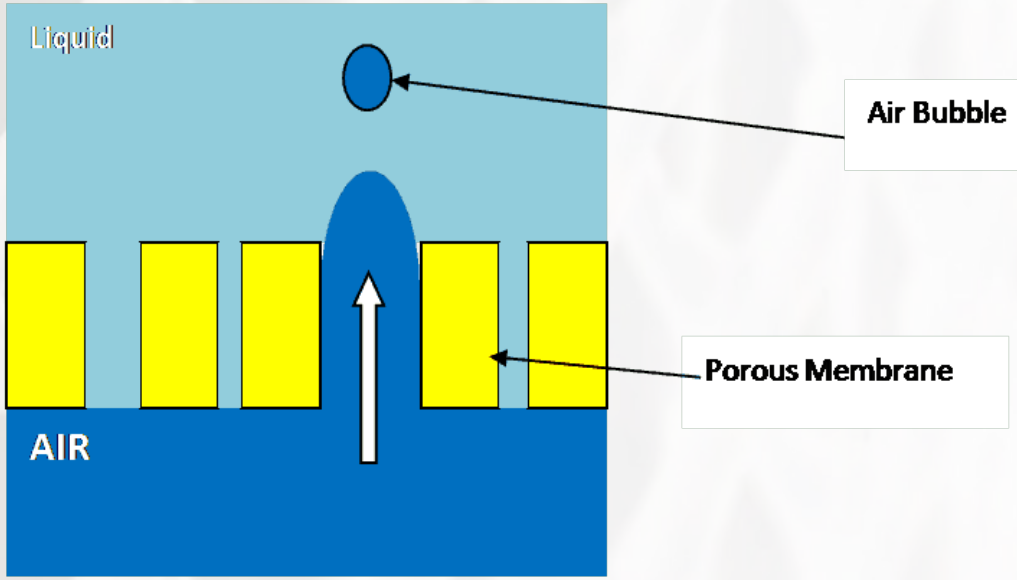
GRAVER TECHNOLOGIES

Technical Topics

INTEGRITY TESTING



INTEGRITY TESTING DEFINED

BUBBLE POINT CALCULATIONS

Antoine Equation

$$log(P_A^*) = A - \frac{B}{T + C}$$

$$y_A * P = x_A * P_A^*$$

$$y_B * P = x_B * P_B^*$$

$$P(y_A + y_B) = P_A^* x_A + P_B^* x_B$$

INTEGRITY TESTING DEFINED

What is an Integrity test?

- Non-Destructive Test - Filter integrity can be measured repeatedly without harming the filter
- Measurement of membrane filter attribute (bubble point, diffusive flow, water intrusion)
- Typically correlated to microbial retention by manufacturer

Why Integrity test?

Manufacturers

- Characterize Membrane Filter Performance
- Quality Control of Manufacturing Process
- Develop and Support Marketing Claims

End User

- Verify Filter Integrity
- Improve Process Effectiveness/Consistency

INTEGRITY TESTING DEFINED

What are the different integrity tests?

- **Bubble Point**
  - **Minimum Critical Bubble Point**
  - **Bulk Flow Bubble Point**
  - **Reverse Bubble Point**
- **Diffusive Flow**
- **Pressure Hold**
- **Water Intrusion (WIT)**

INTEGRITY TESTING: BUBBLE POINT

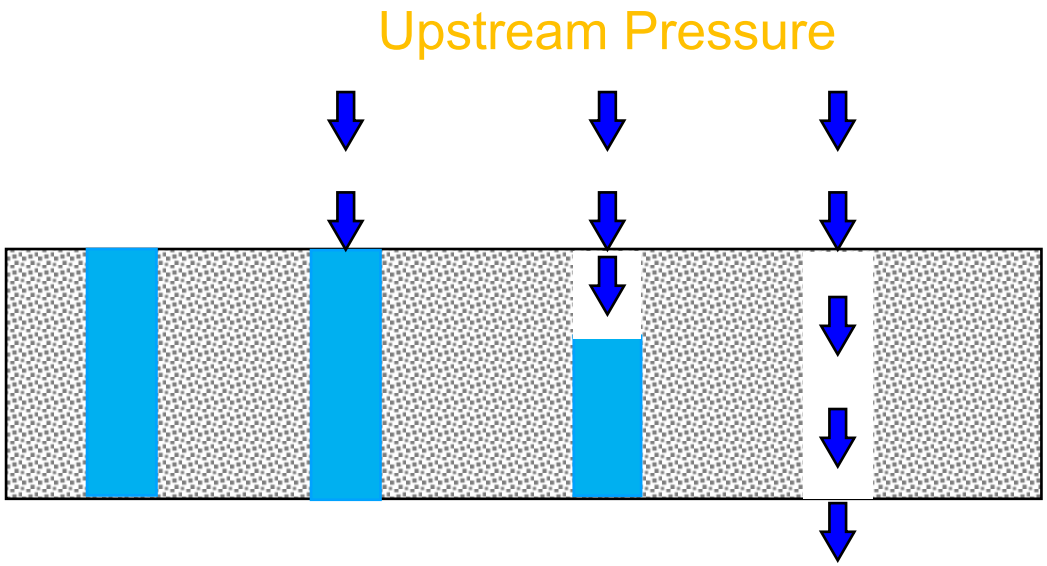
What is Bubble Point ?

The pressure at which the liquid in the pores is displaced.

Reverse Bubble Point - Diagnostic test pressurizing immersed cartridge in the reverse direction (outlet side).

Basic Procedure

- Pre-wet membrane
- Apply pressure to upstream side to 80% of bubble point
- Increase at 1 psi increments until bubbles appear



INTEGRITY TESTING: DIFFUSIVE FLOW

What is diffusive flow?

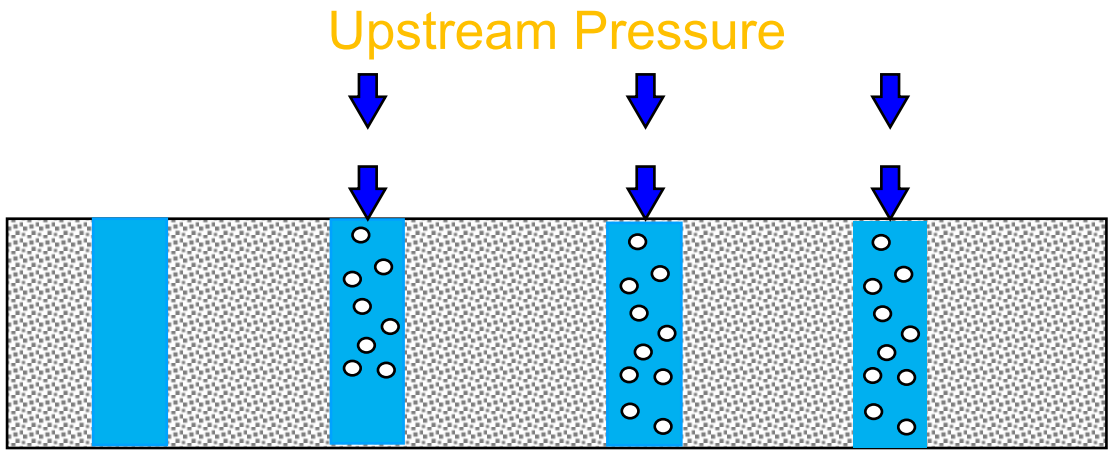
- The volume of gas which permeates a wetted membrane at a given pressure.

FACT: Wetted membranes are impermeable to bulk flow of gas.

- Test typically run at 80% of the bubble point pressure. Also called forward flow, diffusional flow.

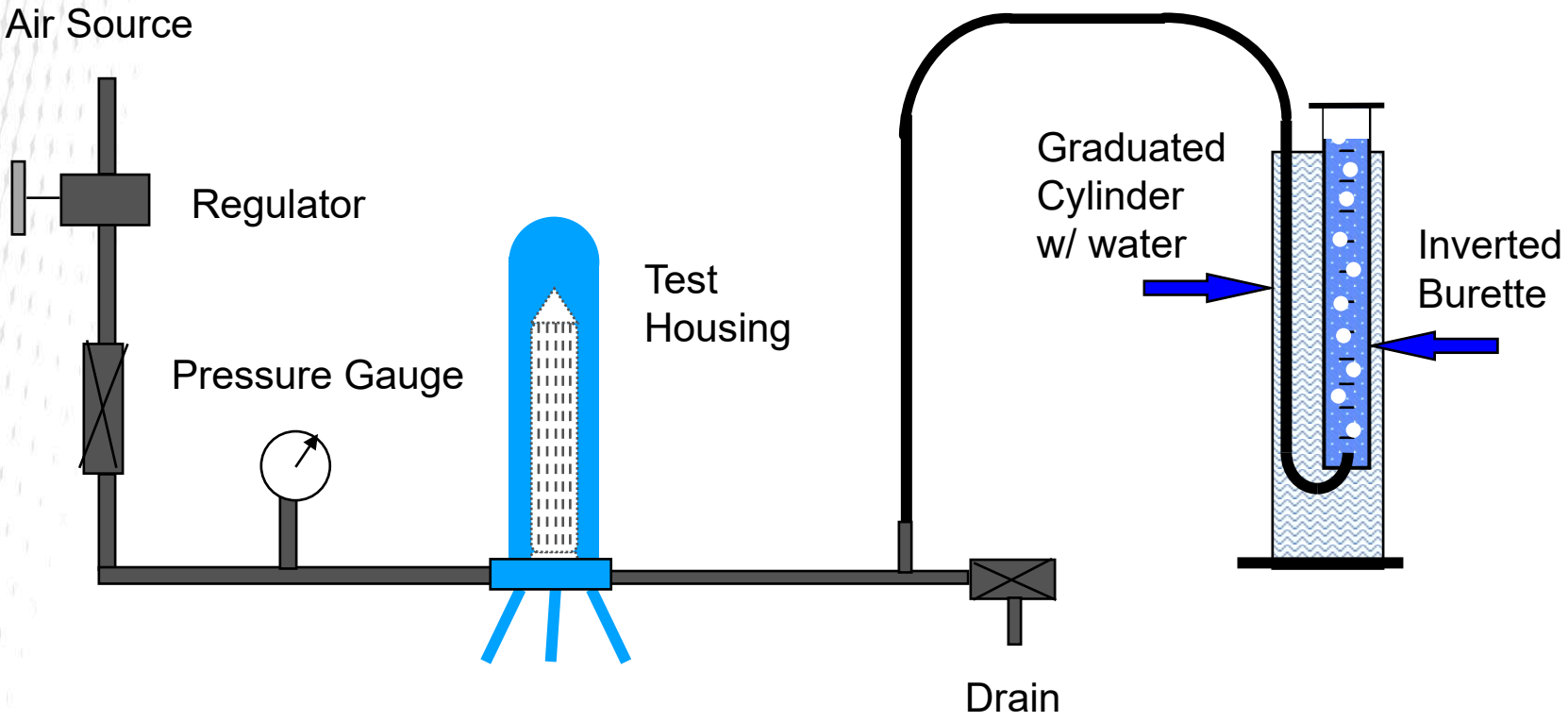
Basic Procedure

- Pre-wet membrane
- Apply pressure to upstream side to 80% of bubble point
- Measure volume of gas collected on downstream side



INTEGRITY TESTING: MANUAL SYSTEM

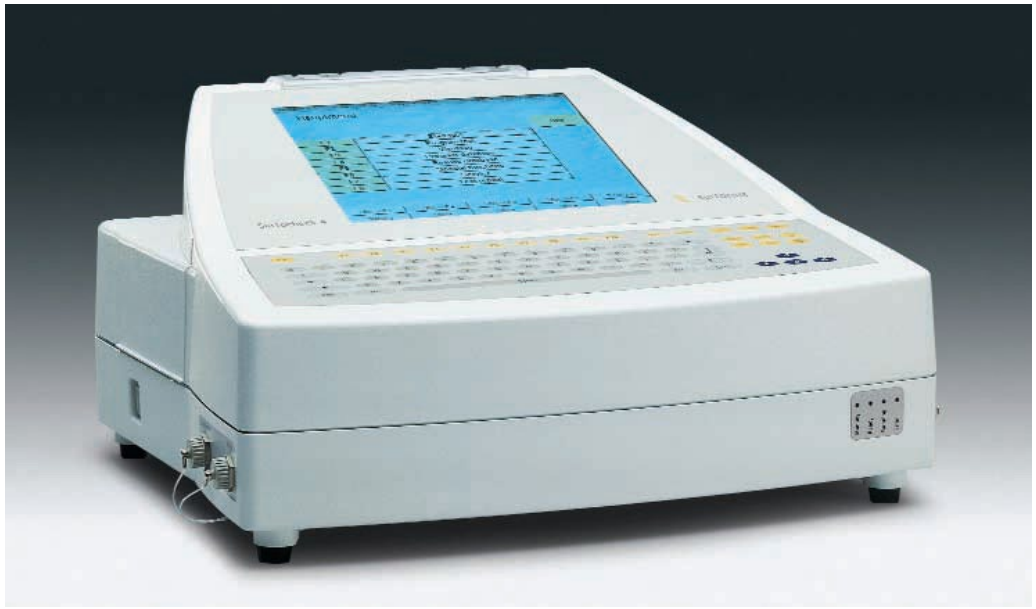
Bubble Point / Diffusional Flow Test Stand



INTEGRITY TESTING: AUTOMATED SYSTEM

What is an Automated Integrity Tester?

- In line system capable of determining most integrity test values.
  - Upstream measurements – avoids downstream contamination
  - Significantly reduces operator error



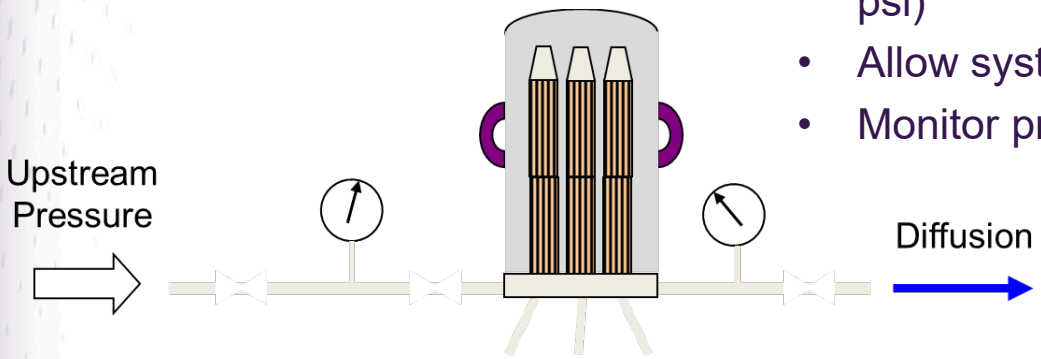
INTEGRITY TESTING: PRESSURE HOLD

What is Pressure Hold?

- Allows for an evaluation of an entire assembly including multi-rounds
- Pressure is applied to a sealed vessel on the upstream side.
  - The maximum amount of pressure loss that is permitted.
  - Pressure loss in an integral system is due *only* to diffusion through the membrane.
  - Must be calculated for each system based upon total volume.

Basic Procedure

- Pre-wet the filter elements
- Apply pressure to upstream side - (typically 10-30 psi)
- Allow system to equilibrate (5-10 minutes)
- Monitor pressure loss over time (5 -10 minutes.)

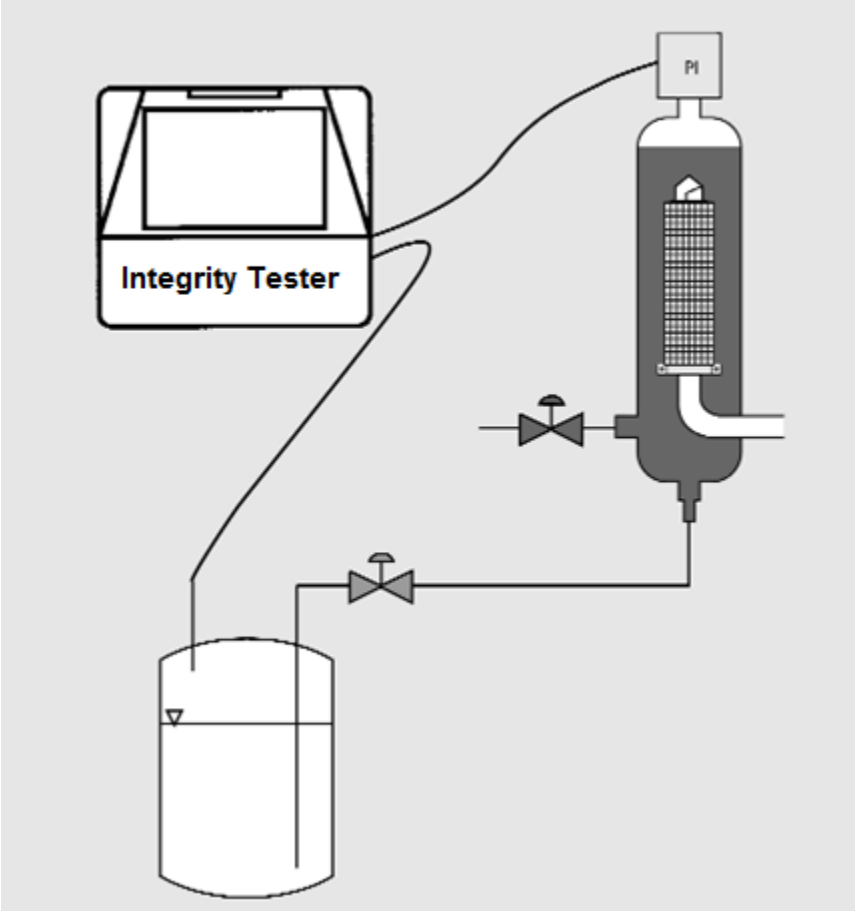


INTEGRITY TESTING: WATER INTRUSION

What is Water Intrusion Test?

An in-situ integrity test for hydrophobic filters.

- Measures the upstream pressure decrease at a prescribed pressure level imposed upon a hydrophobic membrane enveloped in water over10 minutes.
- Performed below the water penetration value of the membrane: 36 psi for 0.2 µm PTFE.
- Does not wet-out a filter, thus the filter can be used immediately (critical in venting applications).



INTEGRITY TESTING DEFINED

- Least Common Cause of Integrity Failure
  - Non integral filter

- Common Causes of Integrity Failure
  - Insufficient wetting
  - O-Ring failure: improper installation
  - Wrong wetting fluid: values differ by fluid
  - Wrong pressure/filter
  - Operator error

INTEGRITY TESTING: SUPPORT

TECHNICAL BRIEF

Graver Technologies

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TB-017

Pre-Wetting Hydrophilic Membranes for Integrity Testing

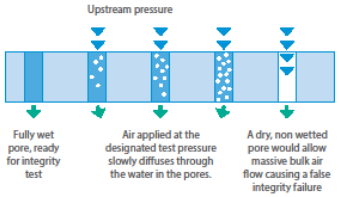
Integrity testing is a critical quality assurance process when using hydrophilic membrane filter cartridges in applications requiring bioburden control. Most manufacturers, including Graver Technologies, conduct an integrity test on each universal segment and/or finished cartridge prior to release to provide assurance that the cartridge will perform as required. This integrity test, typically either a diffusion test or bubble point, is performed on an integrity test system in the manufacturing area with the values recorded as part of the quality program. This ensures the end user that the product they receive will conform to the retention requirements. Nonetheless, it is common practice for the end user to integrity test again, prior to using the cartridges in the application. Occasionally, end users report integrity failures at this stage. But upon further examination these are usually found to be false failures, with the most common culprit being the failure to adequately pre-wet the membrane. Other potential causes are damaged or missing o-rings, incorrect values being utilized on the test equipment or leaks in the test system itself. The least likely cause for integrity failures at this stage is a non-integral cartridge!

A typical membrane cartridge will have anywhere between 6 ft^2 and 8 ft^2 of surface area per 10" filter length.

Assuming a media, such as polyethersulfone (PES), is 70% porous, the filter then has about 6–8 trillion pores, all of which must be filled with liquid in order to conduct a valid integrity test and obtain a passing integrity test value. Therefore the pre-wetting process is extremely critical and the success depends upon many factors that include:

- Characteristics of the wetting fluid (alcohol, water, temperature)
- Characteristics of the membrane (hydrophobic, hydrophilic, material of construction, pore rating)
- Process conditions (time, flow, pressure)

Each membrane may have very specific conditions that must be adhered to in order to get good pre-wetting prior to conducting the integrity test.



The process used to wet one membrane type may be quite different than another type (PES versus nylon for instance) and thus the manufacturer's guideline should be followed to minimize the risk of failure. Even chemically similar membrane types may vary from manufacturer to manufacturer due to slight chemical differences in the membrane. For instance, in the manufacturing of PES membranes, various amounts and types of wetting agents may be added to improve the wettability of a membrane.

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INSTALLATION

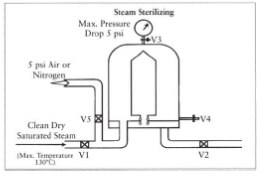
1. Remove the bagged filter from the filter cartridge box. Verify that the part number is correct and record the cartridge lot number if necessary.
2. Carefully open the filter cartridge bag. If the filter is a single open end style, cut the bag at the open end.
3. Do not completely remove the filter cartridge from the bag, but use the bag as a handling device to reduce the possibility of contamination.
4. Install the filter cartridge into the housing. If the cartridge has o-rings, the o-rings should be pre-wetted with a suitable fluid. **CAUTION:** Do not over-tighten compression plate as this may damage filter and void warranty. If the cartridge will be steamed, the top plate must be left loose to allow for expansion of the cartridge.

SANITIZATION/ STERILIZATION

Graver Technologies ZTEC WB filters may be sterilized or sanitized by a variety of methods. Due to varying system designs and requirements, users should validate their procedure in order to demonstrate its efficacy.

In Line Steaming

1.) With the filters installed, close the downstream and gas valves on the housing (V2) and (V5) and open the vent (V3) and drain valve (V4).
2.) Introduce clean, dry, saturated steam into the upstream side of the filter assembly by opening valve (V1). The maximum temperature of the steam must not exceed 275°F (135°C).
3.) When steam issues from the vent and drain, slowly close the vent (V3) and the drain (V4) until they are only slightly open.
4.) Slowly open the downstream valve (V2) to allow steam to pass through the filter. The differential pressure must not exceed 5 psi (0.34 bar) to avoid damage to the filter cartridge.
5.) Continue the flow of steam for the prescribed length of time (typically at least 20 minutes after the filter assembly has reached the desired temperature).
6.) Shut off the steam and close the vent (V3) and the drain (V4) and downstream valve (V2).
Allow the filter to cool while maintaining a positive pressure of gas at 5 psig (0.34 bar) on the upstream side by introducing regulated air or nitrogen.
NOTE: Due to the effects of temperature on o-rings, a new set of o-rings should be installed after every 5 steam cycles.



Hot Water Sanitization

1.) With the cartridges installed, fill the upstream side of the housing with cold water and ensure that all the air has been vented from the housing.
2.) Flow clean, hot water (maximum 180°F/82°C filtered to at least 1 micron nominal) through the filter with a maximum differential pressure of 5 psi (0.34 bar).
3.) Flow the hot water for at least 30 minutes or for a period of time in which sanitization efficacy has been documented.
4.) Stop the flow of hot water. Flow cold water through the filter at low differential pressures to cool the filter to operating temperature.

Autoclaving

Graver Technologies ZTEC WB filters are compatible with all autoclave cycles up to a temperature of 275°F (135°C).

Chemical Sterilization

Graver Technologies ZTEC WB filters may be sterilized/sanitized by many of the commonly used chemicals (Refer to Technical Brief TB-005). It is recommended that compatibility testing be conducted prior to using any specific chemical. For any chemical cleaning regimen, it is important to flush the filter completely to remove any chemical residue.

INTEGRITY TESTING

Graver Technologies ZTEC WB cartridges may be integrity tested by diffusion test or bubble point methods. In general, due to the large surface area, the diffusion test will yield more accurate results. In these circumstances, the bubble point test may show a "false failure" due to the rate of diffusion. If a bubble point test is performed and a failure is recorded, the results should be confirmed by diffusion testing. If the diffusion testing is satisfactory, then the filter can be considered integral.

Cartridge Wetting

With the cartridges installed, flow water through the filter system to thoroughly wet the filters and drive air out of the system. A general recommendation is as follows:

Membrane grade	*Recommended Wetting*
0.2 µm	10 GPM (37.8 lpm) for 20 min
0.45 µm	10 GPM (37.8 lpm) for 20 min
0.65 µm	10 GPM (37.8 lpm) for 20 min
1.2 µm	10 GPM (37.8 lpm) for 20 min

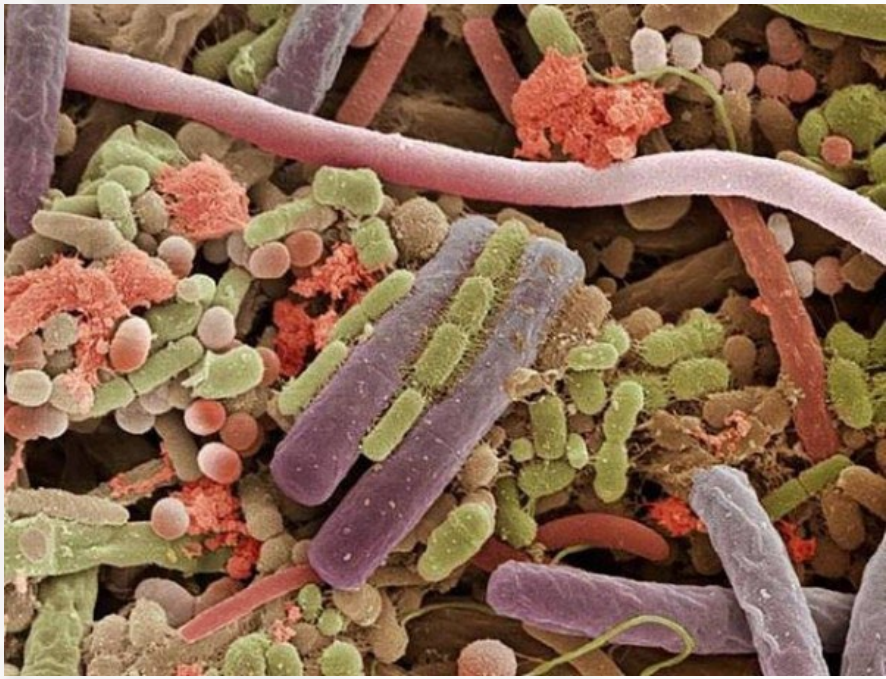
To decrease the time required for wetting, install a pressure gauge (0-30 psi) on the upstream side (inlet side) and a valve on the downstream side (outlet side) of the housing. After initiating flow and purging the air, begin closing the valve until the upstream pressure gauge reads at least 18 PSID (1.24 bar). Continue flow for 5 minutes, then open the valve and begin integrity test.

Diffusion Testing

1.) Complete cartridge wetting procedure outlined above.
2.) With the filter completely wetted, close off water flow and apply 5 psid (0.34 bar) of compressed air to the upstream side of the filter. Allow any water in the housing to pass through the filter and drain on the downstream side of the housing.
3.) Slowly increase the pressure to the value shown in Table 1, "Diffusion Pressure" and allow the system to stabilize for two minutes. The pressure ramp should not exceed 10 psid (0.7 bar) per minute.
4.) Measure the diffusive air flow through the filter system and compare this value with the maximum values in Table 1 for the pore size being tested. If the diffusive flow is equal to or less than the published value, the system is integral. If the value exceeds the maximum, then:
   a. Check the pressure gauges for accuracy
   b. Re-wet the cartridge and repeat the diffusion test from Step1.

Integrity Test Methods and Values

MICROBIAL RETENTION

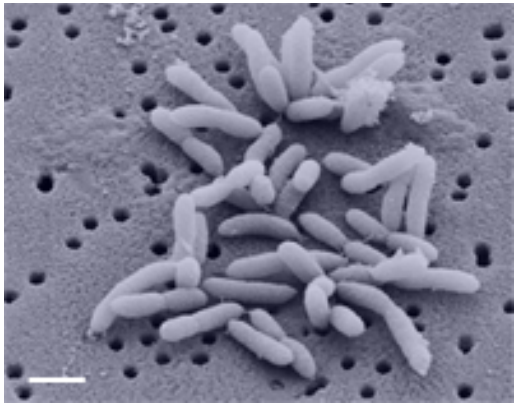


MICROBIAL SCIENCE

- ***What factors must be considered?***
  - Membranes may be used to retain bacteria and yeast.
  - Critical for Food and Beverage and Healthcare applications requiring sterility or some level of bioburden reduction.
    - *Not all membranes* are rated to retain microbes
    - Different microbes are use for different pore ratings and applications
    - There are different levels of retention – LRV = Log Reduction Values
    - Retention must be correlated to integrity test values.
    - Support document: Validation or Qualification Guide

MICROBIAL SCIENCE

Bacteria: A large domain of single cell prokaryotic organisms. Typically a few micrometers in length, bacteria have a wide range of shapes, ranging from spheres to rods to spirals



- *Brevundimonas diminuta – 0.2µ "B" & "P"*
- *Serratia marcescens – 0.45µ "B"*
- *Pseudomonas aeruginosa – 0.2µ "WB"*
- *Lactobacillus brevis – 0.45µ "WB"*
- *Oenococcus oeni - 0.45µ "WB"*

Yeast: Eukaryotic organisms classified as a fungus with 1,500 species currently described (estimated to be 1% of all fungal species). Yeasts are unicellular, although some species with yeast forms may become multicellular. Yeast size can vary greatly depending on the species, typically measuring 3–4 µ in diameter, although some yeasts can reach over 40 µm.

- Saccharomyces cerevisiae - *0.65µ "B", 0.65 µ "WB"*

MICROBIAL SCIENCE

ASTM838 ***-*** *Standard Test Method for Determining Bacterial Retention Of Membrane Filters Utilized For Liquid Filtration.*

- The standard test for determining ability of a membrane to retain microorganisms.
- Challenge level is **$10^7/cm^2$** which equates to about 10^{11} total in a typical membrane filter with 7ft^2 of surface area.
- Values reported as LRV – Log Reduction Value
  - For example, if there were 1000 (10^3) in the effluent, you would get an LRV of 8 (10^{11}- 10^3 = 10^8).
- A sterilizing grade filter = LRV of >10.99
- A bioburden reduction = LRV of <10.99

ZTEC P 0.2µ: *Brevundimonas diminuta*

Lot Number	*Diffusional Flow @ 32 psig*	*Filtrate Count (CFU)*	*LRV*
801954-001	23 ml/min	<1	>10.94
801954-003	46 ml/min	<1	>10.94
801954-005	63 ml/min	<1	>10.94
55054-010	8.4 ml/min	<1	>11.10
55054-017	9.2ml/min	<1	>11.10
55054-023	9.2 ml/min	<1	>11.10
54392-005	9.7 ml/min	<1	>11.12
54392-009	8.7ml/min	<1	>11.12
54392-039	8.8 ml/min	<1	>11.12
121281-11-1-12-002	100 ml/min	1.4×10^6	4.46
121281-11-1-12-0025	113 ml/min	1.4×10^6	4.76

SUPPORT

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Technical Brief

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TB–013

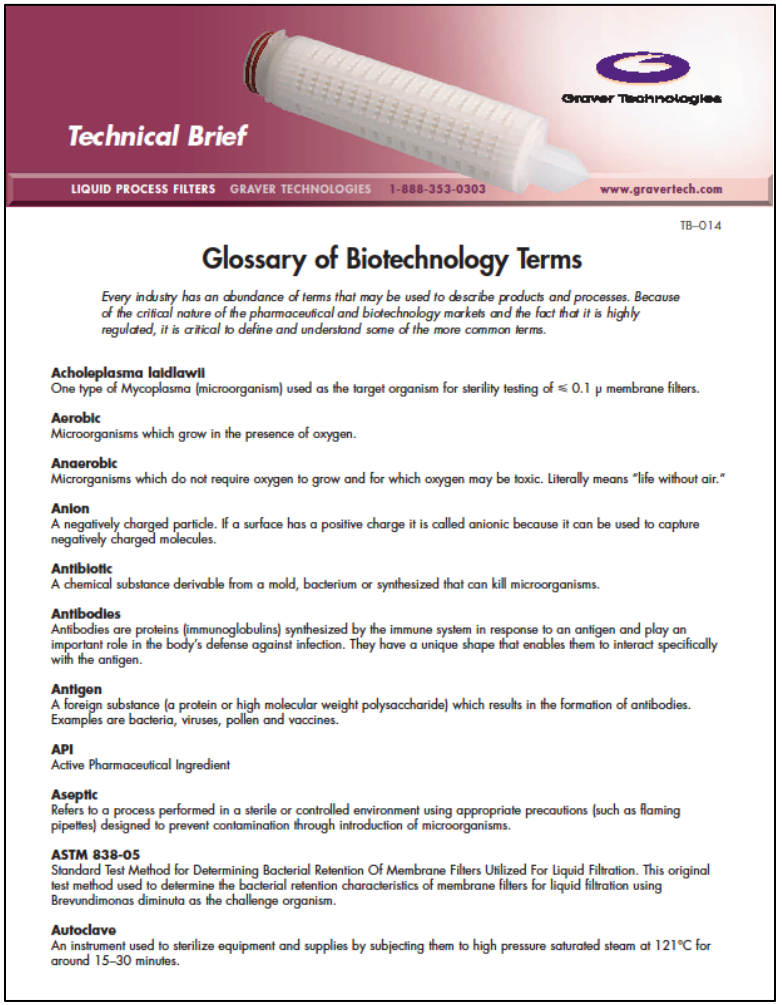
The Role of Membranes in Microbial Retention

Food/ beverage and pharmaceutical customers frequently use microfiltration membranes for removal of microbial contamination in liquid or gas process streams. Microbial contaminants can be any of a variety of species of bacteria and yeast of varying size and concentration. Removal of these organisms is essential in the food/beverage industry to prevent product spoilage or food borne illness and in pharmaceuticals, contamination within a sterile parenteral drug (injectable) can lead to significant side effects such as infection, fever or death. Therefore, to provide products into these markets, filter manufacturers will conduct microbial retention tests withthe filters to demonstrate the efficacy of microbial removal.

Filters that have been validated for microbial removal exhibit much higher removal efficiencies than absolute rated particle filters, such as a pleated polypropylene filter. As a comparison, an "absolute-rated" Beta 5000 particle removal filter exhibits a removal efficiency of 99.98% of particles challenging a filter, while a sterilizing grade liquid filter exhibits a removal efficiency of >99.99999999% of microorganisms challenging the filter. The removal efficiency of a membrane filter is expressed as the log reduction value (LRV) of target microbes, which are selected by virtue of their approximate size and relevance to the application.

Food/Beverage Applications

Microbiological quality is likely the most common food safety objective achieved by filtration. An important method for reducing the risk of microbial contamination is the HACCP (Hazard Analysis and Critical Control Point) principles published by the Food Safety and Inspection Service (FSIS) under the Department of Agriculture. HACCP is a systematic approach to identify and implement proactive programs to analyze, identify, control, monitor, correct, verify and document critical control points in the process control of the biological, chemical, and physical hazards associated with a particular food production process. In conjunction with the guidelines established under FDA CFR Title 21, food manufacturers have the necessary guidance to safeguard consumers.



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TB–014

Glossary of Biotechnology Terms

Every industry has an abundance of terms that may be used to describe products and processes. Because of the critical nature of the pharmaceutical and biotechnology markets and the fact that it is highly regulated, it is critical to define and understand some of the more common terms.

Acholeplasma laidlawii
One type of Mycoplasma (microorganism) used as the target organism for sterility testing of ≤ 0.1 µ membrane filters.

Aerobic
Microorganisms which grow in the presence of oxygen.

Anaerobic
Microrganisms which do not require oxygen to grow and for which oxygen may be toxic. Literally means "life without air."

Anion
A negatively charged particle. If a surface has a positive charge it is called anionic because it can be used to capture negatively charged molecules.

Antibiotic
A chemical substance derivable from a mold, bacterium or synthesized that can kill microorganisms.

Antibodies
Antibodies are proteins (immunoglobulins) synthesized by the immune system in response to an antigen and play an important role in the body's defense against infection. They have a unique shape that enables them to interact specifically with the antigen.

Antigen
A foreign substance (a protein or high molecular weight polysaccharide) which results in the formation of antibodies. Examples are bacteria, viruses, pollen and vaccines.

API
Active Pharmaceutical Ingredient

Aseptic
Refers to a process performed in a sterile or controlled environment using appropriate precautions (such as flaming pipettes) designed to prevent contamination through introduction of microorganisms.

ASTM 838-05
Standard Test Method for Determining Bacterial Retention Of Membrane Filters Utilized For Liquid Filtration. This original test method used to determine the bacterial retention characteristics of membrane filters for liquid filtration using Brevundimonas diminuta as the challenge organism.

Autoclave
An instrument used to sterilize equipment and supplies by subjecting them to high pressure saturated steam at 121°C for around 15–30 minutes.

TESTING & CERTIFICATION

Testing and Certification

Filter products and facilities are not under governed by any specific government agency or standards organization. However, since end users often are, standards and guidance of many agencies are followed:

- **FDA (Food and Drug Administration)** - ensuring that foods, cosmetics and electronic products are safe, and that human and veterinary drugs, biological products, and medical devices are safe and effective
- **USP (United States Pharmacopeia) A**n official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured.
- **NSF/ANSI Standard 61, *Drinking Water System Components - Health Effects*** Establishes minimum health effect requirements for the chemical contaminants and impurities
- **EPA (Environmental Protection Agency)** - United States government agency responsible for protecting the environment and human health due to environmental exposure. Regulating surface water used as a drinking water supply falls under this agency.

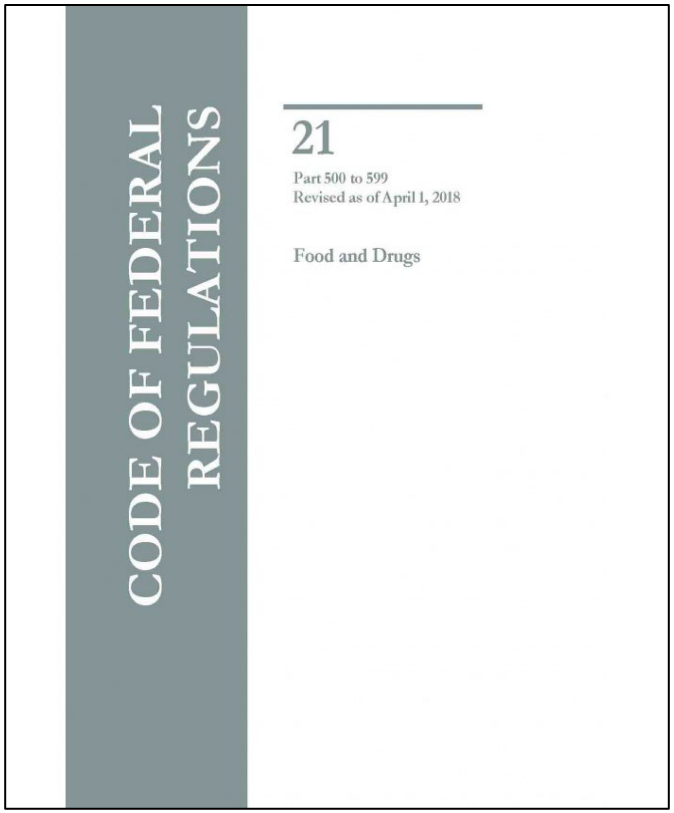
TESTING & CERTIFICATIONS: USP

- USP monograph Chapter 88, *Biological Reactivity Tests, In Vivo Classification of Plastics (Class 1* to VI). The testing consists of three parts:
  - USP Systemic Toxicity Study in the Mouse
  - USP Intracutaneous Toxicity Study in the Rabbit
  - USP Muscle Implantation Study in the Rabbit.
- A negative response on all of the tests signifies the material is suitable for contact with parenteral preparations, use in medical devices, implants and other systems.

Test To Be Conducted	Extracts	USP Class					
		I	II	III	IV	V	VI
Systemic injection test (injection in mouse)	Sodium chloride (intravenous)	X	X	X	X	X	X
	Alcohol saline (intravenous)		X	X	X	X	X
	Polyethylene glycol (intraperitoneal)			X		X	X
	Vegetable oil (intraperitoneal)			X	X	X	X
Intracutaneous test (injection in rabbit)	Sodium chloride (intravenous)	X	X	X	X	X	X
	Alcohol saline (intravenous)		X	X	X	X	X
	Polyethylene glycol (intraperitoneal)					X	X
	Vegetable oil (intraperitoneal)				X	X	X
Implantation test (strips implanted in rabbit)	None				X		X

TESTING & CERTIFICATIONS: FDA

- **Food & Drug Administration (FDA)**
  - Filters and filter manufacturing is not monitored by the FDA, the processes and component materials that are used may fall under FDA review.
  - The FDA *does not* approve products, but rather lists materials that have been tested and deemed safe. “Safe” means “there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use”
  - Code of Federal Regulations (CFR), specifically Title 21 (section or chapter) is a set of general and permanent rules published within the FDA that have relevance.
  - **Title 21:** Chapter of the CFR that governs food and drugs within the United States. For filters utilized in the manufacturing of food and beverage products, two sections are utilized :
    - Parts 174, *Indirect Food Additive - General,*
    - *Part 177, Indirect Food Additives – Polymer*



TESTING & CERTIFICATIONS: NSF

- **NSF/ANSI Standard 42, *Drinking Water Treatment Units - Aesthetic Effects***
  Concerns systems designed to reduce specific aesthetic or non-health-related contaminants (chlorine, taste, odor, and particulates) that may be present in public or private drinking water.

- **NSF/ANSI Standard 53, *Drinking Water Treatment Units - Health Effects***
  Concerns systems designed to reduce specific health related contaminants, such as *Cryptosporidium, Giardia,* lead, volatile organic chemicals (VOCs), and MTBE (methyl tertiary-butyl ether) that may be present in public or private drinking water. Only the cyst removal claims are considered for microfiltration.

- **NSF/ANSI Standard 61, *Drinking Water System Components - Health Effects***
  Establishes minimum health effect requirements for the chemical contaminants and impurities that may be indirectly imparted to drinking water. The standard provides the criteria used to evaluate the public health safety of materials, components, products, or systems that contact drinking water, drinking water chemicals, or both. The extraction methods utilized in this standard are similar to that of NSF 42.

TESTING & CERTIFICATIONS: EPA

- **Safe Water Drinking Act -** the federal law that protects public drinking water supplies throughout the nation by setting standards for drinking water quality and establishing a legal limit for specific contaminants in drinking water or a defining a required treatment technique.

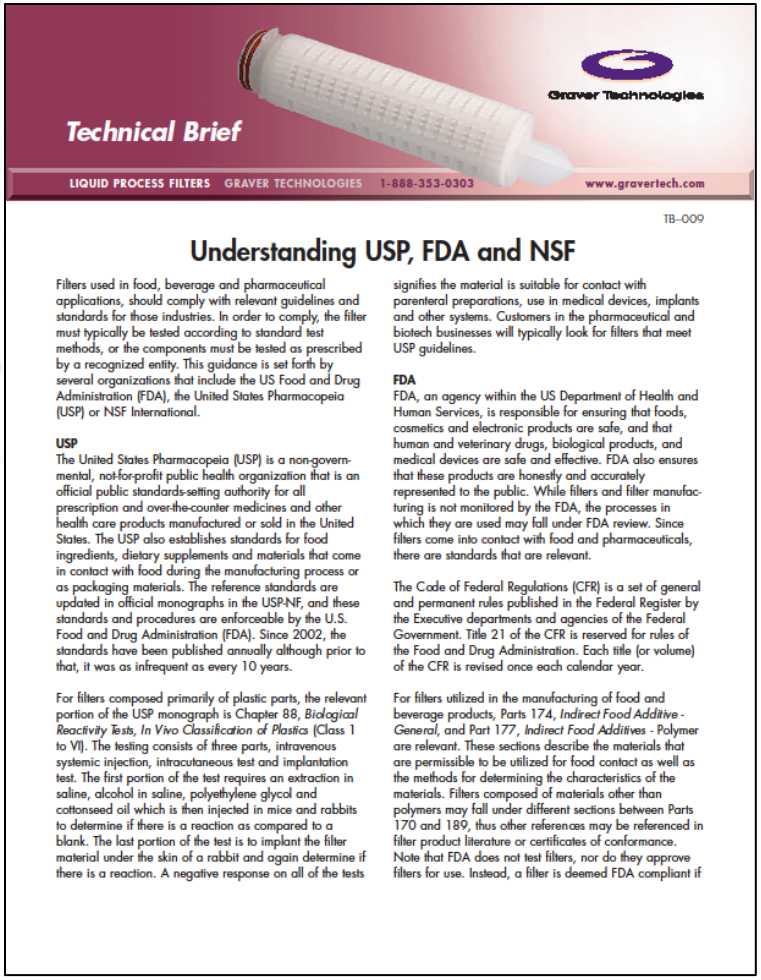
- **Long Term 1 (LT1) Enhanced Surface Water Treatment –** applies to public water systems that use surface water or ground water serving fewer than 10,000 people. Requires 2 log reduction (99%) of *Cryptosporidium*.

- **Long Term 2 (LT2) Enhanced Surface Water Treatment –** identifies a higher standard for certain systems that are deemed high risk, requiring reduction of *Cryptosporidium* by 2 - 3 log (99 – 99.9 %) and *Giardia lamblia* by 3 log (99.9%) depending upon the source and test results.

TESTING & CERTIFICATIONS: EUROPEAN UNION

EU 1935/2004 – a set of regulations established by the European Commission for materials that are intended to come in contact with food. The legislation identifies 17 groups of materials and articles, ranging from cork and glass to plastic and textiles, where specific measures may be adopted. These may include measures such as purity standards and a list of the substances used. The intent is to ensure that these materials do not transfer their components into food in quantities that could endanger human health or change the composition, the taste or the texture of food. These regulations are updated continuously, most recently Regulation 10/2011 (migration testing) which came into effect in January of 2011 and is specific to plastic materials.

SUPPORT



Technical Brief

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TB–009

Understanding USP, FDA and NSF

Filters used in food, beverage and pharmaceutical applications, should comply with relevant guidelines and standards for those industries. In order to comply, the filter must typically be tested according to standard test methods, or the components must be tested as prescribed by a recognized entity. This guidance is set forth by several organizations that include the US Food and Drug Administration (FDA), the United States Pharmacopeia (USP) or NSF International.

USP

The United States Pharmacopeia (USP) is a non-governmental, not-for-profit public health organization that is an official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured or sold in the United States. The USP also establishes standards for food ingredients, dietary supplements and materials that come in contact with food during the manufacturing process or as packaging materials. The reference standards are updated in official monographs in the USP-NF, and these standards and procedures are enforceable by the U.S. Food and Drug Administration (FDA). Since 2002, the standards have been published annually although prior to that, it was as infrequent as every 10 years.

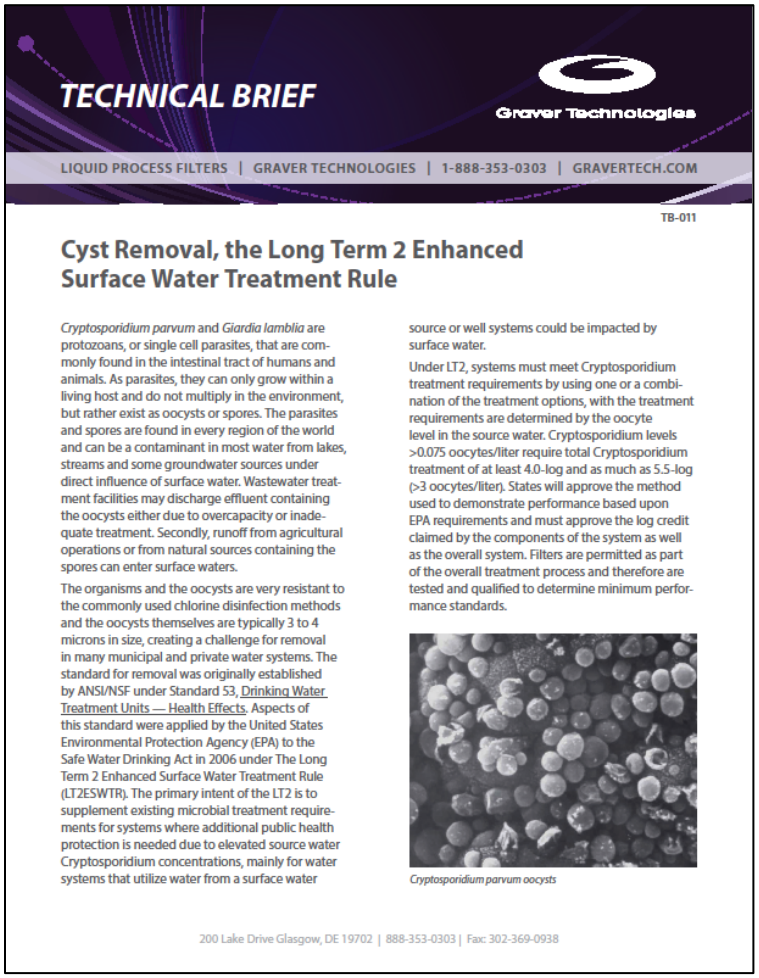
For filters composed primarily of plastic parts, the relevant portion of the USP monograph is Chapter 88, *Biological Reactivity Tests, In Vivo Classification of Plastics* (Class 1 to VI). The testing consists of three parts, intravenous systemic injection, intracutaneous test and implantation test. The first portion of the test requires an extraction in saline, alcohol in saline, polyethylene glycol and cottonseed oil which is then injected in mice and rabbits to determine if there is a reaction as compared to a blank. The last portion of the test is to implant the filter material under the skin of a rabbit and again determine if there is a reaction. A negative response on all of the tests signifies the material is suitable for contact with parenteral preparations, use in medical devices, implants and other systems. Customers in the pharmaceutical and biotech businesses will typically look for filters that meet USP guidelines.

FDA

FDA, an agency within the US Department of Health and Human Services, is responsible for ensuring that foods, cosmetics and electronic products are safe, and that human and veterinary drugs, biological products, and medical devices are safe and effective. FDA also ensures that these products are honestly and accurately represented to the public. While filters and filter manufacturing is not monitored by the FDA, the processes in which they are used may fall under FDA review. Since filters come into contact with food and pharmaceuticals, there are standards that are relevant.

The Code of Federal Regulations (CFR) is a set of general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government. Title 21 of the CFR is reserved for rules of the Food and Drug Administration. Each title (or volume) of the CFR is revised once each calendar year.

For filters utilized in the manufacturing of food and beverage products, Parts 174, *Indirect Food Additive - General*, and Part 177, *Indirect Food Additives* - Polymer are relevant. These sections describe the materials that are permissible to be utilized for food contact as well as the methods for determining the characteristics of the materials. Filters composed of materials other than polymers may fall under different sections between Parts 170 and 189, thus other references may be referenced in filter product literature or certificates of conformance. Note that FDA does not test filters, nor do they approve filters for use. Instead, a filter is deemed FDA compliant if



TECHNICAL BRIEF

Graver Technologies

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TB-011

Cyst Removal, the Long Term 2 Enhanced Surface Water Treatment Rule

Cryptosporidium parvum and *Giardia lamblia* are protozoans, or single cell parasites, that are commonly found in the intestinal tract of humans and animals. As parasites, they can only grow within a living host and do not multiply in the environment, but rather exist as oocysts or spores. The parasites and spores are found in every region of the world and can be a contaminant in most water from lakes, streams and some groundwater sources under direct influence of surface water. Wastewater treatment facilities may discharge effluent containing the oocysts either due to overcapacity or inadequate treatment. Secondly, runoff from agricultural operations or from natural sources containing the spores can enter surface waters.

The organisms and the oocysts are very resistant to the commonly used chlorine disinfection methods and the oocysts themselves are typically 3 to 4 microns in size, creating a challenge for removal in many municipal and private water systems. The standard for removal was originally established by ANSI/NSF under Standard 53, Drinking Water Treatment Units — Health Effects. Aspects of this standard were applied by the United States Environmental Protection Agency (EPA) to the Safe Water Drinking Act in 2006 under The Long Term 2 Enhanced Surface Water Treatment Rule (LT2ESWTR). The primary intent of the LT2 is to supplement existing microbial treatment requirements for systems where additional public health protection is needed due to elevated source water Cryptosporidium concentrations, mainly for water systems that utilize water from a surface water source or well systems could be impacted by surface water.

Under LT2, systems must meet Cryptosporidium treatment requirements by using one or a combination of the treatment options, with the treatment requirements are determined by the oocyte level in the source water. Cryptosporidium levels >0.075 oocytes/liter require total Cryptosporidium treatment of at least 4.0-log and as much as 5.5-log (>3 oocytes/liter). States will approve the method used to demonstrate performance based upon EPA requirements and must approve the log credit claimed by the components of the system as well as the overall system. Filters are permitted as part of the overall treatment process and therefore are tested and qualified to determine minimum performance standards.

Cryptosporidium parvum oocysts

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CLEANING & SANITIZATION

CLEANING & SANITIZATION

Cleaning, sanitizing and sterilizing filters is a common practice

- Healthcare and food and beverage markets requiring bioburden management.
- A number of applications will require the filter to be re-used in order to achieve process economics. This is particularly true for food and beverage applications – beer and wine.
- Cautions
  - Check chemical compatibility of ALL components
  - Increased temperature can may increase the aggressive nature of a cleaning/sanitizing agent
  - Temperature decreases the maximum differential pressure of a cartridge due to softening of the polypropylene components.

CLEANING

Use the following cleaning agents for cleaning filter cartridges. Immerse with cartridge open end up and soak in a container that has the prescribed concentration of the agent for at least 30 minutes.

- Triton X-100: Add 15 drops of Triton X to one gallon (3.79 liters) of warm water and then mix well. Triton X is made by Roche Diagnostics.
- LiquiNox/Alconox: Follow instructions provided by manufacturer on product packaging.
- Minnclean TF: Add 30 grams of Minnclean to one gallon (3.79 liters) of warm water and mix well.
- Acid: Immerse the cartridges in 1% solution of citric, acetic, nitric, phosphoric or hydrochloric acid.
- Caustic: Rinse cartridges or soak overnight in 0.5-5% NaOH solution. Hot caustic at 122° F (50°C) is even more effective.

SANITIZING

Use the following sanitizing agents to properly sanitize cartridges prior to use in critical applications. Immerse with cartridge open end up and soak in the prescribed concentration of the agent for 30-60 minutes..

- Sodium Hypochlorite (Bleach): 5-10 ppm solution in lukewarm water.
- 70% Ethanol: Immerse the cartridges (Buna N O-Rings not compatible).
- Chlorine Dioxide, ClO2: Add 2 oz. (59 ml) of Chorine Dioxide to one gallon (3.79 liters) of lukewarm water (200 ppm).
- 10% Hydrogen Peroxide: Immerse the cartridges in 10% H2O2.
- Quaternary Ammonium “quats”: Add 2 oz. (59 ml) of Ammonium to one gallon (3.79 liters) of water (200 ppm).
- Acid: Immerse the cartridges in 1% solution of citric, acetic, nitric, phosphoric or hydrochloric acid.
- Peracetic Acid: Immerse cartridges in 100-200 ppm solution.
- Caustic: Rinse cartridges or soak overnight in 0.5-5% NaOH solution. Hot caustic at 122° F (50°C) is even more effective.

STERILIZING

Heat is an effective method to sanitize and/or sterilize a filter. Careful monitoring of the differential pressure must be done to assure structural integrity of the filter. Pressure maximum can be reduce to as low as 3 – 5 PSID.

- Hot Water: Raise clean water temperature to 185° F (85°C) and immerse the cartridges with open end up for 30 minutes. For inline hot water flow, do not exceed 3 psid (.21 bar) pressure drop across the cartridge.
- Steam: Raise the steam temperature to 250° F (121°C) and expose the cartridge to steam for 30 minutes. For inline hot steam, do not exceed more than 5.0 psid (.34 bar) pressure drop across the cartridge.
- Autoclave: Install the cartridges in the autoclave chamber. Raise steam temperature to 250° F (121°C) and expose the cartridge for 30 minutes

SUPPORT

TECHNICAL BRIEF

Graver Technologies

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TB-005

Cleaning and Sanitizing Procedure for Graver Filter Products

CLEANING FILTER CARTRIDGES

Use the following cleaning agents for cleaning filter cartridges. Immerse with cartridge open end up and soak in a container that has the prescribed concentration of the agent for at least 30 minutes.

- ***Triton X-100:*** Add 15 drops of Triton X to one gallon (3.79 liters) of warm water and then mix well. Triton X is made by Roche Diagnostics.
- ***LiquiNox/Alconox:*** Follow instructions provided by manufacturer on product packaging.
- ***Minnclean TF:*** Add 30 grams of Minnclean to one gallon (3.79 liters) of warm water and mix well.

SANITIZING FILTER CARTRIDGES

Use the following sanitizing agents to properly sanitize cartridges prior to use in critical applications. Immerse with cartridge open end up and soak in the prescribed concentration of the agent for 30–60 minutes. For proper and effective sanitization, raise the mixture's temperature to 80° F (27°C).

- ***Sodium Hypochlorite (Bleach):*** Prepare a 5–10 ppm solution in lukewarm water.
- ***70% Ethanol:*** Immerse the cartridges (Buna N O-Rings not compatible).
- ***70% IPA:*** Immerse the cartridges.
- ***Chlorine Dioxide, ClO_2:*** Add 2 oz. (59 ml) of Chorine Dioxide to one gallon (3.79 liters) of lukewarm water (200 ppm).
- ***10% Hydrogen Peroxide:*** Immerse the cartridges in 10% H_2O_2.
- ***Quaternary Ammonium "quats":*** Add 2 oz. (59 ml) of Ammonium to one gallon (3.79 liters) of water (200 ppm).
- ***Acid:*** Immerse the cartridges in 1% solution of citric, acetic, nitric, phosphoric or hydrochloric acid.
- ***Peracetic Acid:*** Immerse cartridges in 100–200 ppm solution.
- ***Caustic:*** Rinse cartridges or soak overnight in 0.5–5% NaOH solution. Hot caustic at 122° F (50°C) is even more effective.

STERILIZING FILTER CARTRIDGES

1. ***Hot Water:*** Raise clean water temperature to 180° F (80°C) and immerse the cartridges with open end up for 30 minutes. For inline hot water flow, do not exceed 3 psid (.21 bar) pressure drop across the cartridge.
2. ***Steam*:*** Raise the steam temperature to 250° F (121°C) and expose the cartridge to steam for 30 minutes. For inline hot steam, do not exceed more than 5.0 psid (.34 bar) pressure drop across the cartridge.
3. ***Autoclave*:*** Install the cartridges in the autoclave chamber. Raise steam temperature to 250° F (121°C) and expose the cartridge for 30 minutes.
4. ***Final Rinse:*** Rinse all cleaned and sanitized cartridges with plenty of clean water to remove any cleaning and sanitizing agents.

*Cartridge must be equipped with special end cap insert to withstand autoclaving or steaming (standard on Graver membrane filters except WaterTEC).

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TECHNICAL BRIEF

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TB-008

Graver Cartridge Regeneration Procedures for Wine & Beer Applications

The purpose of this document is to provide suggestions on how to extend the life of Graver filters used in wine, beer and spirits filtration (e.g., ZTEC WB, QMC and PMC) by means of regeneration. These procedures are mainly effective for organic and water soluble contaminants.

FORWARD FLUSH PROCEDURE

This process results in the least amount of stress on your filters.

1. Forward rinse at ambient temperature with pre-filtered water at >5 psid (.34 bar) for 5–10 minutes to remove certain soluble product remnants. This step is critical as it reduces the risk of 'baking' on proteins (e.g., beta-glucans) when introducing hot water.
2. Forward rinse with pre-filtered 125–180°F (50°–80°C) water at 5–30 psid (.34–2.1 bar) for 15–20 minutes. The warmer the water, the better the results, but do not exceed 180°F (80°C).
3. Optional for heavily plugged filters — Soak overnight or longer or forward flush with an oxidizing chemical for 30–60 minutes. See below for chemical suggestions.
4. Cold forward rinse with pre-filtered water at >5 psid (.34 bar) just long enough to cool the filter and remove any residual chemicals (if used).
5. Store filter (see below) or progress to sterilization and integrity testing prior to re-use.

REVERSE FLUSH PROCEDURE

This process is more effective at regenerating filters. However, reverse flushing is discouraged with sterilizing grade membrane filters (i.e., ZTEC WB) as it stresses the filters considerably more than forward flushing; especially when combined with hot water. There is a much greater risk of compromising the integrity of membrane filters by reverse flushing if pressures and elevated temperatures are not closely regulated within the filter's maximum operating parameters.

- Follow the steps in the Forward Flush Procedure outlined above except flow in the reverse direction. If flushing in the reverse direction, do not exceed 5 psid (0.34 bar) at ambient. If using hot water (>50C), reduce the maximum to 2 PSID.

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QUESTIONS?

Any sufficiently advanced technology is indistinguishable from magic”

Arthur C. Clarke

“I’m waiting for them to work out the bugs.”