

GUIDANCE DOCUMENT

REFERENCE VERSION



STERILISATION PROCESSES

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Author:

Title:	Name:
Consultant	Mark Hodkinson

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Author : Mark Hodgkinson		Date: : 08 September 2004

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1. PURPOSE

To provide guidance on the development of Sterilisation Process Validation packages to meet the Current Good Manufacturing Practice (CGMP) requirements of both the [American \(FDA references shown in blue\)](#) and [European \(EC references shown in red\)](#) regulatory bodies.

2. SCOPE

This guide is intended for the validation of sterilisation processes used in the manufacture of Finished Pharmaceuticals (Medicinal Products) and Active Pharmaceutical Ingredients (APIs).

3. INTRODUCTION

This guide contains **over 210** American and European CGMP regulatory points for consideration when developing validation packages for sterilisation processes used in the manufacture of Finished Pharmaceuticals (Medicinal Products) and Active Pharmaceutical Ingredients (APIs).

The term "points for consideration" should be emphasised. The guide is intended to present the American and European regulatory statements on this topic side by side in a single reference text. The applicability of these statements will depend on the unique system under consideration.

The points have been extracted following a detailed review of:

- over **250 regulatory texts**
- over **8,000 regulatory records**
- over **1,500 warning letter extracts**
- over **2,000 FDA 483 observations**
- **to date issues** of the FDA's **Human Drug CGMP Notes**
- the **ISPE Baseline Guide - Water and Steam Systems (First Edition, January 2001)**

Each point for consideration within the guide is supported by one or more regulatory references from which it was derived. [American references are shown in blue](#) and [European references are shown in red](#). Selected [American](#) references, available under the Freedom of Information Act, are included in full.

For ease of review the points have been collated under logical sub-headings. The author appreciates that the grouping of the points is subjective.

4. SUMMARY

"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. Data derived from experiments and control procedures allow conclusions to be drawn about the probability of nonsterile product units (sterility assurance level). Based on the scientific validity of the protocols and methods, as well as on the scientific validity of the results and conclusions, the agency concludes that the efficacy of the sterilization process is validated."

[Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products](#)
(November, 1994)

I. INTRODUCTION

A. Purpose

(para 1)

[VIP ID: 16820]

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“SIP systems for the bulk drug substance industry require considerable maintenance, and their malfunction, has directly led to considerable product contamination and recall. The corrosive nature of the sterilant, whether it is clean steam, formaldehyde, peroxide or ethylene oxide, has caused problems with gaskets and seals. In two cases, inadequate operating procedures have led to even weld failure. For example, tower or pond water was inadvertently allowed to remain in a jacket and was valved shut. Clean steam applied to the tank resulted in pressure as high as 1,000 lbs., causing pinhole formation and contamination. Review the equipment maintenance logs. Review non-schedule equipment maintenance and the possible impact on product quality. Identify those suspect batches manufactured and released prior to the repair of the equipment.

Another potential problem with SIP systems is condensate removal from the environment. Condensate and excessive moisture can result in increased humidity and increases in levels of micro-organisms on surfaces of equipment. Therefore, it is particularly important to review Environmental monitoring after sterilisation of the system.”

REG 07/01/94 GUIDE TO INSPECTIONS OF STERILE DRUG SUBSTANCE MANUFACTURERS
(July, 1994)
V. EQUIPMENT
(para 5 & 6)

5. DOCUMENTATION

- Standards or specifications for the removal of pyrogenic properties shall be written and followed for drug product containers and closures.

21 CFR PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS (April, 2003)
Subpart E-Control of Components and Drug Product Containers and Closures
21 CFR 211.94 (d)
[VIP ID: 96]

“Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.”

- Methods of testing for the presence of pyrogenic properties shall be written and followed for drug product containers and closures.

21 CFR PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS (April, 2003)
Subpart E-Control of Components and Drug Product Containers and Closures
21 CFR 211.94 (d)
[VIP ID: 96]

“Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.”

- Methods of sterilisation shall be written and followed for drug product containers and closures.

21 CFR PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS (April, 2003)
Subpart E-Control of Components and Drug Product Containers and Closures
21 CFR 211.94 (d)
[VIP ID: 96]

“Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.”

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
(November, 1994)
II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES
A. Description of the Process and Product 2.
[VIP ID: 16870]

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“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. Information and data in support of the efficacy of these processes should also be submitted. (See also sections II.B. and II.C. of this guidance.)”

The sterilisation and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be documented.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
(November, 1994)

IV. INFORMATION FOR ASEPTIC FILL MANUFACTURING PROCESSES WHICH SHOULD BE INCLUDED IN DRUG APPLICATIONS

C. Sterilization and Depyrogenation of Containers, Closures, Equipment, and Components
[VIP ID: 17290]

“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.”

- Information and data in support of the efficacy of sterilisation process(es) should be documented.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
(November, 1994)

II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES

A. Description of the Process and Product 2.
[VIP ID: 16870]

“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. Information and data in support of the efficacy of these processes should also be submitted. (See also sections II.B. and II.C. of this guidance.)”

- Validated loading patterns for dry heat sterilisers should be available to the operators.

Interpreted from GMP Trends, Issue #593, 01 Oct 2001
Manufacturing - Sterile Product Controls
Item 5
[VIP ID: 40520]

- A program for routine and unscheduled requalification of production steam sterilisers, including frequency, should be documented.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
(November, 1994)

II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES

A. Description of the Process and Product 6.
[VIP ID: 16910]

“A description of the program for routine and unscheduled requalification of production autoclaves, including frequency, should be provided.”

- There should be a written procedure describing the manual removal of a steam sterilisers memory card and transfer of the data to a PC system.

Interpreted from GMP Trends, Issue #565, 01 Aug 2000
Manufacturing - Sterile Product Controls
Item 1
[VIP ID: 16280]

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8. Steam steriliser validation protocols and SOPs should include specific load configuration patterns.

Interpreted from GMP Trends, Issue #567, 01 Sept 2000
 Manufacturing - Sterile Product Controls
 Item 1
 [VIP ID: 19040]

9. Representative steam steriliser loading patterns should be documented.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
 (November, 1994)
 II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES
 A. Description of the Process and Product
 4.
 [VIP ID: 16890]
 "A description of representative autoclave loading patterns should be provided."

10. Specifications (alert and action levels) for bioburden should be documented.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
 (November, 1994)
 II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES
 C. Microbiological Efficacy of the Cycle
 [VIP ID: 16990]
 "Specifications (alert and action levels) for bioburden should be provided. 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). The methods provided should be specific."

11. The program for routinely monitoring bioburden to ensure that validated and established limits are not exceeded should be documented (e.g., frequency of analysis and methods used in bioburden screening).

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
 (November, 1994)
 II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES
 C. Microbiological Efficacy of the Cycle
 [VIP ID: 16990]
 "Specifications (alert and action levels) for bioburden should be provided. 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). The methods provided should be specific."

12. A description and validation summary of any program that provides for reprocessing (e.g. additional thermal processing) of product should be provided.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
 (November, 1994)
 II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES
 A. Description of the Process and Product
 [VIP ID: 16920]
 "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."

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13. Steam steriliser documentation should include pertinent information such as cycle type (e.g. saturated steam, water immersion, and water spray), cycle parameters and performance specifications including temperature, pressure, time, and minimum and maximum Fo.

[Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products \(November, 1994\)](#)

II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES

A. Description of the Process and Product

3.

[VIP ID: 16880]

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

14. Specific procedures used to monitor and control routine production Ethylene Oxide cycles to assure that performance is within validated limits should be documented.

[Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products \(November, 1994\)](#)

III. OTHER TERMINAL STERILIZATION PROCESSES

A. Ethylene Oxide

2.

[VIP ID: 17160]

“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. Specific procedures used to monitor and control routine production cycles to assure that performance is within validated limits should be provided.”

15. The microbiological methods (growth medium, incubation temperature, and time interval) for cultivating spores from inoculated samples used as part of routine production cycles should be documented.

[Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products \(November, 1994\)](#)

III. OTHER TERMINAL STERILIZATION PROCESSES

A. Ethylene Oxide

3.

[VIP ID: 17170]

“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.”

16. The microbiological methods and controls used to establish, validate, and audit the efficacy of radiation sterilisation cycles should be documented.

[Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products \(November, 1994\)](#)

III. OTHER TERMINAL STERILIZATION PROCESSES

B. Radiation

4.

[VIP ID: 17220]

“The microbiological methods and controls used to establish, validate, and audit the efficacy of the cycle should be described.”

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17. There should be written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
(November, 1994)

II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES

H. Evidence of Formal, Written Procedures.

(para 1)

[VIP ID: 17120]

“Section 211.113(b) of the Code of Federal Regulations requires that written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, be established and followed. Such procedures should include validation of any sterilization process. Therefore, evidence should be provided that there are formal, written procedures describing the elements listed above and that these procedures are followed. Such evidence may consist of SOP's, listing of SOP's, and protocols submitted as part of these elements.”

6. MAINTENANCE SCHEDULES

1. Steriliser maintenance schedules should include when air filters are to be changed.

Interpreted from GMP Trends, Issue #527, 01 Jan 99

Medical Device - Manufacturing Controls

Item 4

[VIP ID: 7040]

2. Steriliser maintenance schedules should include when gas filters are to be changed.

Interpreted from GMP Trends, Issue #527, 01 Jan 99

Medical Device - Manufacturing Controls

Item 4

[VIP ID: 7040]

3. Steriliser maintenance schedules should include other routine maintenance.

Interpreted from GMP Trends, Issue #527, 01 Jan 99

Medical Device - Manufacturing Controls

Item 4

[VIP ID: 7040]

7. STERILISATION RECORDS

1. Sterilisation records should be maintained.

21 CFR PART 600--BIOLOGICAL PRODUCTS: GENERAL

(01 April 2003)

Subpart B--Establishment Standards

600.12 Records.

(c)

[VIP ID: 1860]

“Records of sterilization of equipment and supplies. Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.”

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2. Sterilisation records should include the mode of sterilisation.

21 CFR PART 600--BIOLOGICAL PRODUCTS: GENERAL

(01 April 2003)

Subpart B--Establishment Standards

600.12 Records.

(c)

[VIP ID: 1860]

“Records of sterilization of equipment and supplies. Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.”

3. Sterilisation records should include the date of sterilisation.

21 CFR PART 600--BIOLOGICAL PRODUCTS: GENERAL

(01 April 2003)

Subpart B--Establishment Standards

600.12 Records.

(c)

[VIP ID: 1860]

“Records of sterilization of equipment and supplies. Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.”

4. Sterilisation records should include the duration of the sterilisation.

21 CFR PART 600--BIOLOGICAL PRODUCTS: GENERAL

(01 April 2003)

Subpart B--Establishment Standards

600.12 Records.

(c)

[VIP ID: 1860]

“Records of sterilization of equipment and supplies. Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.”

5. Sterilisation records should be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilisation relates.

21 CFR PART 600--BIOLOGICAL PRODUCTS: GENERAL

(01 April 2003)

Subpart B--Establishment Standards

600.12 Records.

(c)

[VIP ID: 1860]

“Records of sterilization of equipment and supplies. Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.”

6. Records should demonstrate the BIs are shipped and stored within the temperature requirements.

Interpreted from GMP Trends, Issue #520, 15 Sept 98

Manufacturing - Sterile Product Controls

Item 1

[VIP ID: 6754]

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7. Device Master Records should include or refer to the location of production and process specifications to include parameters for ETO sterilisation cycles.

Interpreted from GMP Trends, Issue #563, 01 July 2000
 Medical Device - Manufacturing Controls
 Item 4
 [VIP ID: 15940]

8. Device Master Records should include or refer to the location of quality assurance procedures and specifications to include the allowable and alert limits for bioburden.

Interpreted from GMP Trends, Issue #563, 01 July 2000
 Medical Device - Manufacturing Controls
 Item 5
 [VIP ID: 15950]

9. Device Master Records should include or refer to the location of quality assurance procedures and specifications to include ETO residues.

Interpreted from GMP Trends, Issue #563, 01 July 2000
 Medical Device - Manufacturing Controls
 Item 5
 [VIP ID: 15950]

10. Steam steriliser documentation should include recording the identification, manufacturer and model of the steriliser(s) to be used for production sterilisation.

Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
 (November, 1994)
 II. INFORMATION FOR TERMINAL MOIST HEAT STERILIZATION PROCESSES
 A. Description of the Process and Product
 3.
 [VIP ID: 16880]

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

11. Charts of time, temperature, and pressure should be filed for each steam steriliser load.

GUIDE TO INSPECTIONS OF DOSAGE FORM DRUG MANUFACTURERS - CGMPR'S
 (October, 1993)
 Sterilization
 1. Methods
 (para 2)
 [VIP ID: 2676]

“If steam under pressure is used, an essential control is a mercury thermometer and a recording thermometer installed in the exhaust line. The time required to heat the center of the largest container to the desired temperature must be known. Steam must expel all air from the sterilizer chamber to eliminate cold spots. The drain lines should be connected to the sewer by means of an air break to prevent back siphoning. The use of paper layers or liners and other practices which might block the flow of steam should be avoided. Charts of time, temperature, and pressure should be filed for each sterilizer load.”

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12. The pump speed used to regulate product flow through sterilising filters should be specified in batch records.

Interpreted from GMP Trends, Issue #613, 01 Aug 2002
 Manufacturing - Sterile Product Controls
 Item 3
 [VIP ID: 47060]

13. Product flow rates through sterilising filters should be monitored during production.

Interpreted from GMP Trends, Issue #613, 01 Aug 2002
 Manufacturing - Sterile Product Controls
 Item 3
 [VIP ID: 47070]

8. VALIDATION

8.1 General

1. Sterilisation processes should be validated.

EU Guide to Good Manufacturing Practice: Annex 05 - Manufacture of Immunological Veterinary Medicinal Products (1997)
 Equipment
 24. (para 3)
 [VIP ID: 1618]

21 CFR PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS (April, 2003)
 Subpart F- Production and Process Controls
 21 CFR 211.113 (b)
 [VIP ID: 125]

“Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.”

Interpreted from GMP Trends, Issue #593, 01 Oct 2001
 Manufacturing - Sterile Product Controls
 Item 5
 [VIP ID: 40520]

Interpreted from GMP Trends, Issue #558, 15 Apr 2000
 Manufacturing Controls
 Item 7
 [VIP ID: 14870]

Interpreted from GMP Trends, Issue #587, 01 July 2001
 Manufacturing - Sterile Product Controls
 Item 5
 [VIP ID: 27970]

EU Guide to Good Manufacturing Practice: Annex 05 - Manufacture of Immunological Veterinary Medicinal Products (1997)
 Premises
 17.
 [VIP ID: 1603]

Extracted from FDA warning letter 2002-DAL-WL-02
 USA
 September 5, 2001
 [VIP ID: 41600]