



REGULATORY REQUIREMENTS OF STERILISING FILTRATION OF LIQUIDS

Dr. Christina Bruntner, Pall GmbH, Germany
Validation Specialist

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Sterile Filtration

Historical Development

- 1960th
 - "Cold sterilisation"
 - Use of asbestos and ceramic filters
 - Integrity test methods not available
 - "Sterile filtration"
 - Use of 0.45 μm filter membranes
- 1961
 - Bubble Point filter integrity test
 - Use of membrane discs

Sterile Filtration

Historical Development

- 1960th
 - FDA reports problems with 0.45 μm "sterile filters"
 - Confirmation of the passage of *Pseudomonas diminuta* (currently: *Brevundimonas diminuta*) microorganisms after bacterial challenge with $\geq 10^7$ cfu per cm^2 effective filter area

Sterile Filtration

Historical Development

- 1970th
 - "Sterile Filtration"
 - Use of 0.2 μm (0.22 μm) filter membranes
 - Data collection of bacteria retention and integrity tests by filter manufacturers
 - *Brevundimonas diminuta* as standard microorganism
- 1973
 - Forward Flow filter integrity test
 - Use for membrane filters with large filter area

Sterile Filtration

Historical Development

- 1987
 - FDA Aseptic Processing Guideline¹ for sterile drug products produced by aseptic processing
 - Incorporation of the first formal definition of the term “sterile filter” - 20 (!) years after the first report on microorganism passage through 0.45 µm filters

1 FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, 1987

Sterile Filtration

Historical Development

- 1998
 - PDA Technical Report No. 26¹ as trend-setting monograph for the validation of sterile filtration
 - Involvement of users, manufacturers and FDA (Guidance for the Industry, March 1998)



1 PDA Technical Report No. 26, Sterilizing Filtration of Liquids
Parenteral Drug Association, Inc., 1998

Sterile Filtration

Historical Development

- 2003
 - EU Guide to GMP¹ for sterile manufacture of medicinal products
- 2004
 - FDA Aseptic Processing Guidance² as a revision of the existing FDA guideline³ dating from 1987

1 EU Guide to Good Manufacturing Practice, Revision to Annex 1: Manufacture of Sterile Medicinal Products (EUDRALEX, Volume 4 - Good Manufacturing Practices - Medicinal Products for Human and Veterinary Use), 2003

2 FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, 2004

3 FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, 1987

Sterile Filtration

Historical Development

- 2008
 - Revision of **Annex 1** of the **EU Guide to GMP¹** for sterile manufacture of medicinal products
- 2008
 - Revision of **PDA Technical Report No. 26**

1 EU Guidelines to Good Manufacturing Practice, Annex 1: Manufacture of Sterile Medicinal Products (EUDRALEX, Volume 4 - Good Manufacturing Practices - Medicinal Products for Human and Veterinary Use), 2008 – Implementation in March 2009

2 PDA Technical Report No. 26, Sterilizing Filtration of Liquids, Parenteral Drug Association, Inc., 2008

Sterile Filters

Definitions (1)

- *" ... nominal pore size of 0.22 micron (or less), or with at least equivalent microorganism retaining properties (...) Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas."*

2008 EU Guidelines to GMP¹

1 EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1: Manufacture of Sterile Medicinal Products (EUDRALEX, Volume 4 - Good Manufacturing Practices - Medicinal Products for Human and Veterinary Use), 2008

Sterile Filters

Definitions (2)

- *"A filter which, when challenged with the microorganism Pseudomonas diminuta at a minimum concentration of $10^7/cm^2$ of filter surface, will produce a sterile effluent."*

1987 FDA Aseptic Processing Guidance¹

- *"A filter that, when appropriately validated, will remove all microorganisms from a fluid stream, producing a sterile effluent."*

2004 FDA Aseptic Processing Guideline²

1 FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, 1987

2 FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, 2004

Definitions

Validation

"Validation - Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

Source: FDA CDER Guideline on General Principles of Process Validation, 1987

Validation of Sterile Filters

Objective

"(...) to generate data demonstrating that the filtration process will consistently remove a high level of a standard bacterium or relevant bioburden isolate, suspended within the product (or surrogate fluid), under actual processing conditions."

EU Guidelines to GMP

Annex 1



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH


EU Guidelines to Good Manufacturing Practice

Medicinal Products for Human and Veterinary Use

Annex 1

Manufacture of Sterile Medicinal Products

February, 2008

	EUROPEAN COMMISSION ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL Consumer goods Pharmaceuticals
Brussels, 14 February 2008	
EudraLex The Rules Governing Medicinal Products in the European Union	
Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use	
Annex 1 Manufacture of Sterile Medicinal Products	
Document History	
Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to include guidance on media simulations, bioburden monitoring and capping of freeze-dried vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009 ¹

¹ Note: Provisions on capping of freeze-dried vials should be implemented by 01 March 2010.

Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel - Belgium. Telephone: (32-2) 299 11 11

EU Guidelines to GMP

Annex 1 (83)

- *"All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution."*

EU Guidelines to GMP

Annex 1 (113)

- *"The **time** taken to filter a known volume of bulk solution **and** the **pressure difference** to be used across the filter **should be determined during validation** and any significant **differences** from this during routine manufacturing **should be noted and investigated.**"*

EU Guidelines to GMP

Annex 1 (114)

- *"The same filter should not be used for more than **one working day** unless such use has been validated."*



EU Guidelines to GMP

Annex 1 (115)

- *"The filter should not affect the product by removal of ingredients from it or by release of substances into it."*



FDA Guidance for Industry

Sterile Drug Products Produced by Aseptic Processing



Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5000 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4373
<http://www.fda.gov/cder/guidance/index.htm>

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
<http://www.fda.gov/cber/guidelines.htm>
(Tel) Voice Information System at 800-835-4769 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

September 2004
Pharmaceutical CGMPs

FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice

September, 2004

(www.fda.gov/cder/guidance/5882fnl.pdf)

FDA Aseptic Processing Guidance

IX. Validation of Aseptic Processing and Sterilization

B. Filtration Efficacy

- *"Whatever filter or combination of filters is used, validation should include microbiological challenges to simulate worst case production conditions for the material to be filtered and integrity test results of the filters used for the study."*

FDA Aseptic Processing Guidance

IX. Validation of Aseptic Processing and Sterilization

B. Filtration Efficacy

- *"Filtration is a common method of sterilizing drug product solutions. A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent."*

FDA Aseptic Processing Guidance

IX. Validation of Aseptic Processing and Sterilization

B. Filtration Efficacy

- *"The microorganism **Brevundimonas diminuta** (ATCC 19146) when properly grown, harvested and used, is a common challenge microorganism for 0.2 μm rated filters because of its small size (0.3 μm mean diameter)."*

FDA Aseptic Processing Guidance

IX. Validation of Aseptic Processing and Sterilization

B. Filtration Efficacy

- *"A challenge concentration of at least 10^7 organisms per cm^2 of effective filtration area should generally be used, resulting in no passage of the challenge microorganism."*

FDA Aseptic Processing Guidance

IX. Validation of Aseptic Processing and Sterilization

B. Filtration Efficacy

- *"Factors that can affect filter performance generally include*
 - *(1) viscosity and surface tension of the material to be filtered*
 - *(2) pH*
 - *(3) compatibility of the material or formulation components with the filter itself*
 - *(4) pressures*
 - *(5) flow rates*
 - *(6) maximum use time*
 - *(7) temperature*
 - *(8) osmolality*
 - *(9) and the effects of hydraulic shock*

FDA Aseptic Processing Guidance

IX. Validation of Aseptic Processing and Sterilization

B. Filtration Efficacy

- *"Filter validation should be conducted using the worst-case conditions, such as maximum filter use time and pressure."*

PDA Technical Report No. 26

Sterilizing Filtration of Liquids



Technical Report No. 26
Sterilizing Filtration of Liquids

Revised 2008

PDA Technical Report No. 26

Sterilizing Filtration of Liquids

- 1.0 Introduction → Small changes
- 2.0 Pharmaceutical filtration, Historical Highlights → Glossary added
- 3.0 How filters work → Small changes
- 4.0 Filter selection and characterization → New edition
- 5.0 Filters use, handling and design considerations → New edition
- 6.0 Sterile filter validation/bacterial retention → Small changes
- 7.0 Integrity testing → More comprehensive
- 8.0 Filter sterilization → Small changes
- 9.0 Single use disposable systems → New

PDA Technical Report No. 26

Criteria	Filter User	Filter Manufacturer	
	Device	Membrane Disc	Device
Bacteria retention in water, saline lactose broth (SLB) with integrity test correlation in water or solvent	-	Q, L	Q
Bacteria retention in product	V*	-	-
Chemical compatibility, effects on filter integrity	V	Q	Q
Extractables	V	Q	Q
Leachables	E		
Sterilization method, effects on filter integrity	V	Q	Q
Integrity test (water or solvent)	V	Q, L	Q, L
Integrity test method selection (product)	V	-	-
Toxicity testing - USP Class VI	-	Q	Q
USP bacterial endotoxin	V	-	Q, L
USP particulate matter	E	-	Q
USP non fiber release	E	-	Q
TOC and conductivity- USP Purified Water	E	-	Q

Q=Generic validation, L=Lot release, V=Process validation, V*=Allowed on disc,

E=Reference to generic validation accepted



Life Sciences

PDA Technical Report No. 26

Section 6 – Sterile Filter Validation, Bacterial Retention

- New...
 - If there are no membranes **at or near the manufacturer specifications**, the lowest available membrane should be taken from a manufacturer lot
 - **Grouping of product families** is applicable
 - **Multiple use** of filters is not recommended
 - **Risk assessment** of process filtration parameters is shown

