Technical Report No. 26
Revised 2008
Sterilizing Filtration of Liquids

PDA Journal of Pharmaceutical Science and Technology

PDA SM
Parenteral Drug Association

2008

Supplement

Volume 62

No. S-5

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The content and views expressed in this technical report are the result of a consensus achieved by the authoring task force and are not necessarily views of the organizations they represent.

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Supplement to the
PDA Journal of Pharmaceutical Science and Technology

Vol 62, No. S-5

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1.0 Introduction

Sterilizing filtration is the process of removing microorganisms* from a fluid stream without adversely affecting product quality. *(1–4)* This technical report is intended to provide a systematic approach to selecting and validating the most appropriate filter for liquid-sterilizing filtration applications.

PDA's original Technical Report No. 26, *Sterilizing Filtration of Liquids,* published in 1998, described the use and validation of sterilizing filtration to a generation of pharmaceutical scientists and engineers. This revision of the original report was developed in response to enhancements in filtration technologies and recent additional regulatory requirements within the pharmaceutical industry. References to regulatory documents, standards and scientific publications are provided where more detail and supportive data may be found.

When membrane filters entered the market in the 1960s, 0.45 µm-rated membranes were considered "sterilizing-grade" filters and were used successfully in the sterilizing filtration of parenterals. These filters were qualified using *Serratia marcescens* as a standard bacterium for qualifying membranes used for water quality testing. In a paper published in 1960, however, Dr. Frances Bowman of the U.S. Food and Drug Administration observed a 0.45 µm "sterile-filtered" culture medium to be contaminated with an organism subsequently shown to repeatedly penetrate 0.45 µm-rated membranes in small numbers at challenge levels above 10^4-10^6 per cm^2. *(5)* This led to the development of ASTM F 838, a standard test method for evaluating sterilizing-grade membrane filters. *(6)* Challenge organisms are discussed further in **Section 6.4.**

1.1 Purpose/Scope

The primary objective of the task force has been to develop a scientific technical report on sterilizing filtration. The report does not always address region-specific regulatory expectations, but provides up-to-date scientific recommendations for use by industry and regulators in establishing a sterilizing filtration policy. This report should be considered a guide and is not intended to establish mandatory standards for sterilizing filtration. Concepts presented in this report pertain to processes in which sterilizing-grade filter performance is necessary and may not be universally applicable to all filtration processes (e.g., early stage filtration or routine bioburden). These include, but are not limited to, cell culture media, buffer, intermediate holds in aseptic process, bulk and final sterile filling.

The task force was composed of European and North American industry and regulatory professionals to provide a diverse perspective, thus ensuring that the methods, terminology and practices of sterilizing filtration presented are reflective of sound science and can be utilized globally. This report underwent an 11-week global technical peer review that included feedback from the Americas, Asia-Pacific and Europe.

*__Note:__ Sterilizing filtration is not intended to remove viruses.

2.0 Glossary of Terms

For the purposes of this technical report, the following terms are used and are accompanied by their synonyms, where applicable.

Adsorption
The retention of solutes, suspended colloidal particles or microorganisms to fluid contact surfaces, e.g., the surfaces of pores in filtration membranes.

Aseptic
Free from disease-producing microorganisms. An operation performed in a controlled environment designed to prevent contamination through the introduction of microorganisms.

Assay
Analytical method used to determine the purity or concentration of a specific substance in a mixture.

Bacteria
Single-celled, microscopic organisms typically with a cell wall and characteristic shape (e.g., round, rod-like, spiral or filamentous); lacking a defined nucleus ("prokaryotic").

Bioburden
A population of viable microorganisms in a fluid prior to sterilizing filtration. *(7)*

Bracketing Approach
A validation method that tests the extremes of a process or product. The method assumes the extremes will be representative of all the samples between the extremes. [Synonym: matrix validation.]

Bubble Point
The measured differential gas pressure at which a wetting liquid (e.g., water, alcohol, product) is pushed out of the largest pores of a wetted porous membrane and a steady stream of gas bubbles or bulk gas flow is detected. [Synonym: transition point.]

Bubble Point Test
A test to indicate the maximum pore size of a filter. The differential gas pressure at which a liquid (usually water) is pushed out of the largest pores and a steady stream of gas bubbles is detected from a previously wetted filter under specific test conditions. Used to test filter integrity with specific, validated, pressure values, wetting liquids and temperatures for specific pore-size (and type of) filters.

Cake
Solids deposited on the upstream side of filter media.

Capsule Filter
A self-contained filter device or assembly.

Cartridge Filter
A filter device requiring a housing for use.

Compatibility
Proof that no adverse interaction between the filter and the process fluid has occurred.

Diffusive Flow
The movement of a dissolved gas across a liquid-wetted membrane based on the concentration (e.g., gas pressure) differential.

Diffusive/Forward Flow Test
A test to determine the integrity of a filter. [Synonym: diffusive flow test, forward flow test.]

Direct Interception
Particles with diameters larger than the filter pore diameter that are prevented from passing through the filter.

Downstream Side (of a Filter)
The filtrate or outlet side of the filter.

Effective Filtration Area
The total surface area of the filter available to the process fluid.

Effluent
Fluid that flows out of a process step.

Endotoxin
Lipopolysaccharides from the cell walls of bacteria, the most potent of which derive from Gram-negative organisms. When injected, they are known to cause a febrile, or fever-producing reaction that can cause severe patient reactions, and on occasion, can be fatal.

Extractable
A chemical component that is removed from a material by the application of an artificial or exaggerated force (e.g., solvent, temperature or time).

Filter (noun)
A device used to remove particles from a fluid process stream that consists of a porous medium and a support structure.

Porous material through which a liquid or gas is passed to remove viable and non-viable particles. ***(6)***

Filter (verb)
To pass a fluid through a porous medium whereby bacteria or other particles are removed from the fluid.

Filterability Test
A test to determine the suitability and sizing of a filter with a given fluid.

Filter Efficiency
A measurement of how well a filter retains particles. It is usually expressed as the percentage, or ratio, of the retention of particles of a specific size by a filter.

Filter Element
The basic filter unit from which cartridges or capsules are assembled.

Filtrate
Fluid that has passed through a filter.

Filtration
The process by which particles are removed from a fluid by passing the fluid through a porous material.

Flow rate
The volumetric rate of flow of a solution, expressed in units of volume per time (e.g., L/min or g/day).

Flux
The rate of filtrate flow divided by the membrane area.

Fouling
The result of solutes blinding or blocking membrane pores. It is observed as a decrease in the flux (at constant pressure) or an increase in the filtration differential pressure (at constant flux).

Gamma Irradiation
Ionizing radiation that can be used to sterilize a material.

Gauge Pressure
Gauge pressure is the difference between a given fluid pressure and that of the atmosphere.

Hydrophilic
Literally "water loving." A filter that will wet with aqueous solutions to allow flow at a low pressure differential.

Hydrophobic
Literally "water fearing." A filter that repels aqueous and other high-surface tension fluids and therefore cannot be wetted unless subjected to a high pressure differential. When prewetted with low surface tension fluid, such as alcohol, the membrane will allow water flow at a low pressure differential.

Influent
Fluid that flows into a process step. [Synonym: feed.]

Integrity Test
A nondestructive physical test that can be correlated to the bacterial retention capability of a filter/filter assembly. ***(6)***

Leachable
A chemical component that migrates from a contact surface into a drug product or process fluid during storage or normal use conditions.

Mass Spectroscopy
An analytical test method for identifying the chemical composition of a sample by separating its gaseous component ions according to their mass and charge.

Materials of Construction
Polymers or other materials that make up the components of the filter.

Medium
In filtration, the porous material which retains particles as a fluid passes through during the process of filtration

Membrane
A thin, microporous medium used to remove particles and microorganisms from a fluid stream under pressure.

Microorganism
A microbe; a free-living organism too small to be seen by the naked eye.

Module
Filter element that is incorporated into a cartridge or capsule.

Non-fiber Releasing
Refers to a filter that does not shed fibers into the filtrate.

Particle
Any discrete unit of material structure; a discernible mass having an observable length, width, thickness, size and shape.

Particulate
Relating to, or occurring in the form of, particles.

Permeability
The degree to which a fluid will pass through a porous substance under specified pressure and temperature conditions.

Pore
The channel(s)/path(s) in a membrane through which a fluid may pass.

Porosity
The ratio of void volume to bulk volume of the filter media.

Pre-Filter
Any filter placed upstream of the final filter.

Pressure
Force applied per unit area, usually expressed as psi, mbar, kPa or kg/cm^2.

Back Pressure
Pressure applied downstream of a filter or other piece of equipment.

Differential Pressure
The difference in pressure between the upstream (feed or influent) and downstream (effluent) sides of the filter. (May be modified with the following terms: applied differential pressure, available differential pressure, clean differential pressure, dirty differential pressure, initial differential pressure or maximum differential pressure.) [Synonym: delta P (Δ P), psid or pressure drop]

Inlet Pressure
The applied pressure entering the upstream side of the filter. [Synonym: influent, upstream or line pressure]

Outlet Pressure
The pressure exiting the downstream side of the filter. [Synonym: effluent or downstream pressure]

Redundant Filtration
A type of serial filtration in which a second sterilizing-grade filter is used as a backup in the event of an integrity failure of the primary sterilizing filter.

Serial Filtration
Filtration through two or more filters of the same or decreasing pore size, one after the other.

Sterilization
Validated process used to render a product free of viable microorganisms.

NOTE: In a sterilization process, microbiological death or reduction is described by an exponential function. Therefore, the number of microorganisms that survive a sterilization process can be expressed in terms of probability. While the probability may be reduced to a very low number, it can never be reduced to zero.

Sterilizing-Grade Filter
A filter that reproducibly removes test microorganisms from the process stream, producing a sterile filtrate.

Surface Tension
The tendency of the surface of a liquid to contract to the smallest area possible under defined conditions. It is expressed as dynes per centimeter.

Surfactant
A soluble compound that reduces the surface tension of a liquid or reduces interfacial tension between two liquids (causing the formation of micelles), or between a liquid and a solid.

Throughput
The amount of solution that passes through a filter. It is described as volume through the membrane area. [Synonym: capacity]

Upstream
The influent, or inlet side of the filter.

Validation
A documented program that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

Volatile
Evaporates easily; converts easily from a liquid to a gas.