Pharmsteri™ II GHF PES 0.22 µm Capsule Filter

Validation guide

TABLE OF CONTENTS

SECTION 1: INTRODUCTION

Pharmsteri™ II gamma-stable high flow (GHF) 0.22 µm PES capsule filters are designed and intended for critical, liquid filtration processing steps within pharmaceutical, biopharmaceutical, and medical applications. The Pharmsteri II GHF product family is made of a high-grade, gamma-stable polypropylene shell, and a hydrophilic polyethersulfone (PES) membrane with an absolute pore rating of 0.22 µm. The asymmetric PES membrane is a sterilizing grade and meets bacterial retentiveness per ASTM F838-20. The Pharmsteri II GHF product line offers filter sizes ranging from 50 mm disc capsule up to a 10" capsule. These filters are ideal for low-fouling applications requiring a sterilizing grade filter across upstream and downstream bioprocessing steps. These filters provide high throughput, biocompatibility, excellent flow performance, and gamma-stable materials of construction.

Entegris' cutting edge filter designs have enabled the Pharmsteri II GHF capsule filter to deliver maximized throughput and filtration performance, that is achieved with enhanced effective filtration surface area per device.

Supported by Entegris' world-class quality systems, the Pharmsteri GHF portfolio ensures production of reliable, high-quality devices. In addition, Entegris' strong supply continuity and quality control enable competitive lead times for the Pharmsteri II GHF PES 0.22 µm capsule filters.

Figure 1. Pharmsteri II GHF PES 0.22 µm capsule product portfolio.

SECTION 2: SCOPE

The scope of this document includes the standard Pharmsteri II GHF PES 0.22 µm capsule filters assigned to part number format as shown below. This validation guide pertains only to the Pharmsteri II GHF PES 0.22 µm capsule filters.

Pharmsteri II GHF PES 0.22 µm capsule filter: part number

PST SA 022 _ _ _ _

Capsule type
SU = gamma compatible
GS = gamma sterilized

Membrane
SA = PES single-layer

Pore rating
022 = 0.22 µm

Code and O-ring
TS = 1.5" TC inlet/outlet, silicone O-ring
HS = ½" HB inlet/outlet, silicone O-ring
TH = 1.5" TC inlet, ½" HB outlet
SH = ¼" HB inlet/outlet, disc only

Size
00 = 50 mm disc
03 = 3"
05 = 5"
10 = 10"

Pack
-1 = 1 ea/box
-2 = 2 ea/box
-3 = 3 ea/box

SECTION 3: COMPLIANCE OVERVIEW

Entegris has a long history of environmental compliance in the countries where it operates and distributes its products. Entegris actively reviews products to ensure compliance and conformance with government and customer requirements related to raw materials and substances used in manufacturing processes. Entegris relies on information provided by the suppliers as the foundation for the listed regulatory statement and makes no representations or warranties about any such testing.

Ultimately, end-users must determine that the use of this product is safe, lawful, and technically suited for their intended application and purpose. Entegris assumes no liability for any loss or injury resulting from using the information in this overview. The table below represents compliance claims for Pharmsteri II GHF 0.22 µm PES components as of the time of publishing this validation summary.

3.1 REGULATORY FILING DISCLAIMER

The filters within the Pharmsteri II GHF portfolio are not approved, cleared, or defined as a medical or pharmaceutical product(s) by any regulatory authority. Additionally, the process must be validated for the intended use if the filter comes into contact with a medical or pharmaceutical product. Entegris can assist in providing the appropriate documentation or support by offering validation testing services for the specific application. Entegris can also assist in any required regulatory filings for end-users for a wide range of applications.

Table 1. Validation Testing Summary for Materials of Constructions of the Pharmsteri II GHF Portfolio

Component	USP <88>/ Class VI	USP <87>/ ISO 10993-5 equivalent/ cytotoxicity	USP<85>/ endotoxin	TSE/BSE/ animal origin free	USP<643>/ total organic carbon	USP <645>/ conductivity	USP <788>/ particulate	21 CFR 210.3 (b) (6) Non-fiber releasing
Filtration membrane	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet
Upstream support	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet
Downstream support	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet
Capsule body, inner core, end caps	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet
Film edge	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet
O-ring	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet

SECTION 4: CERTIFICATE OF QUALITY

Pharmsteri II GHF PES 0.22 µm capsule filters will be shipped with a Certificate of Quality (CoQ). Figure 2 shows an example of the 10" capsule CoQ.

Entegris

Pharmsteri™ II GHF PES Liquid Capsule Filter

PSTSU PES 0.22 um TS 10 in 1pc

Part No. : PSTSUSA022TS10-1
Lot No.: G2J653904
Mfg. Date: 2024-03
Quantity: 1 EA

Manufacturing standard
This product was manufactured in accordance with applicable Entegris Standard Procedures.

Quality Management System
The production process of this product complies with the requirement of ISO13485 and ISO9001 quality management system. The whole production process of the product was under strict, ordered quality control.

Manufacturing Environment
100,000 class clean area, similar with ISO Class 8.

Validated Production Process
This product was fabricated with a validated manufacturing process. Principles of statistical process control and determinations of process capability have been applied to critical variables to ensure the stability of filter fabrication processes.

Certificate of Quality

Product Performance Criteria
This product was designed and manufactured to meet the following specifications:

Integrity/Diffusion
Each capsule was integrity tested with air diffusion flow @ 40 psi wetted with DI water @ 25°C, and passed the test with less than or equal to 25.0 mL/min. This test was correlated to the Brevundimonas diminuta challenge test ASTM F838.

Cleanliness
Non-Fiber Releasing: This product was manufactured with materials that conform to the criteria for non fiber release and the final product was tested to criteria 21 CFR 210.3 (b) (6)
Particle Shedding: This product releases particulate matter in quantities below the requirements established in the current USP <788>, Particulate Matter in Injections.
Conductivity: Aqueous samples of effluent was tested of the product post gamma and after water flush, it met the requirements of conductivity for USP <645>.
TOC: Aqueous samples of effluent was tested of the product post gamma and after water flush, it met the requirements of TOC for USP <643>.

Autoclavability
Integrity and performance was preserved after 2 cycles @ 130°C for 30 mins.

Max Operating Temp/Pressure
This product was tested post gamma and maintained integrity and performance for forward pressure with water.
Max Operating Pressure: 80 psi (5.5 bar) @ 25°C
40 psi (2.8 bar) @ 60°C
Max Differential Pressure:
Forward: 60 psi (4.1 bar) @ 25°C
30 psi (2.1 bar) @ 60°C
Reverse: 10 psi (0.7 bar) @ 25°C

Gamma Compatibility
This product was manufactured with gamma compatible raw materials and testing on final filters confirmed product performance was maintained after exposure of 45 kGy.

Bacterial Retention
This product was tested to meet retention for *Brevundimonas diminuta* (ATCC 19146) at a challenge level of >1 x 10^7 CFU/cm^2 as per the ASTM F838.

Toxicity
All components of the product were tested for cytotoxicity as per USP <87> Biological Reactivity Tests, in vitro (cytotoxicity) and found to be non cytotoxic. Component materials were tested and meet the criteria of the USP <88> Reactivity Test for Class VI plastics.

Endotoxin Releasing
Aqueous samples from the product was tested for bacterial endotoxins and determined using the Limulus Amebocyte Lysate (LAL) test to be less than 0.25 EU/mL, meeting the requirements of USP <85>.

Animal Free
Based on all available information from our suppliers, the raw materials used to manufacture this product are not animal derived, therefore the product meets the EU directive for animal free CPMP EMA/410/01 and 21 CFR parts 189.5.

QA Manager:

Figure 2. Certificate of Quality example.

SECTION 5: MANUFACTURING ENVIRONMENT

Pharmsteri II GHF PES 0.22 µm capsule filters are manufactured in a 100,000-class clean area, similar to an ISO Class 8 cleanroom. Entegris certifies that each lot has been manufactured and tested according to approved procedures and specifications under a quality system certified to ISO 13485 and ISO 9001.

The manufacturing and laboratory equipment used to manufacture and test Pharmsteri II GHF filter products have been qualified for their intended use, including installation, operation, performance, and calibration. Additionally, the equipment has maintained qualified status and undergone change control to ensure reproducible process parameters during normal manufacturing operations within established operating limits. Process parameters have been optimized to meet filter device specification and quality attributes of the manufacturing process. Proper facility operator instructions regarding in-house cGMP guidelines, such as gowning, employee hygiene, etc. and operations have been implemented. A controlled environment has been established for control of contamination and ensure that manufactured products meet cleanliness.

SECTION 6: QUALITY MANAGEMENT SYSTEMS

Entegris life science filtration plant implemented Quality Management System ISO9001 and ISO13485.

SECTION 7: QUALITY ASSURANCE

7.1 DESIGN CONTROL

Entegris ensures design control through a new product development process where each product from the Pharmsteri II GHF product portfolio has gone through a robust design, engineering, qualification, and pilot manufacturing review. The design control process includes proper documentation and traceability at each phase of the product development process and post-launch. The manufacturing process, including process parameters and controls, have been qualified and validated to ensure products released to mass production are consistently produced at high-quality levels and meet specifications.

7.2 PRODUCTION AND PROCESS CONTROL

Entegris has implemented a high level of production and process control for production of Pharmsteri II GHF filtration products. Manufacturing controls include raw material reviews in the following processing steps: material qualification, vendor qualification, incoming material inspection for each lot and periodic quality reviews. Manufacturing process limits and batch-to-batch product variability have been validated during validation and pilot runs to maintain stable controls to ensure product performance and quality levels are met. Statistical methods have been used to determine final product specification and to sustain precise process controls during manufacturing. All process inspections are performed and documented for raw materials, semi-finished products, and final products throughout the manufacturing process.

7.3 IDENTIFICATION AND TRACEABILITY

Entegris ensures proper product identification and traceability controls for released products. Pharmsteri II GHF products have labels on the packaged box and the protective plastic bag have clear description of product portfolio name, part number, and lot number. Additionally, the physical filter product has the following information laser-etched with the part number, maximum pressure and temperature, lot number, and serial number. This allows for clear traceability of released products. Entegris maintains manufacturing process records, which includes raw materials used, manufacturing process parameters, material inspections, and filter device test data for full traceability.

SECTION 8: MATERIALS OF CONSTRUCTION

Pharmsteri II GHF PES 0.22 µm capsule filters are made of high-grade, gamma-stable components as shown in below table. All materials of construction meet the FDA requirements as defined in Title 21 Code of Federal Regulations and the Biosafety Tests as defined in the current USP including USP <87> (Biological Reactivity Tests, In Vitro) and USP <88> Class VI Plastics Test (Biological Reactivity Tests, In Vivo).

Table 2. Materials of Construction

Component	Material of construction	Disc	3" Capsule	5" Capsule	10" Capsule
Membrane (media)	Polyethersulfone (PES)	×	×	×	×
Support	Polyester	×	×	×	×
Film edge	Polypropylene/polyethylene (PP/PE) copolymer	–	×	×	×
Core, cage, end caps	Polypropylene (PP)	×	×	×	×
O-ring	Silicone	×	×	×	×

SECTION 9: FILTER MATERIALS VALIDATION

9.1 ANIMAL FREE AND TSE/BSE RISK

Based on the raw material certifications provided by suppliers, no bovine or animal-derived materials are used in the manufacture of Pharmsteri II GHF capsule filters. No filter components contain added animal derivatives, and all meet TSE/BSE and manufacturing requirements defined in EMEA/410 Rev 3. The manufacturing process does not introduce added animal derivatives at any processing step. Therefore, the Pharmsteri II GHF capsule filters are compliant with EMEA/410 Rev 3 and risk-free of TSE/BSE.

9.2 USP <87> BIOLOGICAL REACTIVITY TESTS, IN VITRO

Background:

Cytotoxicity testing assesses the potential of a given material's toxic effect on living cells. Entegris evaluated the Pharmsteri II GHF filter components to confirm compliance with USP <87>.

Method:

Each component of the Pharmsteri II GHF capsule filters was gamma sterilized at 50 kGy and tested in vitro by a certified, independent third-party laboratory in accordance with USP <87> Biological Reactivity Tests.

Results:

Table 3 provides a summary of the results. Complete reports are listed in the appendix for reference. For access to complete reports, please contact your Entegris representative for additional information.

Table 3. UPS<87> Cytotoxicity Test Results

		24 hr exposure	48 hr exposure
Test article	**Test type**	**Final grade**	**Final grade**
Medium	MEM	0	0
Negative control	MEM	0	0
Positive control	MEM	4	4
Resin	MEM	0	0
PES membrane	MEM	0	0
Non-woven support	MEM	0	0
Edge strip	MEM	0	0
O-ring	MEM	0	0

Conclusion:

All filter components of the Pharmsteri II GHF devices were tested for cytotoxicity per USP guidelines USP <87> and found to be non-cytotoxic.

9.3 USP <88> BIOLOGICAL REACTIVITY TESTS, IN VIVO

Background:

The USP <88> Class VI testing assesses the potential toxicity of extracts from the Pharmsteri II GHF capsule filter into live animal models. Dosing is performed systematically, intracutaneously, and implanted. Test animals are monitored for irritation or toxicity.

Method:

The test articles were sterilized with gamma irradiation at 50 kGy before testing. The post-gamma sterilized test articles were exposed at a surface area (cm^2) to extraction solution volume (mL) ratio of 6. Extract medium included: USP 0.9% sodium chloride injection, cottonseed oil, 1:20 (v/v) ethanol in sodium chloride injection, and polyethylene glycol (PEG) 400 at 70°C ± 2°C (158°F ± 3.6°F) for 24 ± 2 hours. These extracts were injected intracutaneously into rabbits and systemically into mice. Each animal was observed and evaluated for a biological response. Moreover, the test article implantation into the paravertebral muscles of rabbits was monitored for seven days to determine signs of irritation or infection.

Results:

Table 4 provides a summary of the results. Complete reports are listed in the appendix for reference. For access to complete reports, please contact your Entegris representative for additional information.

Table 4. USP <88> Test Results on Test Articles

Test items	Test results
Systemic toxicity study in a mouse	Pass
Intracutaneous toxicity study in a rabbit	Pass
Muscle implantation study in a rabbit	Pass

Conclusion:

Pharmsteri II GHF filters meet criteria established per USP guidelines USP <88> Biological Reactivity Tests, In Vivo, Class VI Plastics.

9.4 USP <85> BACTERIAL ENDOTOXIN TESTS

Background:

Endotoxins are lipopolysaccharide complexes found in gram-negative bacterial cell walls. The bacterial endotoxin test is a test to detect or quantify endotoxins from gram-negative bacteria using amoebocyte lysate from the horseshoe crab (*Limulus polyphemus* or *Tachypleus tridentatus*). Entegris evaluated different filter sizes of the Pharmsteri II GHF portfolio.

Method:

The testing performed follows USP <85> testing methodologies and standards. Each test article's flow path was soaked with ultrapure water and incubated at 37°C (98.6°F) for one hour. The positive control was prepared using LAL (*Limulus amebocyte lysate*) reagent water (endotoxin-free) and the endotoxin standard. A positive product control was prepared using the test article extract and the endotoxin standard. The LAL reagent water (endotoxin-free) was used as a negative control. LAL reagent was added to all test and control samples, which were then incubated for one hour before being observed for gel formation in the solution. Filter samples were utilized from the OQ and PQ runs during the IOQ validation phase.

Results:

All samples collected from process limits and process stability validation lots had passing results. All capsule sizes from the GHF portfolio are tested, and the table shows the results of a representative 10" capsule and 50 mm disc from process validation lots. The complete validation reports, including data for the additional filter sizes, are available upon request.

Table 5. The Pharmsteri II GHF Capsules Endotoxin Test Results

Part no.	Lot no.	Serial no.	LAL test results
PSTSUSA022TS10-	G2E589928	-18, -7	Passed
	G2E589926	-18, -4	Passed
	G2E589925	-11, -1	Passed
PSTSUSA022HS10-	G3P064080	-10, -12	Passed
	G3P064081	-11, -3	Passed
	G3P064222	-6, -3	Passed
PSTSUSA022SH00-	G3J956442	-4, -5, -6	Passed
	G3J956443	-4, -5, -6	Passed
	G3E899298	-104	Passed
	G3E899297	-114	Passed

Conclusion:

Based on the positive control, negative control, and positive product control data, the test system was controlled, and the product did not interfere with the test system or results. The endotoxin level was determined to be below the 0.25 EU/mL limit for all filters evaluated within the Pharmsteri II GHF portfolio.

9.5 CLEANLINESS – PARTICLES, TOC AND CONDUCTIVITY

Background:

Entegris evaluated different filter sizes from the Pharmsteri II GHF capsule portfolio for particle content in filtrate, total organic carbon (TOC), and conductivity to assess cleanliness levels. The industry specification was used against each measurement to determine compliance with the Pharmsteri II GHF capsule portfolio.

Method:

For the filter cleanliness study, TOC conductivity and particulates were tested using the same sample collected from both OQ and PQ lots. All samples were subjected to gamma sterilization at 50 kGy before testing. Ultrapure water was flushed through a Pharmsteri II GHF filter at a flow rate of 0.5 L/min for capsules and 0.2 L/min for 50 mm disc. After discarding the first 200 mL of effluent for capsules and 50 mL for 50 mm disc, samples were collected at specific intervals as shown in the results below. TOC, conductivity, and particulates were tested using samples collected at each time point following US Pharmacopeia standards. The recommended testing method from USP <643> Total Organic Carbon was used to measure TOC. The recommended testing method from USP <645> Water Conductivity was used to measure conductivity. The recommended testing method from USP <788> Particulate Matter in Injections was used to measure particulates in effluent.

Results:

All samples from process limits and process stability validation lots passed the test. All capsule sizes from the Pharmsteri II GHF portfolio were tested, and the tables below show the average TOC, conductivity, and particle shedding results of lots from process validation. Complete validation reports and raw data are available upon request. Please contact your Entegris representative for additional information.

Table 6. The Pharmsteri II GHF 10" Capsule Cleanliness Test Results

Part number: PSTSUSA022TS10-

Lot no.	Serial no.	Volume	Conductivity	TOC	Particles ≥10 µm	Particles ≥25 µm
G2E589928	-17 -19 -29	1 L	4.53 µS/cm	>1 mg/L	1.47 pcs/mL	0.17 pcs/mL
		5 L	0.95 µS/cm	0.51 mg/L	1.73 pcs/mL	0.13 pcs/mL
		10 L	0.64 µS/cm	0.33 mg/L	0.87 pcs/mL	0.07 pcs/mL
G2E589926	-3 -10 -13	1 L	4.04 µS/cm	>1 mg/L	3.57 pcs/mL	0.20 pcs/mL
		5L	1.04 µS/cm	0.54 mg/L	1.47 pcs/mL	0.17 pcs/mL
		10 L	0.66 µS/cm	0.30 mg/L	1.10 pcs/mL	0.10 pcs/mL
G2E589925	-2 -8 -24	1 L	4.56 µS/cm	>0.95 mg/L	0.93 pcs/mL	0.10 pcs/mL
		5 L	0.90 µS/cm	0.54 mg/L	1.20 pcs/mL	0.03 pcs/mL
		10 L	0.65 µS/cm	0.35 mg/L	0.67 pcs/mL	0.03 pcs/mL
	Specifications		≤1.3 µS/cm	≤0.5 mg/L	≤25 pcs/mL	≤3 pcs/mL

Table 7. The Pharmsteri II GHF 5" Capsule Cleanliness Results

Part number: PSTSUSA022TS05-

Lot no.	Serial no.	Volume	Conductivity	TOC	Particles ≥10 µm	Particles ≥25 µm
G3H942947	-10 -19 -25	1.0 L	1.48 µS/cm	0.69 mg/L	2.90 pcs/mL	0.10 pcs/mL
		4.0 L	0.57 µS/cm	0.43 mg/L	2.33 pcs/mL	0.03 pcs/mL
		7.5 L	0.38 µS/cm	0.26 mg/L	2.40 pcs/mL	0.00 pcs/mL
G3H942948	-13 -29 -30	1.0 L	1.77 µS/cm	0.43 mg/L	2.60 pcs/mL	0.17 pcs/mL
		4.0 L	0.48 µS/cm	0.43 mg/L	2.80 pcs/mL	0.03 pcs/mL
		7.5 L	0.22 µS/cm	0.25 mg/L	2.07 pcs/mL	0.13 pcs/mL
G3H942949	-14 -25 -29	1.0 L	1.86 µS/cm	0.51 mg/L	2.23 pcs/mL	0.10 pcs/mL
		4.0 L	0.69 µS/cm	0.46 mg/L	2.43 pcs/mL	0.03 pcs/mL
		7.5 L	0.26 µS/cm	0.26 mg/L	2.20 pcs/mL	0.07 pcs/mL
	Specifications		≤1.3 µS/cm	≤0.5 mg/L	≤25 pcs/mL	≤3 pcs/mL

Table 8. The Pharmsteri II GHF 3" Capsule Cleanliness Results

Part number: PSTSUSA022TS03-

Lot no.	Serial no.	Volume	Conductivity	TOC	Particles ≥10 µm	Particles ≥25 µm
G4B131285	-4 -5	1.0 L	1.38 µS/cm	0.50 mg/L	3.35 pcs/mL	0.10 pcs/mL
		4.0 L	0.58 µS/cm	0.17 mg/L	4.55 pcs/mL	0.10 pcs/mL
		7.5 L	0.52 µS/cm	0.09 mg/L	3.20 pcs/mL	0.15 pcs/mL
G4B131286	-6 -24	1.0 L	1.32 µS/cm	0.48 mg/L	4.70 pcs/mL	0.10 pcs/mL
		4.0 L	0.60 µS/cm	0.17 mg/L	3.85 pcs/mL	0.15 pcs/mL
		7.5 L	0.53 µS/cm	0.10 mg/L	3.45 pcs/mL	0.10 pcs/mL
G4B131283	-8 -9	1.0 L	1.34 µS/cm	0.52 mg/L	2.70 pcs/mL	0.10 pcs/mL
		4.0 L	0.59 µS/cm	0.17 mg/L	4.45 pcs/mL	0.00 pcs/mL
		7.5 L	0.54 µS/cm	0.09 mg/L	2.95 pcs/mL	0.05 pcs/mL
	Specifications		≤1.3 µS/cm	≤0.5 mg/L	≤25 pcs/mL	≤3 pcs/mL

Table 9. The Pharmsteri II GHF 50 mm Disc Cleanliness Results

Part number: PSTSUSA022SH00-

Lot no.	Serial no.	Volume	Conductivity	TOC	Particles ≥10 µm	Particles ≥25 µm
G3J956442	-1 -2 -3	1 L	0.19 µS/cm	0.08 mg/L	1.17 pcs/mL	0.07 pcs/mL
		2 L	0.15 µS/cm	0.07 mg/L	0.83 pcs/mL	0.00 pcs/mL
		3 L	0.15 µS/cm	0.07 mg/L	0.40 pcs/mL	0.03 pcs/mL
G3J956443	-1 -2 -3	1 L	0.16 µS/cm	0.08 mg/L	1.20 pcs/mL	0.13 pcs/mL
		2 L	0.12 µS/cm	0.07 mg/L	0.73 pcs/mL	0.00 pcs/mL
		3 L	0.12 µS/cm	0.07 mg/L	0.43 pcs/mL	0.03 pcs/mL
G3E899298	-96 -95	1 L	0.42 µS/cm	0.11 mg/L	2.05 pcs/mL	0.15 pcs/mL
		2 L	0.26 µS/cm	0.09 mg/L	1.70 pcs/mL	0.05 pcs/mL
		3 L	0.24 µS/cm	0.07 mg/L	1.80 pcs/mL	0.00 pcs/mL
	Specifications		≤1.3 µS/cm	≤0.5 mg/L	≤25 pcs/mL	≤3 pcs/mL

Conclusion:

As shown in Tables 6 – 9, the results highlight that Pharmsteri II GHF filters meets TOC, conductivity, and particulate specifications. These results comply with and meet UPS <643>, USP <645>, and USP <788> industry standards. Complete validation reports and raw data are available upon request. Please contact your Entegris representative for additional information.

9.6 NON-FIBER RELEASING

The Pharmsteri II GHF capsules were evaluated for fiber release, and results demonstrated that they comply with Title 21 Code of Federal Regulations, Section 211.72 and 210.3(b) (6) for non-fiber releasing filters. For test results from the fiber release testing, please contact your Entegris representative for additional information.

9.7 CHEMICAL COMPATIBILITY

Background:

Chemical compatibility testing involves exposing filter elements to chemical(s) under controlled process conditions and evaluating its impact on the filter's functionality, performance, and integrity. The Pharmsteri II GHF PES 0.22 µm capsules were evaluated with different chemicals that ranging from 1 – 14 pH levels. A series of tests, pre- and post-exposure, were completed to assess functionality, performance, and integrity of Pharmsteri II GHF PES 0.22 µm capsules.

Method:

A water flow rate and a diffusional flow test were evaluated on Pharmsteri II GHF PES 10" capsules before and after exposure to determine the impact on the function and integrity of the filter. A 10" filter was selected to be worst-case as other sizes within the portfolio have the same material of constructions. The exposure duration for each chemical was approximately 24 hours. For each chemical, one capsule was evaluated to confirm pre- and post-impact. The chemicals evaluated include DI water (control), hydrochloric acid [0.15 M], acetic acid [0.1 M], phosphate citrate [10 mM], PBS, and sodium hydroxide [1 M].

Results:

Device Level: Diffusional Flow Distribution Pre/Post Chemical Exposure for 24-H Period

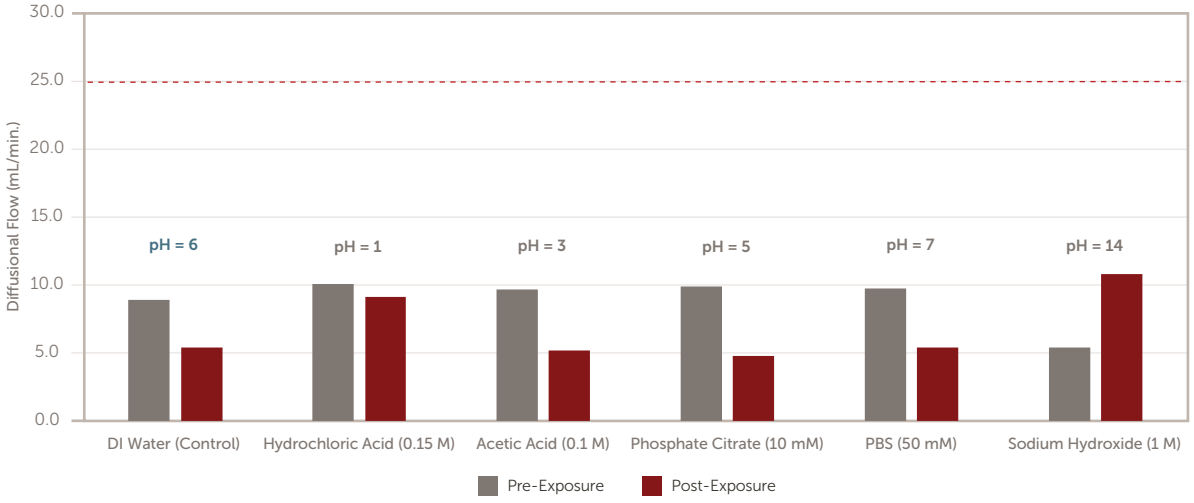

Figure 3. Integrity test results of pre and post exposure for GHF 10" capsules.

Device Level: Flow Rate Distribution Post Chemical Exposure of 24-H Period

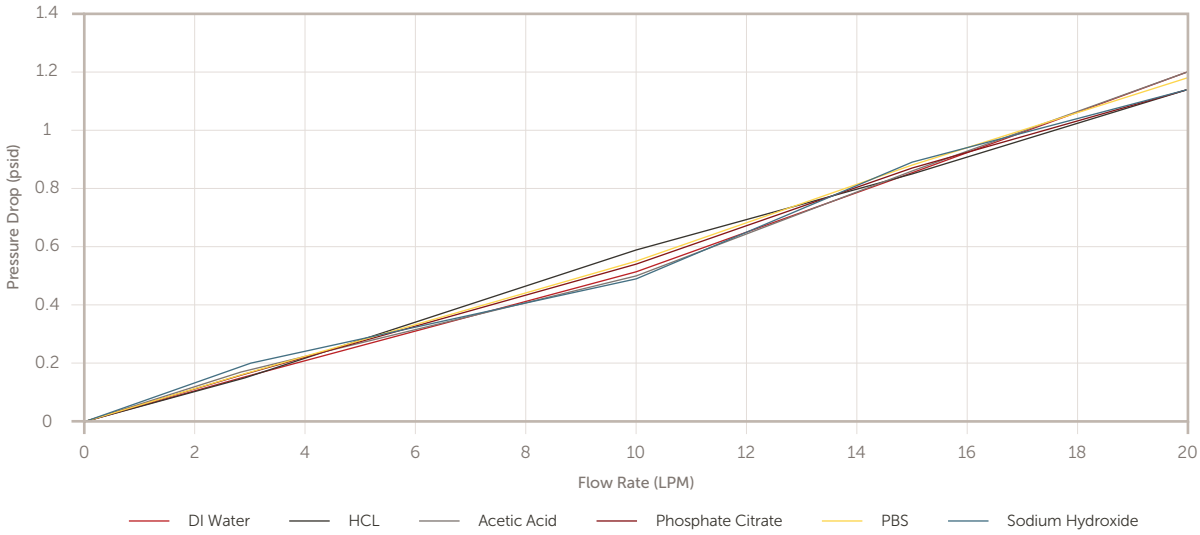

Figure 4. Water flow rate test of post exposure for GHF 10" capsules.

Conclusion:

The result demonstrates no impact on integrity or filter performance with the exposed chemicals. The results support that the Pharmsteri II GHF PES 0.22 µm capsules have broad chemical compatibility and are compatible with chemicals 1 – 14 pH levels.

SECTION 10: FILTER PERFORMANCE VALIDATION

10.1 WATER FLOW CHARACTERISTICS

Purpose:

Each filter device was tested for water flow performance using a constant pressure test stand, where the corresponding flow rate was monitored using a flow meter. Before the flow rate test, each filter was flushed and pre-wet for 10 minutes. The water source used was purified water and tested at room temperature. A minimum of three lots were used to create an average flow curve per filter configuration.

Results:

50 mm Disc

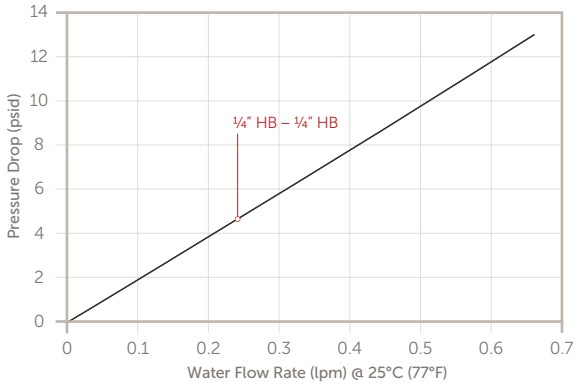

Figure 5. Pharmsteri II GHF 50 mm disc water flow performance.

3-inch Capsules

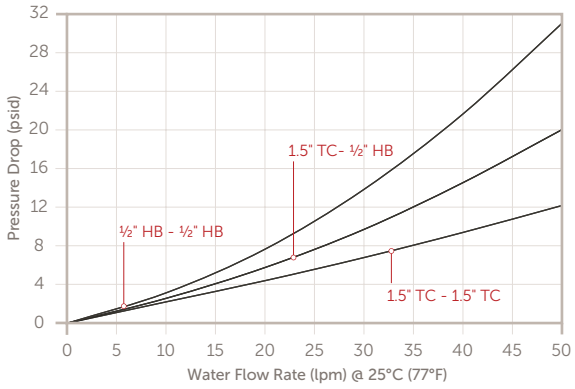

Figure 6. Pharmsteri II GHF 3" capsules water flow performance.

5-inch Capsules

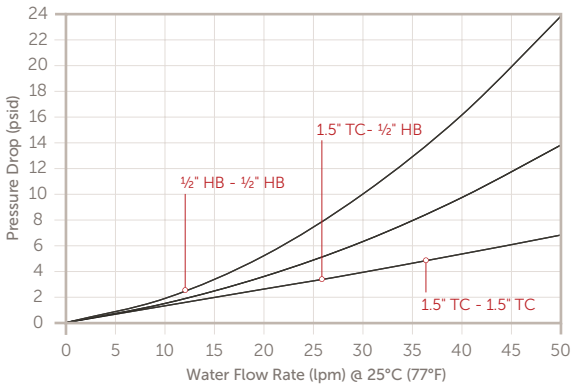

Figure 7. Pharmsteri II GHF 5" capsules water flow performance.

10-inch Capsules

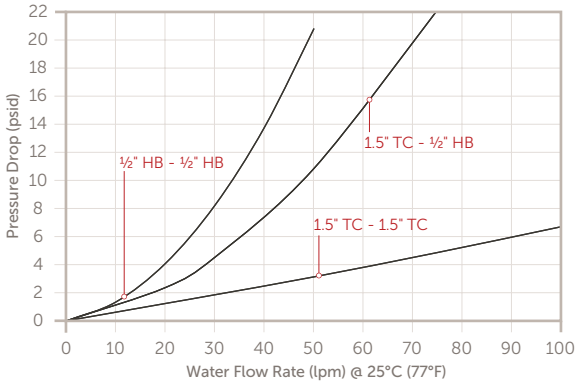

Figure 8. Pharmsteri II GHF 10" capsules water flow performance.

10.2 OPERATING TEMPERATURE AND PRESSURE RANGE

Background:

The max operating pressure was determined at different temperatures to ensure filter function and integrity for various applications. Moreover, the max differential pressure was determined to ensure proper filter functionality and sustained filter integrity during intended uses. Entegris evaluated different filter sizes from the Pharmsteri II GHF portfolio for the maximum allowable operating temperature and differential pressure to ensure the filter can meet operating specifications. The specifications include a maximum operation temperature, forward differential pressure, and reverse differential pressure.

Method:

Entegris used a constant pressure system with water at different temperatures to determine max operating and differential pressure specifications. Different filter sizes from the Pharmsteri II GHF portfolio were evaluated using OQ and PQ lot samples. All filter samples were gamma irradiated at 50 kGy before testing. A filter integrity test was performed after exposure of 30 min to each operating condition to confirm filter integrity.

Results:

All samples collected from process limits and process stability validation lots passed the subjected test. All capsule sizes from the GHF portfolio are tested and the tables below show the results for 10-inch, 3-inch and 50 mm disc. Full validation report and data are available upon request.

Table 10. Pharmsteri II GHF Capsules Max Operating Temperature and Differential Pressure

PART NO.	LOT NO.	SERIAL NO.	TEST CONDITIONS	INTEGRITY TEST RESULT
PSTSUSA022 TS10-	G2E589926	-19, -9, -30	>80 psi (5.5 bar) inlet pressure, >60 psi (4.1 bar) forward differential pressure at 60°C	Passed BP and DF test.
	G2E589925	-6, -28, -13		
	G2E589928	-4, -13, -28		
PSTSUSA022 TS03-	G4B131283	-16, -17, -18		
	G4B131285	-10, -11, -12		
	G4B131286	-19, -20, -18		
PSTSUSA022 TS10-	G2E589926	-29, -26, -15	>30 psi (2.1 bar) inlet pressure, >15 psi (1.0 bar) reverse differential pressure at 25°C	Passed BP and DF test.
	G2E589925	-20, -25, -30		
	G2E589928	-6, -30, -16		
PSTSUSA022 TS03-	G4B131283	-19, -20, -21		
	G4B131285	-16, -17, -18		
	G4B131286	-2, -3, -4		
PSTSUSA022 SH00-	G3J956442	-1, -2, -3 -4, -5, -6	>80 psi (5.5 bar) inlet pressure, >60 psi (4.1 bar) forward differential pressure at 25°C	Passed BP test.
	G3J956443	-19, -20, -21 -22, -23, -24		
	G3J956442	-7, -8, -9 -10, -11, -12	>40 psi (2.8 bar) inlet pressure, >30 psi (2.1 bar) forward differential pressure at 60°C	Passed BP test.
	G3J956443	-25, -26, -27 -28, -29, -30		
	G3J956442	-13, -14, -15 -16, -17, -18	>30 psi (2.1 bar) inlet pressure, >15 psi (1.0 bar) reverse differential pressure at 25°C	Passed BP test.
	G3J956443	-31, -32, -33 -34, -35, -36		

Conclusion:

Table 10 highlights the results of the Pharmsteri II GHF filters tested at different test conditions, and all have passing integrity test results. Each filter was subjected to a bubble point, diffusional flow, or both integrity tests post-exposure to test conditions. Complete validation reports and raw data are available upon request. Please contact your Entegris representative for additional information.

10.3 BACTERIA RETENTION CORRELATION WITH BUBBLE POINT TEST

Background:

Bubble point is a non-destructive integrity test used to determine the integrity of a filter device. To establish a correlation with bacterial retention and a sterilizing grade filter device is critical for determining an appropriate minimum bubble point specification. In accordance with ASTM F838-20 and FDA guidelines, a sterilizing grade filter challenge with a minimum of concentration of 10^7 *Brevundimonas diminuta* organisms/cm^2 of filter area must produce sterile filtrate. Using these guidelines, Entegris used pre- and post- bubble point integrity test during bacterial challenge test to determine a minimum bubble point specification.

Test Method:

The Pharmsteri II GHF 10" filters were integrity tested using an automatic integrity tester to characterize the bubble point distribution and determine the sterilizing cut-off of GHF 0.22 µm PES membrane. Each filter was wetted thoroughly prior to integrity testing using a purified water source. Each filter was subjected to a pre and post bubble point integrity test during a Bacterial Challenge Test, per ASTM F838-20 methodology. The bubble point distribution, with correlation to bacterial challenge test, was evaluated to determine the minimum bubble point specification for the Pharmsteri II GHF portfolio. It should be noted that a minimum of three lots of 10" Pharmsteri II GHF PES 0.22 µm capsules along with 10" filter devices that had a low-bubble point PES membrane were used to determine the sterilizing grade cut-off.

Conclusion:

Based on bubble point distribution of 10" Pharmsteri II GHF PES 0.22 µm capsules and correlation to bacterial retention, the minimum bubble point specification is 53 psi with water pre-wetting. The minimum bubble point specification of 53 psi (3.65 bar) in water pre-wetting applies to any capsule size within the Pharmsteri II GHF capsule portfolio. For a 60% IPA/40% water wetting minimum bubble specification, please contact your Entegris representative for additional information. Lastly, the complete bubble point correlation analysis and report are available upon request.

10.4 BACTERIA RETENTION CORRELATION WITH DIFFUSION FLOW TEST

Background:

The ultimate functionality of a sterilizing-grade filter is to consistently filter out microorganisms and generate sterile filtrate. The testing criteria for this function ability is to demonstrate that the filter can remove *Brevundimonas diminuta* of a bacterial challenge at a minimum 10^7 CFU/cm^2. To ensure the integrity and bacterial retention functionality of a sterilizing-grade filter, a filter manufacturer's objective is to design the filter membrane and device, manufacturing processes, and controls to meet this requirement. A sterilizing grade filter's membrane, device fabrication, and nondestructive integrity testing are the core areas of focus during filter development and qualification. The following three elements provide the foundation of the filter retentive performance claims to ensure a predictive correlation of nondestructive filter integrity test results with the bacteria retentive performance capabilities of the filter.

1. The membrane removes particulate contamination from the fluid stream and provides a sterile effluent post filtration. The device design provides high efficiency and manufacturing process control to ensure the integrity and efficacy of the membrane during and throughout the lifecycle of the filter including pre-use sterilization treatment. The nondestructive maximum diffusive flow specifications allow filter manufacturers and end users to make precise determinations on a given filter's retentive capability.

2. Entegris has utilized a 0.22 µm rated hydrophilic PES membrane capable of retaining at least 1×10^7 CFU/cm² of *B. diminuta*. Quality by Design (QbD) principles were employed during the filter device design and manufacturing process to ensure retentive performance and overall device integrity. Establishing a reliable nondestructive integrity test predictive of bacteria retention performance is a critical step in ensuring a high-quality device. To achieve this goal, Entegris has evaluated a wide array of the Pharmsteri II filters with different diffusive flow integrity test values. The data collected was utilized to establish the diffusive flow cutoff where values below this number indicate retentive performance of the filter with high statistical confidence.
3. Entegris performed a filtration validation study to determine a diffusive flow specification to ensure sterility and functionality of the filter. The study consisted of evaluating a minimum of three-lots of filter per filter size with a sample size of at least 10 samples that were subjected to a non-destructive diffusive flow integrity test followed by a destructive bacterial challenge test per ASTM F838. The diffusive flow test was performed in the forward direction with air pressure at 40 psi and DI water as the pre-wetting fluid. Entegris was able to statistically correlate the diffusive flow with successful BCTs. Each max diffusive flow cutoff specification, per filter size, includes a built-in safety factor to account for different integrity test devices and wetting methods.

Test Method:

The Pharmsteri II GHF filters were integrity tested using an automatic integrity tester to characterize the diffusion flow profile at the test pressure of 40 psi. Each filter was wetted thoroughly prior to integrity testing using a purified water source. Each filter was subjected to a pre and post diffusional flow integrity test during Bacterial Challenge Test. The diffusional flow trend, with correlation to bacterial challenge test, was evaluated to determine the maximum diffusional flow cut-off for each respective size in the Pharmsteri II GHF portfolio.

Results:

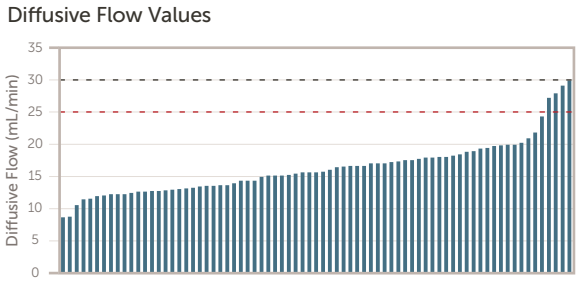

Figure 9. Diffusion flow distribution for Pharmsteri II GHF PES 0.22 µm 10" capsule with a max diffusion cut-off at 25 mL/min.

Conclusion:

The diffusional flow distribution data in Figure 9 demonstrates the Pharmsteri II GHF 10" as a representative sample with a maximum diffusion flow specification correlated to bacterial retention. Each filter size within the Pharmsteri II GHF portfolio completed a similar correlation work to determine a maximum diffusional flow specification. Moreover, the diffusional flow specification was determined to ensure that all filter devices that produce a diffusional flow less than or equal to the specification produce sterile filtrate. Table 11 highlights the maximum diffusional flow value for each filter size within Pharmsteri II GHF portfolio. The complete Pharmsteri II GHF diffusion flow correlation analysis and report are available upon request.

Table 11. The Max Diffusional Flow Specification for Pharmsteri II GHF Filter Sizes

Filter size	Effective filtration area	Pressure set point	Max diffusional flow value (mL/min)
50 mm disc	17.3 cm²	N/A	N/A
3" capsule	1900 cm²	40 psig	≤6.5 mL/min at 25°C (77°F)
5" capsule	3600 cm²	40 psig	≤13 mL/min at 25°C (77°F)
10" capsule	7200 cm²	40 psig	≤25 mL/min at 25°C (77°F)

10.5 GAMMA IRRADIATION COMPATIBILITY

Background:

Gamma stability and compatibility were evaluated on Pharmsteri II GHF PES 0.22 µm capsules to determine the impact on filter integrity, function, and performance upon sterilization. Entegris evaluated post-gamma irradiated Pharmsteri II GHF PES 0.22 µm capsules at a normalized dose of 50 kGY.

Test Method:

Entegris evaluated post-gamma Pharmsteri II GHF filters (50 kGy) using OQ and PQ lots from the validation phase. Each filter lot was tested for bacterial retention of *Brevundimonas diminuta*, following the ATCC 19146 standard, using bacterial challenge test per the ASTM F838-20 standard. In accordance with protocol requirements, every filter device was challenged with a minimum challenge level of *Brevundimonas diminuta* at 1×10^7 colony forming unit (CFU) per cm^2 of effective filtration area (EFA). Additionally, the integrity of each filter device was evaluated using a diffusional flow integrity test for different filter conditions. The conditions assessed included pre-gamma irritation, post-gamma irritation/pre-bacterial challenge test, and post-bacterial challenge test to determine impact.

Results:

Table 12 summarizes the results of the post-gamma sterilized filter samples tested. All capsule sizes from the GHF portfolio are tested and the table below shows the integrity and bacterial challenge test results of 10" capsules. For other test summaries, please refer to sections 9 – 10 that cover results for cytotoxicity, endotoxin, cleanliness, and operation conditions. Complete validation reports are available upon request. Please contact your Entegris representative for additional information.

Table 12.Pharmsteri II GHF Capsule Post-Gamma Bacterial Challenge Test

Part number: PSTSUSA022TS10-

Lot no.	Serial no.	Post-gamma BP test	Post-gamma DF test	Bacteria challenge level	Number of organisms in effluent	Filtrate quality
20220419	-152	PASS	PASS	1.32E+07 CFU/cm²	<1 CFU	Sterile
	-161	PASS	PASS	1.32E+07 CFU/cm²	<1 CFU	Sterile
	-163	PASS	PASS	1.32E+07 CFU/cm²	<1 CFU	Sterile
20220502	-317	PASS	PASS	1.32E+07 CFU/cm²	<1 CFU	Sterile
	-323	PASS	PASS	1.32E+07 CFU/cm²	<1 CFU	Sterile
	-354	PASS	PASS	1.32E+07 CFU/cm²	<1 CFU	Sterile
221101	-322	PASS	PASS	1.08E+07 CFU/cm²	<1 CFU	Sterile
	-349	PASS	PASS	1.08E+07 CFU/cm²	<1 CFU	Sterile
	-359	PASS	PASS	1.08E+07 CFU/cm²	<1 CFU	Sterile

Conclusion:

Based on results for the Pharmsteri II GHF PES 0.22 µm capsule filters, it can be concluded that gamma irradiation has no impact on integrity, retention, or function of filter performance. Furthermore, the material toxicity, endotoxin, and cleanliness were evaluated post-gamma irradiation at 50 kGy and no impact was determined due to gamma sterilization.

10.6 AUTOCLAVE STERILIZATION COMPATIBILITY

Background:

Autoclave stability and compatibility were evaluated on Pharmsteri II GHF PES 0.22 µm capsules to determine the impact on filter integrity, function, and performance upon sterilization. Entegris evaluated post-autoclave Pharmsteri II GHF PES 0.22 µm capsules at a minimum of 2 cycles at 130°C for 30 minutes. A minimum of three manufacturing lots were tested within the Pharmsteri II GHF PES 0.22 µm capsule portfolio.

Test Method:

Entegris evaluated post-autoclaved Pharmsteri II GHF filters at minimum of 2 cycles using both OQ and PQ lots from the validation phase. Each filter lot was tested for bacterial retention of *Brevundimonas diminuta*, following the ATCC 19146 standard, using bacterial challenge test per the ASTM F838-20 standard. Every filter device was challenged with a minimum challenge level of *Brevundimonas diminuta* at 1×10^7 colony forming unit (CFU) per cm^2 of effective filtration area (EFA). Additionally, the integrity of each filter device was evaluated using a diffusional flow integrity test for different filter conditions. The conditions assessed include post-autoclave sterilization/pre-bacterial challenge test, and post-bacterial challenge test to determine impact.

Results:

Table 13 summarizes the results from the post-autoclave sterilization/pre-bacterial challenge test, post-bacterial challenge test, and integrity test results per condition. The results show no impact on bacterial retention or filter integrity for all sizes tested within the Pharmsteri II GHF portfolio. Complete validation reports are available upon request. Please contact your Entegris representative for additional information.

Table 13. Pharmsteri II GHF Capsule Post-Autoclave Bacterial Challenge Test

Part number: PSTSUSA022TS10-

Lot no.	Serial no.	Post-autoclave BP test	Post-autoclave DF test	Bacteria challenge level	Number of organisms in effluent	Filtrate quality
G3N021575	-17	PASS	PASS	2.65E+07 CFU/cm^2	<1 CFU	Sterile
	-19	PASS	PASS	2.65E+07 CFU/cm^2	<1 CFU	Sterile
	-25	PASS	PASS	2.65E+07 CFU/cm^2	<1 CFU	Sterile
G3N021577	-14	PASS	PASS	2.65E+07 CFU/cm^2	<1 CFU	Sterile
	-26	PASS	PASS	2.65E+07 CFU/cm^2	<1 CFU	Sterile
	-34	PASS	PASS	2.65E+07 CFU/cm^2	<1 CFU	Sterile
G3N021578	-40	PASS	PASS	1.12E+07 CFU/cm^2	<1 CFU	Sterile
	-51	PASS	PASS	1.12E+07 CFU/cm^2	<1 CFU	Sterile
	-57	PASS	PASS	1.56E+07 CFU/cm^2	<1 CFU	Sterile

Conclusion:

Based on results for the Pharmsteri II GHF PES 0.22 µm capsule filters, it can be concluded that autoclave sterilization has no impact on integrity, retention, or function of filter performance.

SECTION 11: EXTRACTABLES STUDY

Background:

An extractable study was performed by an independent laboratory following BioPhorum Operations Group (BPOG) recommended protocol. This extractable study aimed to generate an extractables profile for the Pharmsteri II GHF PES 0.22 µm 10" capsule filter when in contact with four solutions within specific conditions to support the extractable assessment in critical product-contact and process applications. Table 14 provides a summary of the test filter, solutions, and test conditions evaluated during the study.

Test Method:

A total of 16 Pharmsteri II GHF PES 0.22 µm 10" capsules from two different manufacturing lots were gamma sterilized at 50 kGy and provided to an independent laboratory to generate the E&L profile. These 16 filters were divided into two lots of filters and were extracted with the following four solutions: 50% EtOH, 0.1 M Phosphate Buffer pH 10, 0.1 M H_3PO_4, and DI water. The extractions were performed at two time periods: 24 hours and seven days. One filter was extracted per solution, per time point, per lot. The resulting extraction samples were evaluated for trace inorganic elements by ICP-MS, volatile organic extractables by HS-GC-MS/FID, volatile/semi-volatile extractable by GC-MS/FID, semi-volatile/nonvolatile organic extractables by LC-MS. These analytical techniques provide a comprehensive strategy for establishing an extractable profile of Pharmsteri II GHF filters. The test articles (filter samples) used in this study are in Table 15. The samples were stored in ambient conditions before testing.

Table 14. Summary of Test filter and Extraction Conditions

DESCRIPTION	EXTRACTION CONDITIONS
Extraction Solutions	50% Ethanol (EtOH) 0.1M Phosphoric Buffer (pH 10) 0.1M Phosphoric Acid (H_3PO_4) 100% Deionized water (DIW)
Filter Lots	Two filter lots per timepoint and extraction solution. The filter lot numbers are shown in Table 15.
Number of Filters	1 filter per extraction solution (4) per lot (2) per time point (2) = 16 filters total
Filter Contact Surface Area	7200 cm² per filter
Extraction Solution Volume	Approximately 1100 mL per filter
Filter Contact Surface Area/ Extraction Solution Volume	6.5 cm²/mL
Filter Rinse	5 L of DI Water
Contact Temperature and Time	T_{24h}: 24 hours, ~35-40°C T_{7d}: 7 days, ~35-40°C

Table 15. Test Filter Sample Information

Part No.	Lot No.	Quantity
PSTSUSA022TS10-	G1P413006	7
	G1M373786	5
	G1S459206	4

Table 16. Analytical Test Methods

		Extraction and Test Control Samples			
Method	**Procedures**	**50% EtOH**	**0.1M Phosphate Buffer (pH 10)**	**0.1M H_3PO_4**	**DI Water**
Trace elements ICP-MS	VRTM 1101[8]	NT	×	×	×
Volatile extractables HS-GC-MS/FID	VRTM 1107[9]	×	×	×	×
Volatile/semi volatile extractables GC-MS/FID	PI 3149[10], VRTM 411[11]	×	×	×	×
Semi volatile/nonvolatile extractables LC-MS	VRTM 120[12], VRTM 121[13]	×	×	×	×

Results:

The organic extractables detected at or above the applicable reporting threshold of 0.1 µg/mL (0.0154 µg/cm²) can be found in the complete reports. A representative extractable profile was obtained for each solution and condition for the Pharmsteri II GHF portfolio. The complete extractable reports are available upon request. Please contact your Entegris representative for additional information.

SECTION 12: SHELF-LIFE STUDY

Background:

Pharmsteri II GHF filters hold a two-year sterility and five-year functional shelf-life for post-gamma filters at a dosage of 50 kGy. Shelf-life study design includes real-time and accelerated studies using aging factors and calculations per ASTM F1980. Entegris does not recommend the use of Pharmsteri II GHF filters beyond the product expiration date. The expiration date is based on the date of manufacture.

Pharmsteri II GHF 10" capsules were selected as the representative size for the shelf-life study. The filter samples represented the final products manufactured, packaged, and stored as specified. Pharmsteri II GHF filters passed the five-year accelerated shelf-life.

Entegris has an ongoing real-time shelf-life study. The validation guide and certificate of quality shall be updated accordingly based on the outcomes of ongoing studies. Entegris does not repeat aging studies on purchased components/materials by qualified suppliers.

The data presented in this report demonstrates that post-gamma (50 kGy) sterilized Pharmsteri II GHF 10" capsule filters maintain their mechanical strength and expected performance after accelerated aging equivalent to storage for up to five years, following gamma irradiation at dose up to 50 kGy. All capsule filters passed the bacterial retention test, confirming post-gamma filter integrity after storage.

Filter cleanliness tests (conductivity, TOC, and particulate) were done on post-gamma sterilized (50 kGy) and accelerated aging shelf-life samples as well. Data shown in section 12.3 demonstrate that after a nominal water flush at 0.5 L/min for 10 L, Pharmsteri II GHF filter shelf-life samples meet the USP requirements for conductivity (USP <645>), TOC (USP <643>), and particulates (USP <788>).

12.1 BACTERIAL RETENTION TEST RESULTS

Table 17. Pharmsteri II GHF 10" Capsule 5-year Accelerated Testing for Bacteria Retention

Part number: PSTSUSA022TS10-

Lot no.	Serial no.	Integrity test	Bacteria challenge level	Number of organisms in effluent	Filtrate quality
G2E589925	-4	PASS	2.30E+07 CFU/cm²	<1 CFU	Sterile
G2E589925	-7	PASS	2.30E+07 CFU/cm²	<1 CFU	Sterile
G2E589925	-18	PASS	2.30E+07 CFU/cm²	<1 CFU	Sterile

12.2 ENDOTOXIN TEST RESULTS

Table 18. Pharmsteri II GHF 10" Capsule 5-year Accelerated Testing for Endotoxin

Part number	Lot no.	Serial no.	LAL test results
PSTSUSA022TS10	G2E589925	-9	Passed
		-8	Passed
		-1	Passed

12.3 CLEANLINESS TEST RESULTS

Table 19. Pharmsteri II GHF 10" Capsule 5-year Accelerated Testing for Cleanliness

Part number: PSTSUSA022TS10-

Lot no.	Serial no.	Volume	Conductivity	TOC	Particles ≥10 µm per mL	Particles ≥25 µm per mL
G2E589925	-17	1 L	6.02 µS/cm	>1 mg/L	4.9 pcs/mL	0.3 pcs/mL
		5 L	1.02 µS/cm	0.71 mg/L	2.2 pcs/mL	0.5 pcs/mL
		10 L	0.75 µS/cm	0.47 mg/L	3.0 pcs/mL	0.1 pcs/mL
	-3	1 L	7.09 µS/cm	>1 mg/L	2.5 pcs/mL	0.2 pcs/mL
		5 L	1.17 µS/cm	0.74 mg/L	3.1 pcs/mL	0.3 pcs/mL
		10 L	0.65 µS/cm	0.44 mg/L	1.8 pcs/mL	0.1 pcs/mL
	-5	1 L	6.96 µS/cm	>1 mg/L	4.7 pcs/mL	0.1 pcs/mL
		5 L	1.71 µS/cm	>1 mg/L	2.1 pcs/mL	0.2 pcs/mL
		10 L	0.85 µS/cm	0.49 mg/L	6.2 pcs/mL	0.3 pcs/mL
	Specifications		≤1.3 µS/cm	≤0.5 mg/L	≤25 pcs/mL	≤3 pcs/mL

12.4 MECHANICAL STRENGTH

The mechanical strength study was designed to verify the integrity of the filter under maximum operation temperature conditions for operating pressure, maximum forward differential pressure, and maximum reverse differential pressure.

Table 20. Pharmsteri II GHF 10" Capsule 5-year Accelerated Testing for Maximum Operating Temperature and Pressure

Part number: PSTSUSA022TS10-

Lot no.	Serial no.	Test conditions	Post-test BP test	Post-test DF test
G2E589925	-1	>80 psig (5.5 bar) inlet pressure, >60 psig (4.1 bar) forward differential pressure at 60°C	PASS	PASS
	-17		PASS	PASS
	-9	>30 psig (2.1 bar) inlet pressure, >15 psig (1.0 bar) reverses differential pressure at 25°C	PASS	PASS

12.5 STERILITY SHELF-LIFE TEST RESULTS:

For sterility shelf life, representative 10" capsule filters with the standard package are gamma-irradiated and stored at room temperature before the sterility test. The sterility test results verified that the double-bag package maintained the sterility of the filter during the extended storage period.

Table 21. Pharmsteri 10" Capsule 2-year Real-time Testing for Sterility

Part no.	Lot no.	Sample ID	Sterility test
PSTGSSA022TS10-	G2E589928	-9	Sterile
	20220501	-338	Sterile
	20220501	-382	Sterile
	20220501	-295-1	Sterile

SECTION 13: GAMMA STERILIZATION VALIDATION

13.1 SUBSTANTIATION OF A SELECTED STERILIZATION DOSE – VDMAX

Background:

Dose Setting-VDmax 25 is to substantiate that 25 kGy as the sterilization dose can enable the product unit to achieve a sterility assurance level (SAL) of 10^{-6} when the bioburden level of the products is less than 1000 CFU.

Methodology:

The bioburden correction factor was determined by assessing three samples using the suspension of *Bacillus atrophaeus* (ATCC 9372). The study used ten filter devices from three manufacturing lots for bioburden determination. The bioburden of each selected product item was determined, and the average bioburden per item for all selected product items was calculated. The dose for VDmax 25 was obtained from ISO 11137-2 using the average bioburden. A single lot of filters were gamma irradiated at the verification dose by cobalt-60 γ irradiation facility. Furthermore, each irradiated product was subjected individually to a sterility test.

Results:

Based on the results from the study, the sterilization dose of the test samples was determined to be at 25 kGy. Furthermore, this enables the test samples to achieve a sterility assurance level of 10^{-6}.

13.2 STERILIZATION PERFORMANCE QUALIFICATION – DOSE MAPPING

Background:

Dose mapping study is used to determine the loading pattern and operation parameters of the products under worst-case scenarios of product packaging (packing density and volume).

Methodology:

A representative, worst-case packaging with 39 carton boxes were used to complete a series of dose mapping tests. The dosimeters were placed in the maximum and minimum absorbed dose area determined by OQ and the contrast area. All dosimeters used within the study were evaluated after irradiation, and their dose values were documented. The acceptance range of sterilization dose is 25~45 kGy, and the measured absorbed dose is further calculated considering the system uncertainty.

Results:

The sterilization process for routine production lots is determined through this study, including the irradiation control time, product loading pattern, and minimum and maximum absorbance dose zone.

SECTION 14: MANUFACTURING PROCESS VALIDATION

Background:

Entegris executed process validations to demonstrate product adherence to functional requirements. All filters evaluated were exposed to a nominal gamma radiation dose of 50 kGy.

Manufacturing equipment was validated as a system to provide evidence that the process, as defined using equipment specified, can consistently make a product that meets final specifications.

Methodology:

Process parameters where variation may impact product quality were identified and studied in process development. The validation of the process occurred through operating limits and process performance qualification. The different ranges in process parameters were validated in the operational qualification (OQ). The process was run using the upper and lower limits of the accepted process ranges of process equipment.

Following the operational qualification (OQ), process performance qualification (PQ) with 3-lot manufacturing was executed to verify the process. Operating at defined parameters in standard operating procedures and ensuring the process can produce filters that meet the release criteria consistently were evaluated. 3-lot samples produced were tested to confirm all product specifications are met, including appearance, dimensions, pressure and temperature tolerance, cleanliness, endotoxin, integrity with bacteria challenge, etc.

Both operating limits and process performance qualification are performed with a specific lot size to meet the testing sample quantity needs and stable continuous manufacturing with complex process capability (CPK) >1.33.

Results:

OQ at upper and lower process limits verified the manufacturing process can produce a quality product within its control limits. A 3-lot PQ confirms that Entegris' manufacturing process can consistently and reliably manufacture Pharmsteri II GHF filters that meet product specifications.

SECTION 15: PACKAGING VALIDATION

Background:

Product packaging was tested per the ISTA 2A-2011, testing for packaged products. Standard ISTA 2A provides a standard set of tests to verify the protection performance of individual inner boxes and outer cartons with multiple boxes. A typical 10" capsule filter was tested as a representative sample, considering its package weight and density are higher than other filter sizes and represent the worst-case scenario. Entegris chose the ISTA 2A Series because the testing requirements align with how the Pharmsteri II GHF capsule filters are packaged and shipped. Furthermore, the conditions tested are representative of the majority of stresses that Pharmsteri II GHF capsule filter packaging would experience.

Test Method:

The packaged product was exposed to the conditions shown in the table below.

Table 22. Packaged Product Exposure Conditions

TEST	INDIVIDUAL INNER BOX	OUTER CARTON WITH 4 BOXES
Laboratory ambient	23.6°C at 55% RH, 6 hours	26.1°C at 55% RH, 6 hours
Controlled temperature and humidity	38.0°C at 85% RH, 72 hours	38.0°C at 85% RH, 72 hours
Machines apply and hold test	754.6 N for 1 hour	1999.2 N for 1 hour
Sinusoidal vibration test method at constant frequency	Frequency 4.8 Hz, amplitude 25 mm, 14,200 cycles	Frequency 5.0 Hz, amplitude 25 mm, 14,200 cycles
Drop test	10 drops at 10 different orientations, height 970 mm	10 drops at 10 different orientations, height 970 mm
Random vibration test	4 frequencies with different orientations at different test duration	4 frequencies with different orientations at different test duration

Following exposure to the conditions above, the Pharmsteri II GHF 10" capsules were tested for:

1. Whether the outer and inner packaging boxes of the products were damaged.
2. Whether the packaging bag and/or vacuum packaging were damaged.
3. Whether there was mechanical damage to the appearance of the product.

In addition, all capsule filters were subjected to a flow rate and integrity test.

Results:

The individual inner box and outer carton with multiple box packaging configurations passed the test. No damage was found in any outer or inner packages. The outer packaging pouch and inner vacuum package were integral. No cosmetic or mechanical defects were observed. All capsules passed the flow rate, pressure, and integrity test. These tests demonstrated that the individual inner box and outer carton package are robust in protecting the capsule filter products during shipping.

SECTION 16: APPENDIX

Below appendixes are only provided upon request and under non-disclosure agreements. Please contact your Entegris representative for additional information.

Appendix 1: USP <87> reports

Appendix 2: USP <88> reports

Appendix 3: BPOG Extractables Study

Appendix 4: VDmax and Dose Mapping Study

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