Graver Technologies

ZTEC WB Performance Qualification Guide

ISO 9001:2008
FM 38860

Preface

Each section of this Validation Guide represents only the summary portion of the actual test. If your company has a need for expanded detail on any particular test method or the actual data, please contact graver Technologies Liquid Filter Group for assistance at 800-249-1990.

Table of Contents

ZTEC WB- Performance Qualification Guide

The Graver Technologies ZTEC WB (0.2 µm, 0.45 µm, 0.65 µm and 1.2 µm) pleated filter cartridges are designed as an exceptionally clean, non-leaching, non-shedding barrier for the clarification of wine, beer and bottled water. These filters offer reliable performance in removing contaminants found in these fluids while maximizing the on-stream life. All ZTEC WB filter cartridges incorporate an asymmetric polyethersulfone membrane with support components (cage, core, end caps and support layers) made entirely of polypropylene, which conform to both CFR for Indirect Food Additives and USP Class VI standards. The ZTEC WB filter cartridges can be sanitized with steam, hot water, chemicals typically used in wine, beer and bottled water applications. Each filter is rinsed with de-ionized water and integrity tested before release from manufacture. All ZTEC WB filter products are fabricated in an ISO 9001, Rev. 2008 Registered manufacturing facility.

This report contains results of laboratory tests performed on Graver Technologies' 0.2 µm, 0.45 µm, 0.65 µm and 1.2 µm ZTEC WB membrane cartridge filters. This document describes:

- Cartridge Integrity Test
- Flow Rate Testing
- Core Collapse (Differential Pressure Stress) Testing
- Sanitization and Sterilization Testing
- Bacteria and Yeast Challenge Test
- Endotoxin Test
- Bio-safety Testing

Product Traceability

ZTEC Filter Elements are manufactured in conformance with established current Good Manufacturing Practice (cGMP) standards. The filter elements are produced and distributed according to a Quality Management System that is registered for compliance to EN ISO 9001:2008. All pharmaceutical grade filters are non-destructively integrity tested and flushed with Purified Water with a maximum conductivity of 1.1 µS/cm @ 20°C (68°F) and a maximum TOC (Total Organic Carbon) content of 0.5 mg (500ppb) of carbon per liter. They are then dried using HEPA filtered air and sealed in a protective polyethylene bag within the cleanroom. To enable full traceability of all pharmaceutical grade filter products, each filter module is marked with an individual serial number, a lot number, product code and general description which is also shown on both the bag label and on the outer product box, therefore all data concerning materials used and production data are documented, accessible and fully traceable.

Cartridge Integrity Test

Graver Technologies, as part of its quality process, integrity tests all ZTEC WB filter cartridges before release from manufacturing. The specific test used is a Diffusion Test. A discussion of this testing procedure is included in the package insert accompanying the ZTEC WB product. For an integral cartridge, the air diffusion rate, which is a measure of the rate at which air diffuses through the water-filled pores of the membrane, must be below a specified value at the Integrity Test pressure. A cartridge with even a minor defect will exhibit much higher airflow rates when measured by this test.

Test Procedure

1) A filter cartridge is installed into the test system and wetted with de-ionized water by flowing water through the cartridge.
2) The water flow is shut off and a pressure of 5 psid (0.34 bard) of compressed air is applied upstream of the filter. Any excess water in the housing passes through the filter and is drained from the downstream side of the housing.
3) The air pressure is increased to the value shown in Table below, "Diffusion Pressure" and the system is allowed to stabilize for 2 minutes
4) The diffusive air flow through the filter system is measured and the filter passes the integrity test only if the diffusion flow value is less than the "Maximum Diffusion" shown in the table below.

Pore Size	Test Pressure psig (bar)	Maximum Diffusion (cc/min) per 10-Inch Cartridge Length	Bubble Point Psig (bar)
0.2 µm	25 psig (1.7 bar)	≤ 35	≥ 30 psig (2.0 bar)
0.45 µm	16 psig (1.1 bar)	≤ 35	≥ 20 psig (1.4 bar)
0.65 µm	14 psig (.97 bar)	≤ 35	≥ 17 psig (1.2 bar)
1.2 µm	11 psig (.8 bar)	≤ 35	≥ 13 psig (0.9 bar)

Flow Rate Testing

To contribute to the overall operating economics of an existing filter system, it is important that process filter cartridges offer high flow rates at low-pressure drops. For new systems, this can also allow a smaller filter housing to be used with a resultant savings in capital cost.

Test Procedure

1) A filter cartridge is installed into the test system and wetted with clean water. An integrity test is performed and the results are recorded. (See Page 4 for Integrity Test Procedure.)
2) The filter system is connected to a source of clean water. The pressure of water can be regulated and was adjusted to 18 psi (1.2 bar).
3) The flow through the filter is adjusted to establish a test differential pressure across the filter of 1 psid (.07 bar).
4) The flow rate through the filter housing is recorded.
5) The test is repeated with several cartridges for each pore size.

Results

The filter cartridges at each pore size tested showed flow rates as summarized below, meeting the minimum specifications for that pore size.

0.2 µm		0.45 µm		0.65 µm			
Cart. ID #	US GPM (lpm) Flow at 1 PSID (.07 bar)	Cart. ID #	US GPM (lpm) Flow at 1 PSID (.07 bar)	Cart. ID #	US GPM (lpm) Flow at 1 PSID (.07 bar)	Cart. ID #	US GPM (lpm) Flow at 1 PSID (.07 bar)
1	3.4 (12.9)	1	5.5 (20.8)	1	7.5 (28.4)	1	7.0 (26.5)
2	3.4 (12.9)	2	7.0 (26.5)	2	8.3 (31.4)	2	7.0 (26.5)
3	2.7 (10.2)	3	8.1 (30.7)	3	7.9 (29.9)		
4	2.7 (10.2)	4	5.8 (22)	4			

Conclusions

Based on this testing, the typical flow rate/pressure drop characteristics of ZTEC WB cartridges per 10-inch cartridge length are:

0.2 µm: 3.0 gpm/PSID (11.5 LPM/0.1 bar)
0.45 µm: 6.6 gpm/PSID (25.9 LPM/0.1 bar)
0.65 µm: 7.9 gpm/PSID (29.9 LPM/0.1 bar)
1.2 µm: 7.0 gpm/PSID (26.5 LPM/0.1 bar)

Core Collapse (Differential Pressure Stress) Testing

In normal use a filter cartridge will be exposed to an increasing differential pressure as the filter accumulates contaminants. In addition, due to normal stops and starts in a production line, the filter will be subjected to numerous differential pressure surges. The limiting factor in a filter cartridge's resistance to differential pressure is the strength of the cartridge core.

The testing regimen below was designed to stress the ZTEC WB filter core under more rigorous conditions than the filter would normally be exposed to in "real world" operation. To pass this test, the filter cartridge must remain integral throughout the pressure testing.

Test Procedure

1) A filter core, bonded to an adapter suitable for a test housing (e.g., -226 or -222 adapter), is encased in a non-porous film to prevent permeability of a test liquid.
2) The core is installed into the filter housing, which is attached to a hydraulic test system.
3) At ambient temperature, hydraulic pressure is slowly increased until the core collapses.
4) The temperature of the hydraulic fluid, and hence the housing/filter core, is increased to 176°F (80°C).
5) The hydraulic pressure is slowly increased until the core collapses.

Results

The filter cores consistently avoided collapse until well over 100 psid (6.9 bard) at ambient temperature (70°F/21°C). The filter cores consistently avoided collapse until well over 60 psid (4.1 bard) at an elevated temperature of 176°F (80°C).

Conclusion

Based on this testing and Graver Technologies ZTEC WB cartridge fabrication methodology, ZTEC-WB cartridge filters can withstand differential pressures up to 80 psid (5.5 bard) at 70°F (21°C), and 40 psid (2.8 bard) at 176°F (80°C) and remain integral.

Sanitization/ Sterilization Test

Steam Sterilization Testing

Under certain conditions it may be required to steam sterilize or sanitize the ZTEC WB cartridge to reduce the incidence of extraneous organisms that may come from the environment or may be filtered from the fluid being processed. Several procedures may be used on the ZTEC WB cartridge. This section outlines the test procedures, results and conclusions used in validating ZTEC WB cartridges for steam sterilization and hot water sanitization.

Test Procedure

1) A filter cartridge is installed into the test system, wetted with clean water, and integrity tested with the data recorded.
2) The filter system is connected to a source of clean, dry, saturated steam with a maximum pressure of 45 psid (3.1 psia).
3) The filter is steamed at a temperature of 275°F (135°C) and a maximum differential pressure of 5 psid.
4) After 30 minutes of steam, the cartridge is allowed to cool for 30 minutes.
5) Steps 2, 3, and 4 are repeated. After every fifth cycle the cartridge is re-wetted, and integrity tested.

Conclusion

Based on this testing, the ZTEC WB filter cartridges remain integral when steam sterilized up to 50 times at 275°F (135°C) for 30 minutes per cycle.

Hot Water Sanitization Testing

A convenient method of sanitizing the filter is to flow hot water (185°F/85°C) through the filter system for at least 30 minutes after the filter has reached a stable temperature. The time will be operating condition dependent and it should be validated for the user's specific system.

Steam sterilization of a filter system is far more rigorous than hot water sanitization. Thus, it can be safely assumed that ZTEC WB filter cartridges can be hot water sanitized at least 50 times under the above specified conditions.

Bacteria and Yeast Challenge Test

Nelson Laboratories Inc., Salt Lake City, Utah, performed the bacteria and yeast challenge tests. The test procedure was adapted from ASTM F838-05 Standard Test Method: "Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration" and the Health Industry Manufacturer's (HIMA) Test Method: "Microbiological Evaluation of Filters for Sterilizing Liquids."

Several American Type Culture Collection (ATCC) yeast and bacteria strains were chosen as challenge organisms because of their significance in the beverage market. The general procedure was similar for all organisms, except that the culture medium and incubation conditions varied for different test organisms. Each 10 inch cartridge was challenged with approximately 10 liters of challenge suspension prepared to contain at least 10^7 organisms per milliliter. The challenge was conducted at high flow rate and a maximum differential pressure of 30 psid. The filtrate was collected and assayed quantitatively by membrane filtration. Integrity tests were performed before and after the microbial challenge procedure. Appropriate positive and negative controls were included for each group of cartridges tested.

Test Procedure

1. The test organism stock cultures were activated by inoculating appropriate culture medium.
2. Identity of the microorganism was confirmed morphologically and biochemically.
3. The challenge suspension was prepared by inoculating sterile broth and incubating at appropriate conditions.
4. A test cartridge was installed in a sanitary filter housing for diffusion testing with purified water.
5. The test filter, in the housing, was steamed in place for 30 minutes at a temperature > 250°F (121°C).
6. An appropriate volume of challenge suspension was added to the pressure vessel to provide at least 1 x 10^7 CFU/ cm^2 of effective filtration area.
7. The challenge suspension was filtered through the test cartridge at a pressure of 30 psid.
8. The filtrate was collected in a sterile carboy.
9. A post challenge diffusion test was conducted.
10. All filtrate was passed through a 0.45 µm 47 mm assay membrane filter.
11. The assay filter was removed from the holder and placed in a petri dish containing the appropriate agar medium. Plates were incubated and colonies counted.
12. The challenge titer was calculated and log reduction value (LRV) for the test filter calculated.

Results

The retention performance of the filter can be expressed as Log Reduction Value (LRV). The LRV is defied as follows:

$$LRV = \text{Log}_{10} \frac{\text{Number of Organisms Challenged to the Filter}}{\text{Number of Organisms in the Effluent from the Filter}}$$

If no organism is detected in the filtrate, the number 1 is used in the denominator ($10^0 = 1$).

ZTEC WB 0.2µ: *Pseudomonas aeruginosa*

Lot Number	*Diffusional Flow @ 25 psig*	*Filtrate Count (CFU)*	*LRV*
20364-001	27ml/min	<1	>11.87
20364002	20 ml/min	<1	>11.87
20364-003	14 ml/min	<1	>11.87

ZTEC WB 0.45µ: *Lactobacillus brevis*

Lot Number	*Diffusional Flow @ 16 psig*	*Filtrate Count (CFU)*	*LRV*
92407-004	<10 ml/min	<1	>12.14
92407-005	<10 ml/min	<1	>12.14
92407-006	<10 ml/min	<1	>12.14
92407-013	<10 ml/min	3.3×10^4	7.62
8021-006	<10 ml/min	<1	>12.11
8021-011	<10 ml/min	<1	>12.11

ZTEC WB 0.45µ: *Oenococcus oeni*

Lot Number	*Diffusional Flow @ 16 psig*	*Filtrate Count (CFU)*	*LRV*
33334-002	5 ml/min	3.5×10^2	10.06
33334-004	3 ml/min	1.9×10^2	10.33
33334-007	6 ml/min	4.0×10^2	10.01
33334-010	5 ml/min	2.1×10^2	10.29
33334-014	4 ml/min	3.3×10^2	10.09

ZTEC WB 0.45µ: *Saccharomyces cerevisiae*

Lot Number	*Diffusional Flow @ 16 psig*	*Filtrate Count (CFU)*	*LRV*
0720226-011	<1 ml/min	<1	>11.12
0720223-005	<1 ml/min	<1	>11.10
0720226-010	<1 ml/min	<1	>11.10
0720223-001	<1 ml/min	<1	>11.16
0720223-003	<1 ml/min	<1	>11.16

ZTEC WB 0.65µ: *Saccharomyces cerevisiae*

Lot Number	*Diffusional Flow @ 14 psig*	*Filtrate Count (CFU)*	*LRV*
33331-011	5 ml/min	1.6×10^2	8.83
33331-006	4 ml/min	1.7×10^2	8.80
33331-003	5 ml/min	1.5×10^2	8.77
33331-007	4 ml/min	1.6×10^2	8.74
33331-008	2 ml/min	1.7×10^2	8.71

ZTEC WB 1.2µ: *Saccharomyces cerevisiae*

Lot Number	*Diffusional Flow @ 14 psig*	*Filtrate Count (CFU)*	*LRV*
8034-1312-001	27 ml/min	<1	>11.10
8034-1312-002	13 ml/min	<1	>11.10
8034-1312-003	8 ml/min	<1	>11.10

Conclusion

ZTEC WB cartridges are well-suited for bioburden reduction and the removal of contaminants in beverage applications. For each rated pore size of ZTEC-WB filter, the LRVs for appropriate challenge organisms are more than sufficient to reduce bio-burdens to acceptable levels.

Minimum LRV per 10" cartridge

Pore Size	*Pseudomonas aeruginosa* ATCC# 9027	*Lactobacillus brevis* ATCC# 4869	Oenococcus Oeni ATCC# 23279	*Saccharomyces cerevisiae* ATCC # 9763
0.2 µm	≥11.8			
0.45 µm		≥7.62	≥ 10.01	≥ 11.1
0.65 µm				≥ 8.71
1.2 µm				≥ 11.1

European Regulation No 1935/2005 and European Directive 82/711/EEC

The underlying principle of these regulations is to ensure that any material or article intended to come into contact directly or indirectly with food must be sufficiently inert to preclude substances from being transferred to food in quantities large enough to endanger human health or to bring about an unacceptable change or deterioration in the composition or properties of the food. Tests for migration behavior in direct food contact were conducted by Belgium Packaging Institute in a variety of liquids to simulate aqueous, acidic, alcoholic, and fatty foodstuffs.

Results

The results of the test demonstrate that 4 to 14 liters of rinse, depending on stimulant, are required to achieve migration levels below the maximum limit of 60 mg/kg.

Sample	Simulant B 3% (w:v) acetic acid	Simulant C 10% (v:v) ethanol	Simulant D 95% ethanol	Simulant D isooctane
Filter	5	4	6	14

Endotoxin Test

Endotoxins are complex polysaccharide molecules (LPS) composed of lipid (lipid A) and polysaccharide sides chains and are integral components of the outer membrane of gram negative bacteria. These molecules are not secreted but are released only when the cells are disrupted or destroyed. Above certain levels, endotoxins elicit an antigenic response, resulting in fever and altered resistance to bacterial infections. Because of this sensitivity, it is important to monitor products which may contact fluids that could be administered to humans or animals.

The detection of endotoxins is accomplished using Limulus Amebocyte Lysate (LAL) Kinetic Chromogenic Assay. In this test, a filter element is extracted with non-pyrogenic Water for Injection (WFI). Endotoxin levels in the extracted fluid are then measured spectrophotometrically and compared to standard concentrations. These values are reported as EU/ml (Endotoxin Units/ml). The US Food and Drug Administration (FDA) has established limits of ≤ 0.5 EU/ml for medical devices and ≤ 0.25 EU/ml for WFI.

Results

NAMSA of Northwood Ohio conducted the testing on two samples of ZTEC WB. Levels were reported at 0.0114 EU/ml and 0.0113 EU/ml. These levels are well below the criteria established by the US FDA.

Bio-safety Testing

The purpose of this testing is to evaluate the biological suitability of the materials of construction for applications in which the ZTEC WB cartridge is typically used.

Toxicity Testing

Some of the most common applicable test methodologies are those specified in The United States Pharmacopoeia, under Group VI Biological Tests for Plastics. The ZTEC WB cartridge filter was submitted to NAMSA, an outside testing laboratory for testing in accordance with current USP procedures.

Samples were evaluated for bio-compatibility in accordance with the guidelines of the current USP. The purpose of the study was to evaluate the potential for a local irritant or toxic response to material implanted in direct contact with muscle tissue. There are three tests to meet the requirements for USP Plastics Class VI. The test article was prepared at a ratio of 4g:20 ml and extracted at 250°F (121°C) for 1 hour and subjected to the following tests:

1. USP Systemic Toxicity Study in the Mouse
2. USP Intracutaneous Toxicity Study in the Rabbit
3. USP Muscle Implantation Study in the Rabbit.

Conclusion

Based on this testing, the results of the tests conducted on the ZTEC WB filter cartridge indicate that it is non-toxic in any of the assays conducted. Full copies of the test report are available upon request.

Notes