ZTEC P Validation Guide

ISO 9001:2015

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.

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Introduction

The Graver Technologies 0.2 µ m ZTEC P pleated filter cartridges are designed as an exceptionally clean, non-leaching, non-shedding barrier for membrane filtration. These filters offer reliable performance in removing both biological and inert contaminants larger than their rated pore sizes. All ZTEC P P filter cartridges incorporate two layers of 0.2 micron polyethersulfone membrane to provide complete retention of *Brevundamonas diminuta* at a challenge level of $\geq 10^7/cm^2$ according to ASTM 838-05*, Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration.* In addition, the ZTEC P cartridge components (cage, core, end caps and support layers) are entirely polypropylene, which conforms to both CFR for Indirect Food Additives and USP Class VI standards. The ZTEC P filter cartridges can be sanitized with steam, hot water, or compatible chemicals. Each filter is rinsed with de-ionized water and integrity tested before release from manufacture. All the ZTEC P filter products are fabricated in an ISO 9001, Rev. 2015 Registered manufacturing facility.

This report contains results of laboratory tests performed on Graver Technologies' 0.2 µm, ZTEC P membrane cartridge filters. This document describes:

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

Nomenclature & Construction

ZTEC P NOMENCLATURE INFORMATION				
Filter Type	**Retention Rating** (microns)	**Nominal Length** (inches)	**End Configuration**	**Gasket or O-Ring**
ZTEC P Series	**0.2**	**–10** **–30** **–20** **–40**	**P2** 226/Flat Single Open End **P3** 222/Flat Single Open End **P7** 226/Fin Single Open End **P8** 222/Fin Single Open End	**B** Buna-N **E** EPDM **S** Silicone **T** Teflon encap. Viton (O-Rings only) **V** Viton
Example: ZTEC P 0.2–20 P2S				
ZTEC P	0.2	–20	P2	S

Materials of Construction

Membrane:	Double layer polyethersulfone (PES) – 6.8 ft^2 (0.63 m^2)
Drainage Layer:	Polypropylene
Core:	Polypropylene
Cage/Outer Sleeve:	Polypropylene
End Caps:	Polypropylene
O-Rings:	Viton (standard) Silicone EPDM Buna-N Teflon Encapsulated Viton

Product Traceability

ZTEC P 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 9001:2015. 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 P filter cartridges in finished format 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 P 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 purified water by flowing water through the cartridge at 10 GPM for 20 minutes.
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	*Diffusion Test Pressure psig (bar)*	*Maximum Diffusion (cc/min) per 10-Inch Cartridge Length*	*Bubble Point psig (bar)*
0.2 µm	32 (2.2)	≤ 30	≥ 40 (2.75)

Flow Rate Test

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.
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		0.2 µm		0.2 µm	
Cart. ID #	*US GPM Flow at 1 PSID*	*Cart. ID #*	*US GPM Flow at 1 PSID*	*Cart. ID #*	*US GPM Flow at 1 PSID*
#1	0.94	#3	1.22	#5	1.32
#2	0.87	#4	1.24	#6	1.27

Conclusions

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

0.2 µm: 1.1gpm/PSID (0.25 m^3/hr)

Core Collapse (Differential Pressure Stress) Test

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 P 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 P cartridge fabrication methodology, ZTEC P 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

Steam Sterilization Test

Under certain conditions it may be required to steam sterilize or sanitize the ZTEC P 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 P cartridge. This section outlines the test procedures, results and conclusions used in validating ZTEC P 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 psia (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 P filter cartridges remain integral when steam sterilized up to 50 times at 275°F (135°C) for 30 minutes per cycle.

Hot Water Sanitization Test

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 P filter cartridges can be hot water sanitized at least 50 times under the above specified conditions.

Bacteria Challenge Test

Nelson Laboratories Inc., Salt Lake City, Utah, performed the bacteria 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."

The American Type Culture Collection (ATCC) bacteria strain was chosen as challenge organism because of the significance in the pharmaceutical market. 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 defined as follows:

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

ZTEC P 0.2µm: *Brevundimonas diminuta*	
Lot Number	***LRV***
1556665-S01 #002	>11
1556665-S01 #003	>11
1556665-S01 #004	>11
1556672-S01 #001	>11
1556672-S01 #003	>11
1556672-S01 #004	>11
1556666-S01 #001	>11
1556666-S01 #002	>11
1556666-S01 #004	>11

Conclusion

ZTEC P cartridges are well-suited for the production of sterile effluent in pharmaceutical and other critical applications. ZTEC P cartridge filters that display an air diffusion value of ≤30ml/minute at 32 PSIG (2.2 bar) are sufficient to reduce bio-burden and produce an LRV that meets or exceeds the value defining a sterilizing grade filter cartridge. The published value provides a safety factor as values up to 63 ml/minute also produce sterile effluent.

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 the USP requirement of 20 EU/device.

Results

NAMSA of Northwood Ohio conducted the testing on a sample of ZTEC P. Levels were reported at 0.005 EU/ml and 5.0 EU/device. This level is well below the criteria established by the US FDA and USP.

European Regulation No 1935/2004 and European Regulation 10/2011

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 test results indicate that the overall migration of all of the individual parts will not exceed the overall migration limit of 10 mg/dm^2 or 60 mg/kg foodstuffs for simulant A (10% ethanol, representing all aqueous foodstuffs), simulant B (3% acetic acid, representing all foodstuffs with a pH below 4.5) and simulant D2 (95% ethanol and isooctane instead of olive oil representing all fatty foodstuffs) using the given conditions. In accordance with the European Regulation No 10/2011 and amendments, conformity with the overall migration limit for simulants A, B and D2 demonstrates suitability for contact with all kinds of foodstuffs. Consequently, ZTEC P samples are suitable for contact with all kinds of foodstuffs up to 70 °C for maximum 2 hours or up to 100 °C for maximum 15 minutes.

Bio-safety Test

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

Toxicity Test

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 P 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 P 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