper, then only one vial neck/stopper (interface) combination need be included in the study.

Describe what measures were taken to ensure that each container/closure system used in the study was exposed to production conditions that might impact container/closure integrity, such as maximum sterilization/depyrogenation conditions, multiple sterilization/ depyrogenation exposures, and extended storage of container/closure components (if applicable).

What is the container/closure design space and change control program in terms of validation?

Q: What information should be presented in this section?

A: If the container/closure design space has been established, then describe the design space parameters (e.g. dimensions, composition, and torque range, residual seal force, storage conditions, sterilization/ depyrogenation conditions, etc.) and corresponding acceptance criteria (including limits and ranges) which were validated for container/ closure integrity of the drug product.

Describe and provide the rationale for any potential changes that may be made within the validated design space, for which no additional validation studies are needed. Describe what criteria must be met for such changes to be considered within the validated design space. Changes made outside the design space would likely

necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

Q: What if a container/closure design space has not been established?

A: If a container/closure design space has not been established, then indicate "Not applicable" or "N/A" as the answer to this question.

Any future changes made after the application has been approved would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

- 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?

Q: What information should be presented in this section?

A: Provide antimicrobial effectiveness testing results using the drug product formulated with the preservative or antimicrobial ingredient at or below the lowest concentration that complies with the finished product release specification or stability specification (whichever is lower). Specify if the USP <51> method is used and, if not, describe the method. Include the preservative content or % label claim for the tested batch(es) and challenge organisms used.

Example:

Study/Report # and date: **Method**: USP <51> **Preservative**: **Preservative content or % label claim**:				
Organism	**Plate Counts, CFU/mL**			
	Day 0	**Day 7**	**Day 14**	**Day 28**
S. aureus (ATCC 6538)				
E. coli (ATCC 8739)				
P. aeruginosa (ATCC 9027)				
C. albicans (ATCC 10231)				
A. niger (ATCC 16404)				

Provide the finished product release and stability preservative content acceptance criteria. If the product is inherently antimicrobial, provide the acceptance criteria for the antimicrobial ingredient(s) (e.g. API).

- Reconstitution, Dilution and Storage (Package insert and product labeling)

Is the drug product packaged as single-use/dose, multi-dose, and/or pharmacy bulk?

Q: What information should be presented in this section?

A: Indicate if the product is labeled as single-use, single-dose, multi-dose, or pharmacy bulk.

Indicate if the labeling provides instructions to discard any unused portion.

If the labeling does not indicate if single-use/dose, multi-dose, or pharmacy bulk, and if the labeling does not provide instructions to discard any unused portion (which would imply single-dose/use), then indicate if the product contains sufficient volume to allow multiple doses to be removed (resulting in multiple entries into the container). In such cases, data may be requested to demonstrate antimicrobial effectiveness.

What are the labeling instructions for reconstitution and further product dilution with regard to diluents used and storage conditions?

Q: What information should be included in this section?

A: Reconstitution: Identify the fluid(s) and volume (or final product concentration) used for reconstitution, and temperature/duration storage conditions for the reconstituted product.

Further product dilution: Identify diluent(s) and dilution volume (or dilution factor or final product concentration) and temperature/duration storage conditions for further storage (if applicable) of diluted product.

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?

Q: What information should be provided in this section?

A: Provide the following information:

- Summary of test method

- Challenge organisms and challenge titers
- Product sample concentration(s) and storage conditions
- Diluent(s) tested
- Summary of results

If these studies were not performed, then provide product risk assessment or scientific justification for not performing the studies. Note that simply stating that the studies were performed or should have been performed during development of the RLD is not a valid justification for not performing studies.

Q: How is "does not support microbial growth over the storage periods/conditions described in labeling" defined?

A: *"Does not support microbial growth over the storage periods/conditions described in labeling"* is defined as $< 0.5 \log_{10}$ increase in challenge titers over incubation periods/conditions specified in labeling.

Q: What microorganisms should be tested?

A: At minimum we recommend compendial organisms. Examples can be found in USP <51> and <71>.

Q: Which diluent(s), product concentration, and storage conditions(s) should be tested?

A: Either test all diluents listed in labeling or a diluent considered worst case (most favorable for microbial growth) among those listed in labeling. If no diluents are specified in labeling, choose a diluent considered worst case (most favorable for microbial growth).

Q: Should the study results meet the acceptance criteria of compendial antimicrobial effectiveness testing?

A: No, a reduction in challenge organism titer is not necessary, only evidence that the drug product does not support growth.

Q: Should the RLD and proposed generic be tested side-by-side?

A: We recommend that RLD and generic be tested in parallel, but parallel testing is not required. Results should meet acceptance criteria of "*does not support microbial growth over the storage*

*periods/ conditions described in labeling" (as describe*d above) for reconstitution studies.

Q: May sterility testing be used to demonstrate that the drug product does not support microbial growth over the storage periods/conditions described in labeling?

A: No, in order to show that the drug product does not support microbial growth, product samples should be challenged with a panel of different species of microorganisms.

If the drug product is a pharmacy bulk product, what are the labeling instructions for product entry and dispensing?

Q: What information should be provided in this section?

A: Indicate the time period for dispensing the product and the number of entries allowed.

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?

Q: What type of study should be performed to support the extended pharmacy bulk dispensing duration?

A: Same as above for reconstitution study.

Q: Should the RLD and proposed generic be tested side-by-side?

A: We recommended that RLD and generic be tested in parallel, but do not require parallel testing. Results should meet acceptance criteria of "does not support microbial growth over the storage periods/ conditions described in labeling" (as described above) for reconstitution studies.

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturers

Where is the drug product manufactured?

Q: What information should be presented in this section?

A: Include the name and address of the facility that performs the compounding, filling, and terminal sterilization of the drug product.

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?

Q: What information should be provided in this section?

A: Provide a general summary of the manufacturing process and in-process controls from the end of compounding through terminal sterilization. Describe any steps performed to minimize bioburden prior to terminal sterilization (i.e. use of filtration and/or aseptic processing prior to terminal sterilization, component/ equipment sterilization, or use of pre-sterilized components). Indicate hold time specifications and hold conditions. (Note: Extended hold times or hold times for products that support microbial growth may necessitate additional studies to assess the microbiological quality of the bulk solution). Describe any routine procedures that are in place to test bioburden and/or container/closure integrity during commercial production, as applicable.

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

Q: What information should be provided in this section?

A: If this question is applicable and parametric release is being requested based on an NDA/ANDA previously approved for parametric release using the identical manufacturing facility, autoclave, container/closure system, critical process parameters, and load patterns, then indicate the NDA/ANDA number and supplement number (if applicable) for the approved drug product(s). Indicate the submission date(s) and approval date(s) <u>for parametric release</u> of the referenced drug product(s).

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?

Q: What information should be provided in this section?

A: Provide a description of the terminal sterilizer(s) to be used for commercial production including make, model/equipment number, and process type (saturated steam, water spray, etc.). Indicate if the process is designed as an overkill, bioburden-based, or combined bioburden/biological indicator-based process. Indicate process control parameters to be used for commercial production including time, temperature, F_0, and pressure set points and acceptance criteria (including limits and ranges), as applicable.

Q: What additional information should be provided if parametric release of the drug product is being requested?

A: Indicate the critical parameters and acceptance criteria that must be met for commercial batch release.

- Autoclave loading patterns

What loading patterns are included in the sterilization process design space for the commercial terminal sterilization of the finished drug product?

Q: What information should be provided in this section?

A: Describe autoclave loading patterns for commercial production, including the following:

  - Indication if the load sizes will range within defined minimum and maximum load sizes or if a fixed load size will be used
  - Number of drug product units per minimum, maximum, or fixed load
  - Arrangement of the drug product units within the load

- 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?

Q: What information should be provided in this section?

A: Indicate the types of monitors used and the location of each within the chamber for monitoring the critical parameters during commercial production. Indicate how the critical parameters are controlled (i.e. by a PLC or otherwise).

Q: What additional information should be provided if parametric release of the drug product is being requested?

A: The following information should be provided if parametric release is being requested for the drug product:

- Description of the load monitors
- Performance characteristics of the load monitors and a description of how these performance characteristics were evaluated
- Numbers and locations of the load monitors during commercial production
- Acceptance criteria for load monitors exposed to the terminal sterilization process
- Evaluation method to determine acceptable sterilization results for exposed load monitors

If a description of the evaluation method and performance characteristics of the load monitors has previously been submitted and approved, the NDA/ANDA number and supplement number (if applicable), submission date, and approval date for the submission that contained the relevant information may be cited.

- Requalification of production autoclaves

What is the sterilization process requalification/revalidation program?

Q: What information should be provided in this section?

A: Describe the routine requalification program for the terminal sterilizer(s) including the frequency of requalification, types of studies performed (i.e. empty chamber HD and or loaded chamber HP/BI challenge, etc.), and number of runs performed for each study type. Describe the loads to be used during requalification, if applicable.

- Reprocessing

Will the drug product be re-processed or re-sterilized and how has the impact of any reprocessing/ re-sterilization procedure been assessed?

Q: What information should be provided in this section?

A: Indicate if reprocessing or re-sterilization of the drug product is to be performed for commercial batches of the drug product. If so, then describe studies performed to assess the impact of reprocessing/ re-sterilization procedures on microbiological aspects of the drug product including container/closure integrity, hold times, and endotoxin content.

- Environmental monitoring including product bioburden

What are the in-process microbiological controls in place for monitoring the manufacturing environment and product prior to sterilization?

Q: What information should be provided in this section?

A: Provide a description of the bioburden monitoring and control program as follows: (Note that in-depth descriptions of air, surfaces, and personnel monitoring normally submitted for aseptically processed drug products are not necessary for terminally sterilized drug products.)

- Provide a description of bulk solution bioburden monitoring including at what production stage(s) the bulk is sampled for bioburden. Describe monitoring of filled units and container/closure components, as applicable.
- Indicate the alert and action levels for bioburden of the bulk solution and filled containers, if applicable.
- Indicate the alert and action levels and test frequencies for bioburden and endotoxin testing of WFI used for compounding.
- If the sterilization process uses process water that directly contacts the drug product in its container/closure system (e.g. cooling water for water overspray processes), then provide microbiological acceptance criteria for the process water.
- Describe the action plans taken and risk assessment performed in the event that any alert and/or action levels are exceeded.
- Depending on the design of the manufacturing and sterilization processes, additional information such as the heat resistance of bioburden organisms associated with the product solution, the container and closure components, and/or the facility to date, as well as a description of methods for the detection of spores and heat resistance testing of bioburden may be necessary. For example, more information may be needed for bioburden-based

or low thermal input autoclave processes than for overkill processes.

COMPONENT DEPYROGENATION

Q: Is component depyrogenation necessary for all terminally sterilized drug products?

A: The combination of the following factors should be used in determining whether or not component depyrogenation is necessary:

- Non-pyrogenic label claim
- Capacity of the container/closure components to withstand depyrogenation processes
- Component manufacturing process, component design, and depyrogenation feasibility (e.g. Blow-Fill-Seal processes)
- Route of administration

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?

Q: What information should be provided in this section?

A: Indicate how container/closure components are depyrogenated. Include the manufacturer and model number of the equipment used to perform the depyrogenation process, and critical process control parameters, and acceptance criteria (including limits and ranges, if applicable) to be used for depyrogenation of components during commercial production.

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

Q: What information should be provided in this section?

A: Indicate how the critical parameters are controlled (i.e. by a PLC or otherwise), and monitored (i.e. TCs, RTDs for dry heat).

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?

Q: What information should be provided in this section?

A: Describe loading patterns for commercial production, including the following:

- Indication if the load sizes will range within defined minimum and maximum load sizes or if a fixed load size will be used
- Number of units per minimum, maximum, or fixed load
- Arrangement of the container/closure components within the load

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

Q: What information should be provided in this section?

A: Describe the routine requalification program for each depyrogenation process, including the frequency of requalification, types of studies performed (i.e. empty chamber HD and or loaded chamber HP/EI challenge, etc.), and number of runs performed for each study type. Describe the loads to be used during requalification, if applicable.

COMPONENT STERILIZATION

Q: Is this section needed for all applications?

A: No, this section applies to components such as port tube-closure assemblies for flexible containers that are sterilized separately prior to attachment to the container during manufacture. The moist heat of the terminal sterilization process may not adequately penetrate into septated compartments within the ports, resulting in dry heat conditions. As a result, any microorganism located in these areas might not be killed during the terminal sterilization process. Therefore, ancillary sterilization of port assemblies prior to attachment to the drug product container may be necessary to achieve sufficient lethality at these sites.

Separate sterilization processes for stoppers and seals do not need to be described in this section, as these components are adequately sterilized by the terminal sterilization process.

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?

Q: What information should be supplied in this section?

A: Indicate the method of sterilization, sterilizer used, and critical parameters and acceptance criteria for sterilization of components to be used for commercial production. Include pre-sterilization bioburden acceptance criteria (including limits and ranges), if applicable.

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

Q: What information should be provided in this section for radiation sterilization processes?

A: Indicate how the critical parameters are controlled and monitored including numbers and locations of dosimeters and/or BIs, if applicable.

Q: What information should be provided in this section for dry or moist heat sterilization processes?

A: Indicate how the critical parameters are controlled and monitored including numbers and locations of TCs/RTDs.

Q: What information should be provided in this section for ethylene oxide sterilization processes?

A: Indicate how the critical parameters are controlled and monitored, including the types of monitoring devices used and their locations. Describe how residuals are monitored.

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?

Q: What information should be provided in this section?

A: Describe loading patterns for commercial production, including the following:

- Indication if the load sizes will range within defined minimum and maximum load sizes or if a fixed load size will be used
- Number of units per minimum, maximum, or fixed load
- Arrangement of the container/closure components within the load

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

Q: What information should be provided in this section?

A: Describe the routine requalification program for the component sterilization process including the frequency of requalification, types of studies performed (i.e. empty chamber HD and or loaded chamber HP/BI challenge, etc.), and number of runs performed for each study type. Describe the loads to be used during requalification, if applicable.

2.3.P.3.5 Process Validation and/or Evaluation

Note that original process validation data should be provided. However, if these data are several years old, then also provide data for the most recent available revalidation or requalification studies using the relevant equipment and relevant load/cycle.

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?

Q: What information should be provided in this section?

A: If the same validation data provided in the subject application has been provided to support the manufacturing process for an approved drug product, then provide a list of approved ANDA(s)/NDA(s) and supplement number(s) (if applicable) for which the identical process, process control parameters, container/closure system, and load patterns are used. Include the submission date(s) and approval date(s).

- 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?

Q: What information should be provided in this section?

A: Provide a summary of the heat distribution (HD) and heat penetration (HP) studies that validate the production terminal

sterilization cycle for all production loads. These data should be derived from at least 3 consecutive successful sterilization runs using the cycle parameters that are the same as the production cycle parameters or are sub-process cycle parameters. Note that the validation data in the submission should be derived from the validation studies for the sterilization of the commercial/ production load size(s) and not sterilization studies of the exhibit batch load size(s).

The following minimum details of the process are recommended:

- Dates of performance and study report numbers
- Identity of the equipment used for the validation studies
- Validation study design and rationale
- Validation and production parameters used
- Description of the container/closure system and the load size used for validation
- Identity of the solution in the containers and indication of the fill volume
- Number and location of HD and HP thermal monitors
- HD and HP acceptance criteria
- HD and HP thermal data

Some examples of the type of results that could be provided are (such information can be presented in a table format):

- Maximum variation of the reference probe from the thermocouples (TCs)
- Duration that all TCs have a temperature greater than or equal to the sterilizing temperature
- Minimum and maximum HD and HP temperatures, and corresponding TC number and/or location, achieved during the dwell phase
- Minimum and maximum F_0 values, and corresponding TC number and/or location, achieved during the dwell phase and entire sterilization cycle
- Maximum change in temperature during the dwell phase.
- Average temperature during the dwell phase

Q: What types of studies are considered to be heat distribution and heat penetration?

A: HD studies are considered to be those studies that map or monitor the heat within the air space exterior to the items in a loaded autoclave chamber. HP studies are considered as those studies that map or monitor the temperature within (interior) the load (i.e., within the solution in the specific container). HD and HP studies may be conducted concurrently with the microbial efficacy studies. In the study design rationale, clarify how HD and HP were assessed and clearly indicate the data specific for HD monitoring relative to HP monitoring.

Q: Do the load(s)/container(s) have to be the same as production?

A: No, the load size(s) can be the same as the production load(s), can bracket production load size(s), or can be worst-case when compared to the production load size(s). Likewise the container chosen for validation can be representative of the container of the drug product if it has been determined that the representative container would present the same or a worst-case challenge to the sterilization cycle. If alternate loading patterns or container/closure size will be used for validation, then provide a rationale and justification.

Q: Should empty chamber temperature mapping study data also be included in the submission?

A: Yes, it is recommended that temperature mapping studies of the empty autoclave chamber be performed to identify cold spots and demonstrate heat reproducibility and heat uniformity. A brief description of those studies and a brief summary of the results should be provided. At a minimum, provide a discussion of any cold spots.

Q: What if multiple autoclaves will be used for production terminal sterilization of the drug product?

A: If multiple autoclaves will be used for production, it is acceptable to validate the terminal sterilization process in one autoclave and then use several additional qualified autoclaves for the production terminal sterilization process without the need for submission of separate validation studies for the other autoclaves if each of the following conditions is met:

- If the additional autoclaves are of the same make, model, and chamber size as the autoclave validated for terminal sterilization of the drug product
- If the additional autoclaves will use the same sterilization process and controls as the autoclave validated for terminal sterilization of the drug product
- If the same sterilization loads and sterilization cycle parameters/acceptance criteria are used as those used for the autoclave validated for terminal sterilization of the drug product

If such conditions apply, then data from only one autoclave may be necessary for submission. However, periodic studies on the additional autoclaves, as defined in the requalification/revalidation plan, would be expected to be performed.

- 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?

Q: What information should be provided in this section?

A: Provide a summary of the studies performed using biological indicators (BIs) to demonstrate that the sterilization cycle results in a SAL of 1×10^{-6}. The data should be derived from at least 3 consecutive successful sterilization runs that include the use of BIs and cycle parameters that are the same as the production cycle parameters or are sub-process cycle parameters. The microbial efficacy of the sterilization cycle should be demonstrated for the production load size range.

The following minimum details are recommended (such information can be presented in a table format):

- Dates of performance and study report numbers
- Identity of the equipment used for the validation studies
- Description of the study design and rationale
- Validation and production parameters used

- Description of the container/closure system and the load size used for validation
- Identity of the solution in which the BI is immersed and the solution in all unchallenged containers in the load
- Fill volume in all containers
- Number and location of BI challenge containers within the load (cold spots previously identified should be among the locations challenged with BIs)
- Complete BI information (genus/species, carrier, manufacturer, lot, expiry, D-value (manufacturer's D-value and D-value of BI microorganisms suspended in product), population, and indication if the population was confirmed prior to use)
- Acceptance criteria for the challenge and control BIs
- Results for the challenge and control BIs

Q: Do the load(s)/container(s) have to be the same as used for production?

A: No, the load size(s) can be the same as the production load(s), can bracket production load size(s), or can be worst-case when compared to the production load size(s). Likewise the container chosen for validation can be representative of the container of the drug product if it has been determined that the representative container would present the same or a worst-case challenge to the sterilization cycle. Provide a rationale and scientific justification for alternate loading patterns or container/closure sizes.

Q: What types of biological indicators can be used?

A: The BIs selected for the studies can include microorganisms that are purchased or prepared in-house. BIs (whether purchased or prepared in-house) should at least meet the minimum standards defined in the USP. If a plant bioburden organism is chosen for the validation studies, then the same performance criteria as described for commercial indicators apply. Note that the selection of the BI should be appropriate for the specific terminal sterilization process for the drug product (e.g., use spores in suspension to assess the sterilization of liquids, rather than spore strips placed in liquid).

Q: What additional information should be provided in instances where the BI is suspended in a solution other than the drug product?

A: If the microbial efficacy studies are conducted using a solution other than the drug product filled into the containers in which the BIs will be suspended or if the BI is enclosed in an ampoule that is suspended into the container, then provide justification for the alternate solution (as appropriate) and provide D-value comparisons between the BI suspended in drug product and the BI suspended in the alternate solution.

Q: Does information regarding the identification and characterization of the bulk solution bioburden need to be included in this section?

A: If bulk solution isolates will be used to assess the efficacy of the production terminal sterilization cycle during the validation studies, then provide the information regarding these microbial isolates here. Otherwise, this information can be described with the environmental monitoring information in Section 2.3P.3.3.

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

Q: What information should be provided in this section?

A: Describe and provide the rationale for any potential changes that may be made within the validated design space, for which no additional validation studies are needed. Describe what criteria must be met for such changes to be considered within the validated design space. Changes made outside the design space would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

- 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?

Q: Are bulk hold studies necessary for products that are terminally sterilized, and if so, what information should be included in this section?

A: Depending on the drug product attributes (such as promoting growth of microorganisms), the length of holding, the conditions under which the bulk solution or filled product is held, and any additional manufacturing steps used to reduce bioburden prior to holding (such as filtration), studies may be necessary to support any holding periods of the bulk solution or of the filled drug

product that might contribute to excessive growth of microorganisms. Although the terminal sterilization process may kill microorganisms, the sterilization process cannot remove endotoxin and other released toxins and metabolites that could result from microbial growth during extended hold periods.

Validation study information should include:

- Date(s) of performance and study report numbers
- Holding conditions of time, temperature, storage vessel
- Indication if the storage vessel is sterilized prior to use
- Description of any bioburden reducing steps used prior to storage (such as pre-filtration)
- Description of sampling plan
- Description of how the samples were assessed for growth
- Acceptance criteria for the validation study

For holding periods not validated, include a scientific justification for not performing these studies.

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?

Q: What information should be provided in this section?

A: Provide a list of approved ANDA(s)/NDA(s) and supplement number(s) (if applicable) for which identical depyrogenation equipment, process control parameters, container/closure component, and load patterns are used. Include the submission date(s) and approval date(s).

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?

Q: What information should be provided in this section?

A: A summary of the studies performed to validate the production depyrogenation of each container/closure component of the drug product should be provided. The studies should demonstrate $\geq 3 \log_{10}$

reduction of endotoxin from the components. These studies should be derived from 3 consecutive successful depyrogenation runs that utilize an endotoxin indicator (EI) spiked onto the component to be tested and are performed using production cycle parameters or sub-process cycle parameters.

The following minimum details are recommended (such information can be presented in a table format):

- Dates of performance and study report numbers
- Identity of the equipment used for the validation and production
- Description of the study design and rationale
- Validation and production parameters
- Description of the component(s) and the load size(s) used in validation
- Number and location of challenge EIs within the load
- Complete EI information (genus, manufacturer, lot, expiry, and amount added to component)
- Results for the challenge and control EIs
- Acceptance criteria for the validation studies

Q: Do the loads have to contain the same items as the production loads?

A: No, the component(s) of the loads for the depyrogenation study can be representative of the component(s) in the production loads (such as a worst-case vial or stopper) or can be the component of the drug product. Likewise, the load size(s) can be the same as the production load(s), can bracket the production load size(s), or can be worst-case when compared to the production load size(s). Only components that have product contact are subject to such studies (i.e., flip-off seals generally do not have contact with the drug product and therefore are not subject to validation of removal of endotoxin). Provide a rationale for the component and load size choice of the validation loads.

Q: Should thermal data be provided for a dry heat depyrogenation process?

A: Yes, for depyrogenation achieved by dry heat, it is recommended that additional information, such as the number and location of HP thermal monitors and the thermal results, be provided. For hot air ovens and tunnels, temperature mapping of the empty oven/tunnel is recommended to identify cold spots and to demonstrate heat

reproducibility and heat uniformity. At a minimum, discuss identification of any cold spots.

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

Q: What information should be provided in this section?

A: Describe and provide the rationale for any potential changes that may be made within the validated design space, for which no additional validation studies are needed. Describe what criteria must be met for such changes to be considered within the validated design space. Changes made outside the design space would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

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?

Q: What information should be provided in this section?

A: Provide a list of approved ANDA(s)/NDA(s) and supplement number(s) (if applicable) for which identical sterilization equipment, process control parameters, container/closure component, and load patterns are used. Include the submission date(s) and approval date(s).

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?

Q: Is this section necessary for all applications?

A: No. This section applies to components such as port tube-closure assemblies for flexible containers that are sterilized separately prior to attachment to the container during manufacture. The moist heat of the terminal sterilization process may not adequately penetrate into septated compartments within the ports.

Separate sterilization processes for stoppers and seals on the container of the finished drug product that will be subject to the terminal sterilization cycle do not need to be described in this section, as these

components are adequately sterilized by the terminal sterilization process.

Q: What information should be provided in this section?

A: A summary of the studies performed to validate the production sterilization of a component of the container/closure system of a terminally sterilized drug product that may not achieve a sterility assurance level of 1×10^{-6} during the production terminal sterilization process should be provided. Data should be derived from at least 3 consecutive successful sterilization validation runs using cycle parameters that are the same as the production cycle parameters or are sub-process cycle parameters.

The following minimum details are recommended (such information can be presented in a table format):

- Dates of performance and study report numbers
- Identity of the equipment used for the validation studies
- Description of the study design and rationale
- Validation and production parameters
- Description of the load composition and load size or density used for validation
- Number and location of process monitoring devices in the validation load (physical and biological, as appropriate)
- Acceptance criteria for the validation studies
- Complete BI information (if applicable) (genus/species, carrier, manufacturer, lot, expiry, D-value population, and indication if the population was confirmed prior to use)
- Results from physical and biological monitoring devices, as appropriate

Q: What additional information should be provided for radiation sterilization processes?

A: For radiation sterilization processes, include additional details from dose-auditing, dose-verification, and dose-mapping studies. If applicable, indicate the appropriate AAMI/ANSI/ISO technical documents used for the validation studies. Note that use of a BI for radiation sterilization validation studies is optional.

Q: What additional information should be provided for dry or moist heat sterilization processes?

A: For dry heat or moist heat sterilization processes (e.g., by tunnels, ovens, and autoclaves), the use of BIs is recommended, and data from BI, HD, and HP studies should be provided. In addition, it is recommended that separate temperature mapping studies of the empty chamber/tunnel be performed to identify cold spots and to demonstrate heat reproducibility and heat uniformity. At a minimum, discuss cold spots.

Q: What additional information should be provided for ethylene oxide sterilization processes?

A: For ethylene oxide (EO) sterilization processes, the use of BIs is recommended, and BI and thermal results should be provided. Details from monitoring the time, temperature, humidity, and EO concentration in the pre-conditioning, dwell, and aeration phases should be discussed. In addition, indicate the acceptable levels of EO residuals after the appropriate aeration period.

Q: Do the loads have to contain the same items as the production loads?

A: No, the components in the study can be representative of the production component(s) (such as a worst-case port tube assembly) or can be the production component for the drug product. Likewise, the load size(s) can be the same as the production load(s), can bracket production load size(s), or can be worst-case when compared to the production load size(s). Provide a rationale for choice of the validation loads.

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

Q: What information should be provided in this section?

A: Describe and provide the rationale for any potential changes that may be made within the validated design space, for which no additional validation studies are needed. Describe what criteria must be met for such changes to be considered within the validated design space. Changes made outside the design space would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

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?

Q: How should this information be presented?

A: The following table is an **example** of how the information may be presented. Only the applicable microbiological tests need be included in the table.

Test	Test Method	Acceptance Criteria	Exhibit Batch # Results
Endotoxin *(if applicable)*			
Sterility			

Q: If parametric release is proposed for the drug product, what information should be included in this section?

A: The designated critical process parameters for parametric release, including the sterilization load monitor, and corresponding acceptance criteria for all critical process parameters should be presented in this section. Also include a reference to the location in Module 3 of the revised proposed finished product specifications or Certificate of Analysis(es) that indicate parametric release and the proposed Master Batch Records containing parametric release information.

Note that the product release specifications and/or Certificate of Analysis(es) for the finished drug product should be modified to signify that parametric release is being used in lieu of sterility testing for commercial product release. These modifications should include commitment statements (such as indication that use of the sterility test will not be permitted for lot release when critical release criteria are not achieved) and a list of or reference to the critical process parameters and associated acceptance criteria.

For further information on how to submit applications for products proposed for parametric release, refer to the document, "Guidance for Industry: Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes."

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

Q: What information should be considered when calculating the endotoxin acceptance criterion?

A: Consider the following in calculating the endotoxin acceptance criterion:

- Greatest exposure/ maximum dose, among all indications, that a patient could conceivably receive in a one-hour period if dosed according to the package insert.
- Agency-established exposure limits:
  - For products administered by intravenous, intramuscular, or subcutaneous route, not more than (NMT) 5.0 EU/kg/hr; however, if the product is administered on a body surface basis, then NMT 2.5 EU/kg/hr
  - For products administered by intrathecal or epidural route, NMT 0.2 EU/kg/hr
- Patient population (adult vs. pediatric vs. neonate)

Q: If a product has an endotoxin acceptance criterion listed in a USP monograph, must the application specify the same acceptance criterion?

A: No, a risk-based approach should be used (considering maximum drug dose per body weight or body surface area, route of administration, established Agency limits for endotoxin exposure, and **current** drug product labeling) in calculating the endotoxin acceptance criterion.

Note: Compendial endotoxin acceptance criteria may not reflect dosage and administration information specified in current labeling.

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?

- Pyrogen or Endotoxin

  Q: What information should be provided for endotoxin testing?

  A: Provide the endotoxin test validation information including the following:

- Description of endotoxin test method or reference to compendial method (including a description of how the test sample is prepared)
- MVD calculations
- Determination of noninhibitory concentration
- Inhibition/enhancement data
- Routine test dilution used for product release testing

Q: What information should be provided for other detection methods?

A: Provide a brief description of the assay method and justification of acceptance criteria or reference to compendial method and method validation (if applicable).

- Sterility

Q: What information should be provided for sterility testing?

A: Provide the sterility test validation information (method suitability test) including the following:

- Description of sterility test method or reference to compendial method (including a description of how the test sample is prepared)
- Bacteriostasis/fungistasis test validation data, including enumeration of the challenge inocula
- Growth promotion data
- Demonstration of equivalency to compendial method (if method significantly differs from compendial method)

Q: Should sterility test validation be included for a product for which parametric release is proposed?

A: Yes, because the data is needed for the evaluation of exhibit batch sterility test results.

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?

Q: What Microbiology-related information should be provided in this section?

A: Provide a statement indicating the proposed 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?

Q: What information should be provided in this section?

A: Provide the post-approval stability commitment.

Provide the microbiological tests, test methods, acceptance criteria, and testing schedule for the post-approval stability program.

The following tables are **examples** of how this information may be presented. Only the applicable microbiological tests need be included in each table.

Test	Test Method	Acceptance Criteria
Endotoxin		
Sterility		
Container/Closure Integrity		

Stability storage conditions:_____

Test	Time (Months)								
	0	**3**	**6**	**9**	**12**	**15**	**18**	**24**	**36**
Endotoxin	X				X			X	X
Sterility	X								
Container/Closure Integrity	X				X			X	X

Q: What additional information needs to be provided if container/closure integrity is performed in lieu of sterility testing?

A: If container/closure integrity testing is used in lieu of sterility testing, then provide container/closure integrity test validation (if the method for container/closure integrity testing for the stability program differs from what is provided in Section 2.3.P.2.5).

Q: How should the stability test stations be described for products for which parametric release is proposed?

A: Specify parametric release for Time = 0 months, and container/closure integrity testing (or sterility testing) for subsequent test stations.

2.3.P.8.3 Stability Data

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

Q: What information should be presented in this section?

A: For stability batches analyzed to date, present a summary of any microbiological test results such as container/closure integrity, sterility, and bacterial endotoxin (if applicable).

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?

Q: What materials are considered of "biological origin or derived from biological sources"?

A: "Biological origin or derived from biological sources" includes any animal tissues or tissue culture, cell culture, or any processed animal material used to manufacture culture/fermentation media.

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)?

Q: What type of documentation should be provided?

A: Provide a risk assessment of the starting material source and drug substance / drug product processing which includes documentation or statements indicating any of the following:

- The drug substance starting material is obtained from non-TSE/BSE animals/herds/countries.
- The animal-derived materials are processed using dedicated equipment.
- The source animal is not susceptible to TSE agents.

- Processing steps during manufacture are known to inactivate TSE agents

If this information is contained in a DMF, then cite the DMF that contains the appropriate documentation.

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?

Q: How should this information be presented in this section?

A: The following table is an **example** of how the information may be presented (for two executed batches):

	Executed Batches		**Commercial Batch**
Batch #			--
Bulk Volume/Weight			
# Containers Filled			

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?

Q: What information should be provided in this section?

A: Indicate the sterilization/depyrogenation process parameters and cycle numbers, and corresponding equipment used for manufacturing the exhibit batches (or alternatively include references to SOPs), and reference the location of this information in the batch records. If parameters, cycles, or equipment differ from those intended for production, an explanation should be provided. A comparison of exhibit batch and commercial production equipment may be provided in a table format.

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?

Q: What information should be presented in this section?

A: Describe the anticipated post approval change, and include the following:

- Comparison of the change proposed in the Comparability Protocol versus what is proposed in the relevant sections of the application
- Potential impact on sterility assurance
- Summary of the Comparability Protocol including the following:
    - Test methods and analytical procedures that will be used
    - Acceptance criteria that will be achieved to assess the effect of the changes
    - Description of data to be supplied
    - Validation study designs
    - Proposed reporting category for implementation of the proposed change

Include the detailed Comparability Protocol in Module 3.