Guideline for Sterilization Process Validation

(Date:1995-11-01)

Chapter I. INTRODUCTION

According to the GMP regulations, to avoid microbiological contamination on aseptic products, a manufacturer must set up and exactly comply with the documented manufacture process. This documentation must include the validation of all sterilization process.

The efficacy of a given sterilization process for a specific drug product is evaluated on the basis of a series of protocols and scientific experiments designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product.

Regardless of whether the applicant uses terminal sterilization or aseptic processing to manufacture a drug product that is purported to be sterile, the information about the validation of that process should be submitted for all types of sterilization.

Whether a product is sterilized by a terminal sterilization process or by an aseptic filling process, the efficacy of the sterilization process may be validated without the manufacture of three production batches.

Sterilization process validation data, however, should be generated using procedures and conditions that are fully representative and descriptive of the procedures and conditions proposed for manufacture of the product in the application.

This document is intended to provide guidance for the submission of information and data in support of the efficacy of sterilization processes in drug applications. This document will be used as a reference when the manufacturers execute validation on the aseptic drug products.

Chapter Ⅱ. TERMINAL MOIST HEAT STERILIZATION PROCESSES

Section 1. Description of the Process and Product

1. The Drug Product and Container-Closure System

Descriptions of the drug product and the container-closure system (s) to be sterilized (e.g., size (s), fill volume, or secondary packaging).

2. The Sterilization Process

(1)A description of the sterilization process used to sterilize the drug product in its final container-closure system, as well as a description of any other sterilization process (es) used to sterilize delivery sets, components, packaging, bulk drug substance or bulk product, and related items.
(2) Information and data in support of the efficacy of these processes should also be submitted. (See also chapter Ⅱ 2. and chapter Ⅱ 3. Of this guidance.)

3. The Autoclave Process and Performance Specifications

(1)A description of the autoclave process, including pertinent information such as cycle type (e.g., saturated steam, water immersion, and water spray), including the manufacturer and model, of the autoclave.
(2)A description of performance specifications (e.g., temperature, pressure, time, and minimum and maximum FO) . Identify the autoclave(s) to be used for production sterilization.

4. Autoclave Loading Patterns

A description of representative autoclave loading patterns should be provided.

5. Methods and Controls to Monitor Production Cycles
Methods and controls used to monitor routine production cycles (e.g., thermocouples, pilot bottles, and biological indicators) should be described, including the number and location of each as well as acceptance and rejection specifications.

6. Requalification of Production Autoclaves
A description of the program for routine and unscheduled requalification of production autoclaves, including frequency, should be provided.

7. Reprocessing
A description and validation summary of any program that provides for reprocessing (e.g., additional thermal processing) of product should be provided. Please note that the stability program is also affected by additional thermal processing.

Section 2. Thermal Qualification of the Cycle

1. Heat Distribution and Penetration Studies
(1)Heat distribution and penetration study protocols and data summaries that demonstrate the uniformity, reproducibility, and conformance to specifications of the production sterilization cycle should be provided.
(2) Results from a minimum of three consecutive, successful cycles should be provided to ensure that the results are consistent and meaningful.

2. Thermal Monitors
The number of thermal monitors used and their location in the chamber should be described. A diagram is helpful.

3. The Effects of Loading on Thermal Input
(1)Data should be generated with minimum and maximum load

to demonstrate the effects of loading on thermal input to product. Additional studies may be necessary if different fill volumes are used in the same container line.
(2)Data summaries are acceptable for these purposes. A summary should consist of, for example, high and low temperatures (range), average temperature during the dwell period, minimum and maximum FO values, and dwell time, run date and time, and identification of the autoclave(s) used.
(3)These data should have been generated from studies carried out in production autoclave(s) that will be used for sterilization of the product that is the subject of the application.

Section 3. Microbiological Efficacy of the Cycle

Validation studies that demonstrate the efficacy (lethality) of the production cycle should be provided. A sterility assurance of 10-6 or better should be demonstrated for any terminal sterilization process. This level of sterility assurance should be demonstrated
for all parts of the drug product (including the container and closure, if applicable), which are claimed to be sterile.
The specific type of study and the methods used to carry out the study (or studies) are product and process specific and may vary from manufacturer to manufacturer. In general, the following types of information and data should be provided.

1. Identification and Characterization of Bioburden Organisms

The amount and type of information supplied may be dependent on the validation strategy chosen. For example, more information may be needed for bioburden-based autoclave processes than for overkill processes.
Information concerning the number, type, and resistance of bioburden organisms may be necessary, including those organisms associated with the product solution and the container

and closure.
Describe the methods and results from studies used to identify and characterize bioburden organisms. It may be necessary to identify the most heat-resistant bioburden organisms.

2. Specifications for Bioburden
(1)Specifications (alert and action levels) for bioburden should be provided.
(2)A description should be included of the program for routinely monitoring bioburden to ensure that validated and established limits are not exceeded (e.g., frequency of analysis and methods used in bioburden screening).

3. Identification, Resistance, and Stability of Biological Indicators
(1) Information and data concerning the identification, resistance (D and Z values), and stability of biological indicators used in the biological validation of the cycle should be provided.
(2) If biological indicators are purchased from a commercial source, it may be necessary to corroborate the microbial count and resistance, and provide performance specifications.

4. The Resistance of the Biological Indicator Relative to That of Bioburden
(1) A description of characterizing the resistance of the biological indicator relative to that of bioburden may be necessary.
(2) Resistance in or on the product (i.e., in the product solution or on the surface of container or closure parts or interfaces) should be determined as necessary.
(3) If spore carriers are used the resistance of spores on the carrier relative to that of directly inoculated product should be determined, if necessary.

5. Microbiological Challenge Studies
Microbiological validation studies should be submitted that demonstrate the efficacy of the minimum cycle to provide a

sterility assurance of 10-6 or better to the product under the most difficult to sterilize conditions (e.g., the most difficult to sterilize load with biological indicators at microbiological master sites or in master product or both). Use of a microbiological master product or site should be supported by scientific data. Microbiological master sites or solutions are those sites or solutions in which it is most difficult to kill the biological indicator under sterilization cycles that simulate production conditions.

Section 4. Microbiological Monitoring of the Environment

The establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures,in-process materials, and drug products conform to appropriate quality standards. Therefore, a microbiological monitoring program for production areas along with a bioburden-monitoring program for components and process water should be established. Process water includes autoclave-cooling water. Applicants should provide information concerning this program. Frequency, methods used, action levels, and data summaries should be included. A description of the actions taken when specifications are exceeded should be provided.

Section 5. Container-Closure and Package Integrity

1. Simulation of the Stresses from Processing
Experimental designs should simulate the stresses of the sterilization process, handling, and storage of the drug and their effects on the container-closure system. Physical, chemical, and microbiological challenge studies may be necessary.

2. Demonstrate Integrity Following the Maximum Exposure
(1)Container-closure integrity should be demonstrated on product units that have been exposed to the maximum sterilization cycle(s).
(2)If a product is exposed to more than one process, then exposure to the maximum cycle of all processes should be incorporated into the study design.

3. Multiple Barriers
Each barrier that separates areas of the drug product claimed to be sterile should be separately evaluated and validated.

4. The Sensitivity of the Test
The sensitivity of the experimental method used for container-closure integrity testing should be specified and provided.

5. Integrity over the Product Shelf Life
Microbial integrity of the container-closure system should be demonstrated over the shelf life of the product.

Section 6. Bacterial Endotoxins Test and Method

The bacterial endotoxins test used for the product should be described. The description should include qualification of the laboratory, inhibition and enhancement tasting and results, determination of noninhibitory concentration and maximum valid dilution.

Section 7. Sterility Testing Methods and Release Criteria
1.Sterility test methods should be described and should include the protocol for the selection of representative units during

production.
2.Testing performed within barrier systems should be described.
3.Information concerning validation of the barrier system may be necessary.

Chapter Ⅲ. OTHER TERMINAL STERILIZATION PROCESSES

Although the information above (Chapter II Section 1 through Section7 of this guidance) directly addresses moist heat processes, the same type of information would pertain to other terminal sterilization processes used singly or in combination to sterilize a drug product.
The types of information outlined are, in general, also applicable to ethylene oxide and radiation (gamma and electron beam). These other processes should be addressed as each applies to the drug product, sterile packaging and in-process sterilization of components. Examples of such information might include: descriptions of loading configurations; qualification and validation of master load configurations; determination and validation of the efficacy of the minimum cycle to provide sterility assurance at the product master sites; requalification of the cycle; provisions for resterilization; specifications and monitoring program for product bioburden; and container-closure integrity. Additional information relating to the effects of the sterilization process on the chemical and physical attributes of the drug substance or drug product may be applicable.

Section 1. Ethylene Oxide

1. Sterilizer
The sterilizer(s) and controlled site(s) for prehumidification and aeration of the product load should be described (A diagram is helpful).

2. Cycle Parameters
(1) The parameters and limits for all phases of the cycle, e.g., prehumidification, gas concentration, vacuum and gas pressure cycles, exposure time and temperature, humidity, degassing, aeration, and determination of residuals should be specified.
(2)Specific procedures used to monitor and control routine production cycles to assure that performance is within validated limits should be provided.

3. Microbiological Methods
The microbiological methods (growth medium, incubation temperature, and time interval) for cultivating spores from inoculated samples during validation experiments should be described as well as the microbiological methods used as part of routine production cycles.

4. Stability
The program for monitoring the stability of packaging and the integrity of the container-closure system barrier over the claimed shelf life should be described.

Section 2. Radiation

1. The Facility and the Process
(1)The radiation facility should be identified (A diagram is helpful).
(2) The radiation source, method of exposure (i.e., movement through the irradiator), and the type and location of dosimeters used to monitor routine production loads should be described. If the low dose site is not used for routine monitoring, data that shows the dose relationship between the two sites should be provided.

2. The Packaging of the Product
The packaging of the drug product within the shipping carton and within the carrier should be described.

3. Multiple-Dose Mapping Studies
Multiple-dose mapping studies for identification of low and high dose sites and demonstration of uniformity and reproducibility of the process should be described.

4. Microbiological Methods and Controls
The microbiological methods and controls used to establish, validate, and audit the efficacy of the cycle should be described.

5. Monitoring Stability
The program for monitoring the stability of packaging and the integrity of the container-closure system barrier over the claimed shelf life should be described.

Chapter Ⅳ. ASEPTIC FILL MANUFACTURING PROCESSES

Section 1. Buildings and Facilities

A brief description of the manufacturing building and facilities should be provided. The following information should be included:

1. Floor Plan
(1)A floor plan of the areas holding the aseptic filling facilities including preparation and holding areas, filtering and filling areas, and gowning rooms should be included.
(2) Class 100, Class 10,000, Class 100,000 should be identified.
(3)Isolators or barrier systems should be identified.

2. Location of Equipment
(1)The placement of all critical equipment, including, but not limited to, laminar flow hoods, autoclaves, lyophilizers, and filling heads, should be identified.

(2) Equipment within barrier or isolation systems should be noted.

Section 2. Overall Manufacturing Operation

The overall manufacturing operation including, for example, material flow, filling, capping, and aseptic assembly, should be described.

The normal flow (movement) of product and components from formulation to finished dosage form should be identified and indicated on the floor plan described above.

The following information should be considered when describing the overall manufacturing operation:

1. Drug Product Solution Filtration

(1)The specific bulk product solution filtration processes, including tandem filter units, prefilter, and bacterial retentive filters, should be described.

(2)A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product. Any effects of the filter on the product formulation should be described, e.g., adsorption of preservatives or active drug substance, or extractable

2. Specifications Concerning Holding Periods

GMP Regulations requires, in part, when appropriate, the establishment of time limits for completing each phase of production to ensure the quality of the drug product. Therefore, specifications concerning any holding periods between the compounding of the bulk drug product and its filling into final containers should be provided. These specifications should include, for example, holding tanks, times, temperatures, and conditions of storage. Procedures used to protect microbiological quality of the bulk drug during these holding periods should be indicated. Maintenance of the microbiological quality during holding periods may need verification.

3. Critical Operations
The critical operations that expose product or product contact surfaces to the environment (such as transfer of sterilized containers or closures to the aseptic filling areas) should be described. Any barrier or isolation systems should be described.

Section 3. Sterilization and Depyrogenation of Containers, Closures, Equipment, and Components

The sterilization and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be described.
A description of the validation of these processes should be provided including, where applicable, heat distribution and penetration summaries, biological challenge studies (microbiological indicators and endotoxin) and routine monitoring procedures.
Validation information for sterilization processes other than moist heat should also be included.
Methods and data (including controls) demonstrating distribution and penetration of the sterilant and microbiological efficacy of each process should be submitted. (See Chapter II)

1. Bulk Drug Solution Components That are Sterilized Separately
If the bulk drug solution is aseptically formulated from components that are sterilized separately, information and data concerning the validation of each of these separate sterilization processes should be provided.

2. Sterilization Information in the Batch Records
The completed batch record supplied with the application should identify the validated processes to be used for sterilization and depyrogenation of any container-closure components. This information may be included in the batch record by reference to

the validation protocol or SOP.

Section 4. Procedures and Specifications for Media Fills
The procedures and specifications used for media fills should be described.
Summaries of results for validation using the same container-closure system and filling process that is to be used for the product should be described.
Any procedural differences between the media fill and the production process should be indicated.
A summary of recent media fill results, including failures, should be provided.
These data should be obtained using the same filling line(s) that are to be used for the drug product.
The following are recommended to be included with the data summary for each media fill run described
1. The filling room
Identify the aseptic filling area used and relate this to the floor plan provided in Chapter IV Section 1.1 of this guidance.

2. Container-closure type and size

3. Volume of medium used in each container

4. Type of medium used

5. Number of units filled

6. Number of units incubated

7. Number of units positive

8. Incubation parameters
The incubation time and temperature for each group of units

incubated and specifications for any group of units subjected to two (or more) different temperatures should be specified.

9. Date of each media fill

10. Simulations
The procedures used to simulate any steps of a normal production fill should be described. This might include, for example, slower line speed, personnel shift changes, equipment failure and repair, mock lyophilization and substitution of vial headspace gas.

11. Microbiological monitoring
The microbiological monitoring data obtained during the media fill runs should be provided (see Chapter 4 section 6 of this guidance).

12. Process parameters
The parameters used for production filling and for media fills (e.g., line speed, fill volume, number of containers filled, or duration of fill) should be compared.

Section 5 Actions Concerning Product When Media Fills Fail

The disposition of product made before and after a failed media fill should be described. The description should include details of investigations, reviews, and how decisions are made to reject or release product.

Section 6 Microbiological Monitoring of the Environment

The microbiological monitoring program used during routine production and media fills should be described. The frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications and precise descriptions of the actions taken when specifications are exceeded should be included.

1. Microbiological Methods

The microbiological materials and methods used in the environmental monitoring program should be described. Methods may include sample collection, transport, and neutralization of sanitizers, incubation, and calculation of results.
The following are sources of microbial contamination and their monitoring that should be addressed, including specifications:
(1)Airborne microorganisms
(2)Microorganisms on inanimate surfaces
(3) Microorganisms on personnel
(4) Water systems
(5)Product component bioburden

2. Yeasts, Molds, and Anaerobic Microorganisms
A description of periodic or routine monitoring methods used for yeasts, molds, and anaerobes should be provided.

3. Exceeded Limits
A description of the actions taken when specifications are exceeded should be provided.

Section 7 Container-Closure and Package Integrity
1.The methods and results demonstrating the integrity of the microbiological barrier of the container-closure system should be summarized. This should include testing for initial validation. The procedures used for the stability protocol also should be described. For initial validation of microbiological integrity of container-closure systems, product sterility testing is not normally considered sufficient.

2. The sensitivity of the experimental method used for container-closure integrity testing should be specified and provided.

Section 8 Bacterial Endotoxins Test and Method

The bacterial endotoxin test used for the product should be described, if applicable. This description should include qualification of the laboratory, inhibition and enhancement testing and results, determination of noninhibitory concentration and maximum valid dilution.

Section 9 Sterility Testing Methods and Release Criteria

1. Sterility test methods should be described and should include the protocol for the selection of representative units during production.
2. For a drug product represented to be a drug recognized in an official compendium, when test methods differ significantly from official compendial test methods, a demonstration of the equivalency to the official compendial method should be provided.
3. Testing performed within barrier systems should be discussed, and information concerning validation of the barrier system may be necessary.

Chapter Ⅴ. MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY:

Section 1 Container-Closure Integrity

1.The ability of the container-closure system to maintain the integrity of its microbial barrier, and, hence, the sterility of a drug product throughout its shelf life, should be demonstrated.
2.Referencs are made to Chapter II section 5 and Chapter IV section7 of this guidance. As previously stated, sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container-closure system. Documentation of the sensitivity of the container-closure integrity test should be provided.

Section 2 Preservative Effectiveness

1.The efficacy of preservative systems inadvertently introduced during drug product use should be demonstrated at the minimum concentration specified for drug product release or at the minimum concentration specified for the end of the expiration dating period, whichever is less.

2.Since the efficacy of preservative systems is judged by their effect on microorganisms, microbial challenge assays should be performed.

3.For purposes of the stability protocol, the stability protocol, the first three production lots should be tested with a microbial challenge assay at the beginning and end of the stability period.

4.Chemical assays to monitor the concentration of preservatives should be performed at all test intervals.

5.For subsequent lots placed on stability, chemical assays may be adequate to demonstrate the presence of specified concentrations of preservatives, and such testing should be carried out according to the approved stability study protocol.

Section 3 Pyrogen or Endotoxin Testing

For drug products purporting to be pyrogen free, it is recommended that pyrogen or endotoxin tests be carried out at the beginning and end of the stability period as part of the approved stability study protocol.