Pharmsteri™ II PES 0.22 Buffer Capsule Filters

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INTRODUCTION

10" Pharmsteri™ II PES 0.22 buffer capsule filters (Pharmsteri II filters) are made of high-grade, gamma-stable polypropylene shell and a hydrophilic polyethersulfone (PES) membrane with nominal pore rating at 0.22 µm. The asymmetric PES membrane is sterilizing grade and meets bacterial retentiveness per ASTM F838. The filter can be used within buffer sterilization or low-fouling applications during upstream or downstream bioprocessing steps. With Entegris' optimized filter design, the filter has more effective filtration area to maximize throughput and filter lifetime. Entegris has optimized its manufacturing process with high level quality controls to ensure production of integral devices with top tier quality. Moreover, Entegris' strong supply continuity and controls allow for a competitive lead time for Pharmsteri II filters. In summary, Pharmsteri II filters provide high throughput, great biocompatibility, excellent flow performance, and best-in-class lead time.

SCOPE

This validation guide pertains only to the Pharmsteri II filters with a part number shown in Figure 1.

PST	SU	SA	022	TS	10	1	-XX
Pharmsteri	Single use	Membrane: PES 1st	Retention rating	Code	Length	Number per box	OEM

Figure 1. Pharmsteri II filter part number matrix.

COMPLIANCE OVERVIEW

Entegris has a long history of environmental compliance in countries of operation/distribution. Entegris actively review products for compliance and conformance with government and customer requirements affecting raw materials/substances that may be used in manufacturing processes. Entegris relies on information provided by the suppliers as the foundation for the listed compliance statement, and Entegris makes no representation or warranty about any such testing.

Ultimately, customers must assess the product and ensure that use of this product is safe, lawful, and technically suited for their intended application and purpose. It is important to note that Entegris assumes no liability for any loss or injury that may result from the use of the information contained in this overview. Table 1 represents compliance claims for Pharmsteri II filter components acquired at the time of publishing this validation summary.

Table 1. Validation testing summary

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
Filtration membrane	Pass	Pass	Pass	Yes	Pass	Pass	Pass
Upstream support	Pass	Pass	Pass	Yes	Pass	Pass	Pass
Downstream support	Pass	Pass	Pass	Yes	Pass	Pass	Pass
Capsule body, inner core, end caps	Pass	Pass	Pass	Yes	Pass	Pass	Pass
Film edge	Pass	Pass	Pass	Yes	Pass	Pass	Pass
Vent filter O-ring	Pass	Pass	Pass	Yes	Pass	Pass	Pass

CERTIFICATE OF QUALITY

Pharmsteri II filters will be shipped with a Certificate of Quality, Figure 2.

Certificate of Quality

Entegris

Pharmsteri™ II PES 0.22 Buffer Capsule Filter

PSTSU PES 0.22 um TS 10 in 1pc

Part No. : PSTSUSA022TS101
Lot No.:
Mfg. Date:
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.

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.

Particulates
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℃ 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℃
40 psi (2.8 bar) @ 60℃
Max Differential Pressure:
Forward: 60 psi (4.1 bar) @ 25℃
30 psi (2.1 bar) @ 60℃
Reverse: 10 psi (0.7 bar) @ 25℃

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: Jeff Xu

Ver.: D/0

Figure 2. Certificate of Quality example.

MANUFACTURING ENVIRONMENT

Pharmsteri II filters are manufactured in an ISO Class 8 cleanroom. Entegris certifies that each batch has been manufactured and tested according to approved procedures and specifications under the defined quality system certified to ISO 9001 and ISO 13485.

MATERIALS OF CONSTRUCTION

Pharmsteri II filters are made of high-grade, gamma-stable components as shown in Table 2. All materials of construction meet the Biosafety Tests as defined in the current USP including USP <87> (Biological Reactivity Tests, In Vitro)[1] and USP <88> Class VI Plastics Test (Biological Reactivity Tests, In Vivo).[2]

Table 2. Materials of construction

Component	Material
Membrane (media)	Polyethersulfone (PES)
Support	Polyester
Body, core, and caps	Polypropylene (PP)
Film edge	Polypropylene/ polyethylene (PP/PE) copolymer
O-ring	Silicone

COUNTRY OF ORIGIN

Pharmsteri II filters are made in China. Certain components such as the membrane are manufactured outside of China.

ANIMAL DERIVATIVE CONTENT AND TSE/BSE RISK

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

WATER FLOW CHARACTERISTICS

The water flow characteristics for a typical Pharmsteri II filter is presented in Figures 3a and 3b. Figure 3a demonstrates consistent water flow performance in nine different filters. The performance is compared to four similar products in the market, Figure 3b.

Entegris filters presented consistent water flow performance across multiple lots and superior water flow performance compared to current market offerings.

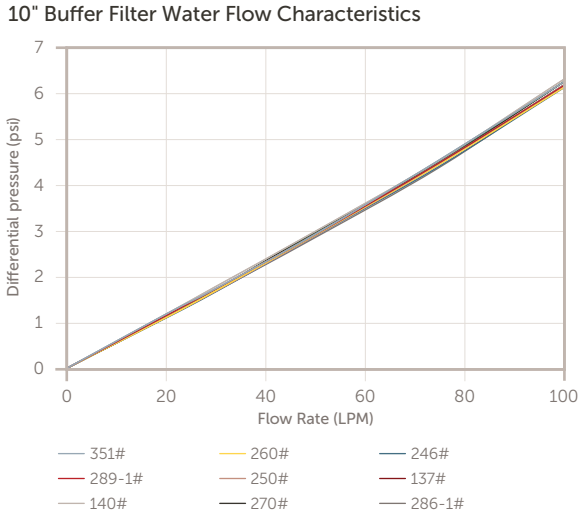


Figure 3a. Water flow vs. differential pressure.

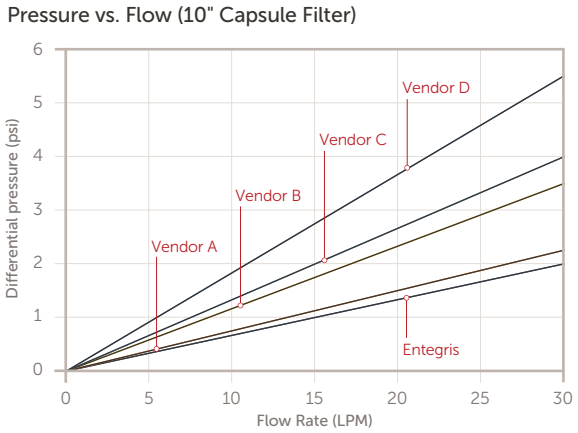


Figure 3b. Water flow rate performance comparison to market available filters.

INTEGRITY CORRELATION BETWEEN DIFFUSIVE FLOW CUTOFF AND BACTERIAL CHALLENGE TEST

The ultimate functionality of a sterilizing-grade filter is to consistently filter out microorganisms and generate sterile filtrate. The testing criteria for this functionality is to demonstrate that the filter can remove *Brevundimonas diminuta* of a bacterial challenge at a minimum 10^7 CFU/cm². 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 non-destructive 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 tested 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 total of 75 filters that were subjected to a nondestructive diffusive flow integrity test followed by a destructive Bacterial Challenge Test (BCT) test per ASTM F838 as shown in Figure 4. The diffusive flow test was performed in the forward direction with air pressure at 40 psig and DI water as the pre-wetting fluid. All filters passed the BCT test with maximum diffusive flow at 30 mL/min (black dotted line in Figure 4). Entegris was able to statistically correlate the diffusive flow with successful BCTs. A diffusive flow cutoff value of 25 mL/min at 40 psig (red dotted line in Figure 4) was chosen to include a safety factor of 5 mL/min (17%) of the max diffusive flow value observed for 75 filters passing the BCT test, Figure 4. This maximum diffusive flow cutoff specification with a built-in safety factor is intended to account for variability of different integrity test devices and wetting methods. Customers should assess their own sources of variability.

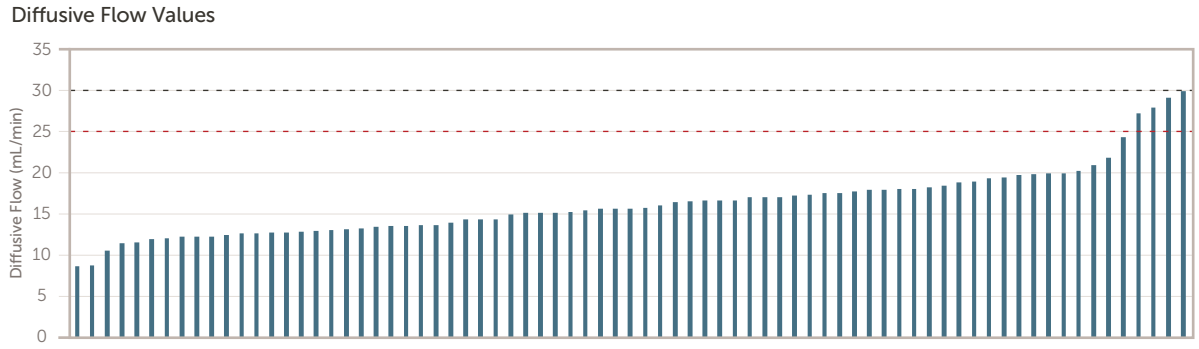


Figure 4. Diffusive flow value for 75 retentive Pharmsteri II filters.

QbD principles are not only applied on device product design and process control, but also on raw material quality controls. The components used for the Pharmsteri II filters are regulatory compliant and can be utilized within the biopharmaceutical industry. To ensure integrity and sterility of the filters manufactured from these materials, Entegris applies QbD principles on incoming raw materials quality control. Every lot of key components at Entegris' manufacturing facility is sampled and tested to ensure final product quality. For some materials, a more stringent internal specification is selected to add QbD rigor to quality control incoming raw materials.

POST-GAMMA FILTER INTEGRITY TEST (BACTERIAL CHALLENGE TEST)

Entegris evaluated post-gamma Pharmsteri II filters (50 kGy) using three manufacturing lots and tested for bacterial retention of *Brevundimonas diminuta* (ATCC 19146) using bacterial challenge tests (BCT) defined by ASTM F838-20 Standard Test Method. In accordance with protocol requirements, every Pharmsteri II filter was challenged with a minimum challenge level of *Brevundimonas diminuta* at 1 x 10^7 colony forming unit (CFU) per cm^2 of effective filtration area (EFA). As shown in Table 3, all 24 capsule filters with a diffusive flow less than 25 mL/min passed the BCT, indicating the integrity of these capsule filters.

Table 3. Post-gamma filter integrity test with BCT

Filter ID	Flow rate	Bacterial challenge level	Post-diffusive flow	Bacterial count in effluent	Test sample pass/fail
1	2.08 mL/min/cm²	1.12*10⁷ CFU/cm²	17.2 mL/min	0 CFU	Pass
2	2.04 mL/min/cm²	1.12*10⁷ CFU/cm²	12.9 mL/min	0 CFU	Pass
3	2.01 mL/min/cm²	1.12*10⁷ CFU/cm²	14.6 mL/min	0 CFU	Pass
4	2.08 mL/min/cm²	1.12*10⁷ CFU/cm²	14.1 mL/min	0 CFU	Pass
5	2.07 mL/min/cm²	1.12*10⁷ CFU/cm²	13.7 mL/min	0 CFU	Pass
6	2.05 mL/min/cm²	1.12*10⁷ CFU/cm²	13.4 mL/min	0 CFU	Pass
7	2.18 mL/min/cm²	1.47*10⁷ CFU/cm²	15.0 mL/min	0 CFU	Pass
8	2.01 mL/min/cm²	1.47*10⁷ CFU/cm²	15.0 mL/min	0 CFU	Pass
9	2.11 mL/min/cm²	1.47*10⁷ CFU/cm²	11.3 mL/min	0 CFU	Pass
10	2.32 mL/min/cm²	1.47*10⁷ CFU/cm²	14.4 mL/min	0 CFU	Pass
11	2.22 mL/min/cm²	1.47*10⁷ CFU/cm²	11.7 mL/min	0 CFU	Pass
12	2.27 mL/min/cm²	1.47*10⁷ CFU/cm²	13.8 mL/min	0 CFU	Pass
13	2.01 mL/min/cm²	1.57*10⁷ CFU/cm²	16.4 mL/min	0 CFU	Pass
14	2.08 mL/min/cm²	1.57*10⁷ CFU/cm²	17.3 mL/min	0 CFU	Pass
15	2.07 mL/min/cm²	1.57*10⁷ CFU/cm²	15.8 mL/min	0 CFU	Pass
16	2.22 mL/min/cm²	1.57*10⁷ CFU/cm²	17.2 mL/min	0 CFU	Pass
17	2.06 mL/min/cm²	1.57*10⁷ CFU/cm²	16.3 mL/min	0 CFU	Pass
18	2.18 mL/min/cm²	1.57*10⁷ CFU/cm²	16.7 mL/min	0 CFU	Pass
19	2.14 mL/min/cm²	1.26*10⁷ CFU/cm²	19.5 mL/min	0 CFU	Pass
20	2.08 mL/min/cm²	1.26*10⁷ CFU/cm²	15.4 mL/min	0 CFU	Pass
21	2.21 mL/min/cm²	1.26*10⁷ CFU/cm²	12.3 mL/min	0 CFU	Pass
22	2.10 mL/min/cm²	1.26*10⁷ CFU/cm²	15.9 mL/min	0 CFU	Pass
23	2.44 mL/min/cm²	1.26*10⁷ CFU/cm²	15.5 mL/min	0 CFU	Pass
24	2.13 mL/min/cm²	1.26*10⁷ CFU/cm²	14.2 mL/min	0 CFU	Pass

FILTER INTEGRITY POST-GAMMA STERILIZATION (DIFFUSIVE FLOW TEST)

Test method: Nine buffer capsule filters were irradiated at a nominal sterilization dose of 50 kGy. Following gamma sterilization, the capsules were integrity tested using diffusive flow to confirm product integrity. As shown in Table 4, all nine filters had a diffusive flow below 25 mL/min after gamma irradiation, which is below the specified diffusive flow of 25 mL/min for integral filters. These nine filters were subjected to the standard bacterial retention test.

Result: All nine filters passed the bacterial challenge test, confirming the integrity of these filters with diffusive flow cutoff value at 25 mL/min, Table 4.

Table 4. Diffusive flow below cutoff value vs. filter integrity

ID	Bacterial challenge level	Pre-BCT diffusive flow	Bacterial count in effluent	Test sample pass/fail
1	$1.32*10^7$ CFU/cm²	17.1 mL/min	0 CFU	Pass
2	$1.32*10^7$ CFU/cm²	20.0 mL/min	0 CFU	Pass
3	$1.32*10^7$ CFU/cm²	16.5 mL/min	0 CFU	Pass
4	$1.32*10^7$ CFU/cm²	21.0 mL/min	0 CFU	Pass
5	$1.32*10^7$ CFU/cm²	14.0 mL/min	0 CFU	Pass
6	$1.32*10^7$ CFU/cm²	17.1 mL/min	0 CFU	Pass
7	$1.19*10^7$ CFU/cm²	21.9 mL/min	0 CFU	Pass
8	$1.19*10^7$ CFU/cm²	19.9 mL/min	0 CFU	Pass
9	$1.19*10^7$ CFU/cm²	17.4 mL/min	0 CFU	Pass

OPERATING TEMPERATURE AND PRESSURE RANGE

It is necessary to provide a maximum operating pressure claim for Pharmsteri II filters that is high enough to allow customers to perform bubble point test, which is around 60-70 psi with DI water at room temperature.

The supporting validation test data is listed in Table 5.

Table 5. Maximum operating pressure/temperature testing data from OQ & PQ (average of 15 capsules)

	Upstream pressure	Differential pressure	Temperature
Forward	92 psi	66 psi	60°C (140°F)
Reverse	41 psi	18 psi	26°C (79°F)

Table 6. Burst pressure testing data from OQ (22 capsules, post gamma)

25°C (77°F)	Burst Pressure
Minimum	188 psi
Maximum	269 psi

As shown in Table 5, the maximum operating pressure test was performed at maximum pressure/temperature combination, which is considered worst case scenario, and this data supports our maximum operating pressure/temperature claims in Table 7. Our burst pressure testing data, Table 6 also supports these claims with 2x safety factor to ensure safe operations.

Table 7. Maximum operating conditions

Maximum Operating Pressure:	
	80 psi @ 25°C (77°F)
	40 psi @ 60°C (140°F)
Maximum Differential Pressure:	
Forward:	60 psi @ 25°C (77°F)
	30 psi @ 60°C (140°F)
Reverse:	10 psi @ 25°C (77°F)

SHELF LIFE (POST-GAMMA FILTER)

Pharmsteri II filters carry a three-year shelf life for post-gamma filters at a dosage of 50 kGy. Five-year shelf life testing is in progress.

Shelf life study design includes real-time and accelerated studies using aging factors and calculations per ASTM F1980. Entegris does not recommend use of Pharmsteri II filters beyond the product expiration date. The expiration date is based on the date of manufacture.

The shelf life samples were selected from three Pharmsteri II filter lots, which were representative of the products that are manufactured, packaged, and stored as specified for the product. Pharmsteri II filters meet the stated three-year shelf life. Entegris has an ongoing validated shelf life study including accelerated and real-time aging. The Validation Guide and Certificate of Quality shall be updated accordingly as the data generated from these studies is available. 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 filters retain their strength and expected performance after accelerated aging equivalent to storage for up to three 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 for up to three years, Table 8.

Filter cleanliness tests (conductivity, total organic carbon [TOC], particulates, fiber release) were done on post-gamma sterilized (50 kGy) and accelerated aging shelf life samples as well. Data shown in tables 8, 9, 10, and 11 demonstrate that after a nominal water flush at 0.5 L/min for 10 L, Pharmsteri II filter shelf life samples meet the USP requirements for conductivity (USP <645>), TOC (USP <643>), and particulates (USP <788>).

The particle shedding test performed demonstrates that the Pharmsteri II filter is a non-fiber releasing filter and potentially does not release measurable particles into product solutions during use, as per 21 CFR 210.3 (b)(6) after an above-mentioned flushing pretreatment. The filter flush effluent is compliant as it meets the compendium guidelines of particulate matter in injections under USP <788>, as per Technical Report No. 26 Section 4.2 requirements.

Table 8. Shelf life samples BCT test results

Sample ID	Accelerated aging duration (oven 55°C [131°F] @ 80% RH)	Shelf life based on accelerated aging	Bacterial count in effluent	Test sample fail/pass
1	20 days	6 months – sample 1	0 CFU	Pass
2	20 days	6 months – sample 2	0 CFU	Pass
3	20 days	6 months – sample 3	0 CFU	Pass
4	40 days	1 year – sample 1	0 CFU	Pass
5	40 days	1 year – sample 2	0 CFU	Pass
6	40 days	1 year – sample 3	0 CFU	Pass
7	80 days	2 years – sample 1	0 CFU	Pass
8	80 days	2 years – sample 2	0 CFU	Pass
9	80 days	2 years – sample 3	0 CFU	Pass
10	120 days	3 years – sample 1	0 CFU	Pass
11	120 days	3 years – sample 2	0 CFU	Pass
12	120 days	3 years – sample 3	0 CFU	Pass

Table 9. 6-month shelf life samples cleanliness test results

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
191	0 min	0.2 L	30.700 µS/cm	>1 mg/L	3.5/mL	0.0/mL	13.3 mL/min
	2 min	1.2 L	7.170 µS/cm	>1 mg/L	2.1/mL	0.0/mL	
	5 min	2.7 L	3.130 µS/cm	0.981 mg/L	2.1 /mL	0.0/mL	
	8 min	4.2 L	2.330 µS/cm	0.770 mg/L	2.6/mL	0.0/mL	
	10 min	5.2 L	1.869 µS/cm	0.630 mg/L	2.3/mL	0.1/mL	
	12 min	6.2 L	1.505 µS/cm	0.550 mg/L	2.1/mL	0.0/mL	
	15 min	7.7 L	1.322 µS/cm	0.447 mg/L	1.9/mL	0.1/mL	
	18 min	9.2 L	1.038 µS/cm	0.396 mg/L	2.0/mL	0.0/mL	
	20 min	10.2 L	0.802 µS/cm	0.321 mg/L	3.5/mL	0.1/mL	
	Background		0.346 µS/cm	0.047 mg/L	1.0/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min
162	0 min	0.2 L	33.400 µS/cm	>1 mg/L	2.5/mL	0.1/mL	12.50 mL/min
	2 min	1.2 L	7.880 µS/cm	>1 mg/L	2.9/mL	0.1/mL	
	5 min	2.7 L	2.580 µS/cm	0.987 mg/L	2.6/mL	0.2/mL	
	8 min	4.2 L	1.744 µS/cm	0.711 mg/L	2.1/mL	0.2/mL	
	10 min	5.2 L	1.308 µS/cm	0.598 mg/L	2.4/mL	0.1/mL	
	12 min	6.2 L	1.185 µS/cm	0.539 mg/L	2.6/mL	0.0/mL	
	15 min	7.7 L	1.028 µS/cm	0.466 mg/L	1.9/mL	0.0/mL	
	18 min	9.2 L	0.910 µS/cm	0.421 mg/L	1.7/mL	0.1/mL	
	20 min	10.2 L	0.878 µS/cm	0.338 mg/L	1.7/mL	0.1/mL	
	Background		0.346 µS/cm	0.047 mg/L	1.0/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
127	0 min	0.2	32.400 µS/cm	>1 mg/L	5.9/mL	0.2/mL	16.30 mL/min
	2 min	1.2 L L	8.790 µS/cm	>1 mg/L	2.9/mL	0.1/mL	
	5 min	2.7 L	2.890 µS/cm	>1 mg/L	2.7/mL	0.1/mL	
	8 min	4.2 L	1.825 µS/cm	0.797 mg/L	3.3/mL	0.1/mL	
	10 min	5.2 L	1.777 µS/cm	0.671 mg/L	1.9/mL	0.1/mL	
	12 min	6.2 L	1.461 µS/cm	0.563 mg/L	2.5/mL	0.1/mL	
	15 min	7.7 L	1.232 µS/cm	0.495 mg/L	2.7/mL	0.1/mL	
	18 min	9.2 L	1.342 µS/cm	0.483 mg/L	2.2/mL	0.1/mL	
	20 min	10.2 L	1.245 µS/cm	0.387 mg/L	2.2/mL	0.1/mL	
	Background		0.346 µS/cm	0.047 mg/L	1.0/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

Table 10. 1-year shelf life samples cleanliness test results

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
195	0 min	0.2 L	33.40 µS/cm	>1 mg/L	0.8/mL	0.1/mL	13.70 mL/min
	2 min	1.2 L	7.31 µS/cm	>1 mg/L	2.7/mL	0.1/mL	
	5 min	2.7 L	2.400 µS/cm	1 mg/L	3.0/mL	0.1/mL	
	8 min	4.2 L	1.613 µS/cm	0.805 mg/L	7.2/mL	0.0/mL	
	10 min	5.2 L	1.376 µS/cm	0.673 mg/L	1.8/mL	0.1/mL	
	12 min	6.2 L	1.207 µS/cm	0.585 mg/L	1.7/mL	0.1/mL	
	15 min	7.7 L	1.080 µS/cm	0.5 mg/L	2.1/mL	0.2/mL	
	18 min	9.2 L	0.899 µS/cm	0.431 mg/L	2.5/mL	0.1/mL	
	20 min	10.2 L	0.860 µS/cm	0.418 mg/L	1.5/mL	0.0/mL	
	Background				0.8/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min
109	0 min	0.2 L	26 µS/cm	>1 mg/L	2.0/mL	0.3/mL	13.80 mL/min
	2 min	1.2 L	5.46 µS/cm	>1 mg/L	2.3/mL	0.3/mL	
	5 min	2.7 L	3.13 µS/cm	1 mg/L	2.1/mL	0.1/mL	
	8 min	4.2 L	1.854 µS/cm	0.817 mg/L	1.9/mL	0.5/mL	
	10 min	5.2 L	1.46 µS/cm	0.68 mg/L	0.7/mL	0.1/mL	
	12 min	6.2 L	1.221 µS/cm	0.602 mg/L	0.9/mL	0.0/mL	
	15 min	7.7 L	1.077 µS/cm	0.532 mg/L	1.2/mL	0.1/mL	
	18 min	9.2 L	0.999 µS/cm	0.468 mg/L	1.2/mL	0.1/mL	
	20 min	10.2 L	0.939 µS/cm	0.429 mg/L	2.8/mL	0.1/mL	
	22 min		0.906 µS/cm	0.403 mg/L	1.3/mL	0.3/mL	
	24 min		0.836 µS/cm	0.376 mg/L	1.1/mL	0.1/mL	
	Background				0.8/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
104	0 min	0.2 L	27.3 µS/cm	>1 mg/L	1.9/mL	0.2/mL	13.90 mL/min
	2 min	1.2 L	6.05 µS/cm	>1 mg/L	2.2/mL	0.1/mL	
	5 min	2.7 L	2.88 µS/cm	1 mg/L	1.6/mL	0.1/mL	
	8 min	4.2 L	2.06 µS/cm	0.795 mg/L	1.7/mL	0.2/mL	
	10 min	5.2 L	1.443 µS/cm	0.678 mg/L	3.4/mL	0.1/mL	
	12 min	6.2 L	1.188 µS/cm	0.593 mg/L	0.5/mL	0.1/mL	
	15 min	7.7 L	1.052 µS/cm	0.511 mg/L	0.9/mL	0.1/mL	
	18 min	9.2 L	1.053 µS/cm	0.427 mg/L	0.6/mL	0.1/mL	
	20 min	10.2 L	0.92 µS/cm	0.423 mg/L	0.9/mL	0.1/mL	
	22 min		0.853 µS/cm	0.392 mg/L	0.9/mL	0.3/mL	
	24 min		0.797 µS/cm	0.372 mg/L	0.9/mL	0.0/mL	
	Background				0.8/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

Table 11. 2-year shelf life samples cleanliness test results

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
379	0 min	0.2 L	31.800 µS/cm	>1 mg/L	1.9/mL	0.3/mL	18.3 mL/min
	2 min	1.2 L	5.700 µS/cm	>1 mg/L	3.4/mL	0.1/mL	
	5 min	2.7 L	1.924 µS/cm	>1 mg/L	1.3/mL	0.1/mL	
	8 min	4.2 L	1.523 µS/cm	0.856 mg/L	0.4/mL	0.1/mL	
	10 min	5.2 L	1.325 µS/cm	0.696 mg/L	1.7/mL	0.1/mL	
	12 min	6.2 L	1.153 µS/cm	0.656 mg/L	2.3/mL	0.1/mL	
	15 min	7.7 L	0.963 µS/cm	0.556 mg/L	1.4/mL	0.0/mL	
	18 min	9.2 L	0.878 µS/cm	0.483 mg/L	1.1/mL	0.1/mL	
	20 min	10.2 L	0.782 µS/cm	0.449 mg/L	1.1/mL	0.0/mL	
	22 min	11.2 L	0.743 µS/cm	0.417 mg/L	1.3/mL	0.1/mL	
	24 min	12.2 L	0.745 µS/cm	0.395 mg/L	1.2/mL	0.0/mL	
	Background		0.460 µS/cm	0.051 mg/L	0.3/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min
369	0 min	0.2 L	32.500 µS/cm	>1 mg/L	1.9/mL	0.4/mL	15.5 mL/min
	2 min	1.2 L	5.240 µS/cm	>1 mg/L	3.7/mL	0.1/mL	
	5 min	2.7 L	1.700 µS/cm	0.968 mg/L	3.2/mL	0.1/mL	
	8 min	4.2 L	1.390 µS/cm	0.750 mg/L	0.5/mL	0.1/mL	
	10 min	5.2 L	1.442 µS/cm	0.692 mg/L	1.0/mL	0.0/mL	
	12 min	6.2 L	1.255 µS/cm	0.619 mg/L	1.5/mL	0.1/mL	
	15 min	7.7 L	1.041 µS/cm	0.531 mg/L	1.1/mL	0.1/mL	
	18 min	9.2 L	0.916 µS/cm	0.470 mg/L	2.1/mL	0.1/mL	
	20 min	10.2 L	0.863 µS/cm	0.442 mg/L	1/mL	0.1/mL	
	22 min	11.2 L	0.768 µS/cm	0.408 mg/L	1.1/mL	0.0/mL	
	24 min	12.2 L	0.715 µS/cm	0.378 mg/L	1.8/mL	0.0/mL	
	Background		0.413 µS/cm	0.049 mg/L	0.4/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
297-1	0 min	0.2 L	25.900 µS/cm	>1 mg/L	2.7/mL	0.5/mL	14.1 mL/min
	2 min	1.2 L	4.990 µS/cm	>1 mg/L	1.9/mL	0.5/mL	
	5 min	2.7 L	2.140 µS/cm	>1 mg/L	1.6/mL	0.3/mL	
	8 min	4.2 L	1.543 µS/cm	0.796 mg/L	0.8/mL	0.1/mL	
	10 min	5.2 L	1.251 µS/cm	0.680 mg/L	0.5/mL	0.0/mL	
	12 min	6.2 L	1.095 µS/cm	0.598 mg/L	0.9/mL	0.1/mL	
	15 min	7.7 L	0.937 µS/cm	0.509 mg/L	1.1/mL	0.1/mL	
	18 min	9.2 L	0.848 µS/cm	0.454 mg/L	0.5/mL	0.1/mL	
	20 min	10.2 L	0.820 µS/cm	0.425 mg/L	1.8/mL	0.0/mL	
	22 min	11.2 L	0.751 µS/cm	0.401 mg/L	0.6/mL	0.1/mL	
	24 min	12.2 L	0.761 µS/cm	0.377 mg/L	3.3/mL	0.1/mL	
	Background		0.413 µS/cm	0.049 mg/L	0.4/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

Table 12. 3-year shelf life samples cleanliness test results

		TEST VALUE				
FILTER ID	SAMPLING TIME	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
358	0 min	28.300 µS/cm	>1 mg/L	0.7/mL	0.0/mL	15.90 mL/min
	2 min	4.290 µS/cm	>1 mg/L	0.9/mL	0.1/mL	
	5 min	1.858 µS/cm	1.015 mg/L	2.1/mL	0.0/mL	
	8 min	1.327 µS/cm	0.770 mg/L	2.7/mL	0.1/mL	
	10 min	1.162 µS/cm	0.668 mg/L	0.9/mL	0.1/mL	
	12 min	1.050 µS/cm	0.656 mg/L	1.1/mL	0.1/mL	
	15 min	0.929 µS/cm	0.520 mg/L	1.3/mL	0.0/mL	
	18 min	0.801 µS/cm	0.456 mg/L	1.3/mL	0.1/mL	
	20 min	0.759 µS/cm	0.405 mg/L	1.0/mL	0.1/mL	
	22 min	0.703 µS/cm	0.403 mg/L	1.1/mL	0.1/mL	
	Background	0.447 µS/cm	0.053 mg/L	1.1/mL	0.0/mL	
	SPEC	≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤20 mL/min
314	0 min	34.900 µS/cm	>1 mg/L	0.7/mL	0.1/mL	16.20 mL/min
	2 min	5.240 µS/cm	>1 mg/L	1.1/mL	0.1/mL	
	5 min	1.726 µS/cm	1.028 mg/L	0.3/mL	0.0/mL	
	8 min	1.322 µS/cm	0.741 mg/L	1.7/mL	0.0/mL	
	10 min	1.196 µS/cm	0.646 mg/L	0.9/mL	0.2/mL	
	12 min	1.057 µS/cm	0.597 mg/L	0.7/mL	0.1/mL	
	15 min	0.959 µS/cm	0.515 mg/L	0.9/mL	0.0/mL	
	18 min	0.833 µS/cm	0.463 mg/L	4.7/mL	0.0/mL	
	20 min	0.821 µS/cm	0.416 mg/L	1.5/mL	0.1/mL	
	22 min	0.746 µS/cm	0.389 mg/L	0.5/mL	0.1/mL	
	Background	0.447 µS/cm	0.053 mg/L	1.1/mL	0.0/mL	
	SPEC	≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤20 mL/min

VALIDATION SUMMARY FOR PHARMSTERI II CAPSULE FILTERS

		TEST VALUE				
FILTER ID	**SAMPLING TIME**	**CONDUCTIVITY**	**TOC**	**PARTICLES ≥10 µM**	**PARTICLES ≥25 µM**	**DIFFUSIVE FLOW**
373	0 min	31.500 µS/cm	>1 mg/L	2.4/mL	0.3/mL	16.90 mL/min
	2 min	6.080 µS/cm	>1 mg/L	1.3/mL	0.1/mL	
	5 min	1.844 µS/cm	1.009 mg/L	1.4/mL	0.0/mL	
	8 min	1.229 µS/cm	0.740 mg/L	1.1/mL	0.1/mL	
	10 min	1.085 µS/cm	0.651 mg/L	1.4/mL	0.0/mL	
	12 min	0.979 µS/cm	0.586 mg/L	0.6/mL	0.0/mL	
	15 min	0.886 µS/cm	0.518 mg/L	3.1/mL	0.2/mL	
	18 min	0.829 µS/cm	0.461 mg/L	2.8/mL	0.1/mL	
	20 min	0.768 µS/cm	0.429 mg/L	1.4/mL	0.1/mL	
	22 min	0.716 µS/cm	0.403 mg/L	1.8/mL	0.0/mL	
	Background	0.379 µS/cm	0.051 mg/L	0.2/mL	0.0/mL	
	SPEC	≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤20 mL/min

GAMMA STERILIZATION

BIOBURDEN ASSESSMENT

A certified and independent third-party laboratory conducted a bioburden baseline study prior to sterilization for five filters sampled from five lots. Total bioburden is determined by summing the aerobic and fungi counts. Testing was performed in accordance with ISO 11737-1:2018. Test information and results can be found in Tables 13 and 14. Based on these results, the bioburden baseline level for this filter is at <85 CFU/device. This low bioburden baseline enables customers to integrate the filter into their validated sterility program with single-use systems.

Table 13. Test information

Code	N/A*
Lots	59, 72, 74, 68, 35, 12, 43, 269, 44, 58, 18, 31, 66, 268, 78, 259, 277, 275, 227, 243, 45, 93, 276, 17, 32, 266, 257, 230, 247, 40
Number of samples	30
SIP	1.0 (Internal pathway)
Incubation condition	TSA @ 30° – 35°C (86° – 95°F) for 3 – 7 days and SDA @ 30° – 35°C (86° – 95°F) for 5 – 7 days

*N/A: No information from customer

Table 14. Filter bioburden test results

Filter number	Aerobic	Fungal
59	<13 CFU/device	<13 CFU/device
72	<13 CFU/device	<13 CFU/device
74	<13 CFU/device	13 CFU/device
68	13 CFU/device	<13 CFU/device
35	<13 CFU/device	<13 CFU/device
12	<13 CFU/device	<13 CFU/device
43	<13 CFU/device	<13 CFU/device
269	<13 CFU/device	<13 CFU/device
44	<13 CFU/device	<13 CFU/device
58	<13 CFU/device	<13 CFU/device
18	<13 CFU/device	<13 CFU/device
31	13 CFU/device	<13 CFU/device
66	<13 CFU/device	<13 CFU/device
268	13 CFU/device	<13 CFU/device
78	65 CFU/device	13 CFU/device
259	13 CFU/device	<13 CFU/device
277	<13 CFU/device	<13 CFU/device
275	<13 CFU/device	<13 CFU/device
227	<13 CFU/device	13 CFU/device
243	<13 CFU/device	<13 CFU/device
45	<13 CFU/device	<13 CFU/device
93	<13 CFU/device	<13 CFU/device
276	<13 CFU/device	<13 CFU/device
17	13 CFU/device	<13 CFU/device
32	<13 CFU/device	26 CFU/device
266	<13 CFU/device	<13 CFU/device
257	<13 CFU/device	<13 CFU/device
230	<13 CFU/device	<13 CFU/device
247	<13 CFU/device	13 CFU/device
40	<13 CFU/device	<13 CFU/device
Correction Factor		3.0
Bioburden Estimate		<84.5 CFU/device

VALIDATION OF GAMMA STERILIZATION PROCESS (STERILITY ASSURANCE)

The VDmax study for sterility assurance is ongoing. Data related to validation of the gamma sterilization process and sterility assurance will be available in the next version of the Validation Guide.

FILTER CLEANLINESS – TOC, CONDUCTIVITY, PARTICULATES, FIBER RELEASE

Test method: For filter cleanliness study, total organic carbon (TOC), conductivity, particulates, and fiber release were tested with the same sample collected from three lots of Pharmsteri II filters. All samples were subjected to gamma sterilization at 50 kGy before testing. Ultrapure water was flushed through a Pharmsteri II filter at a flow rate of 0.5 L/min. After discarding the first 200 mL of effluent, samples were collected at certain intervals as shown in Table 15. 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[3] was used to measure TOC. The recommended testing method from USP <645> Water Conductivity[4] was used to measure conductivity. The recommended testing method from USP <788> Particulate Matter in Injections[5] was used to measure particulates in effluent.

Test Results: As shown in Table 15, after flushing Pharmsteri II filters at 0.5 L/min with ultrapure water volume no less than 6.2 L, post-gamma Pharmsteri II filters met the required conductivity of USP <645> at ≤1.3 µS/cm, TOC of USP <643> at ≤0.5 mg/L, particulates of USP <788> at equal or less than three particles ≥25 µm, equal or less than 25 particles ≥10 µm.

Table 15. Filter cleanliness test result of TOC, conductivity, and particulates

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
135	0 min	0.2 L	17.500 µS/cm	>1 mg/L	1.3/mL	0.3/mL	12.9 mL/min
	2 min	1.2 L	3.110 µS/cm	>1 mg/L	2.9/mL	0.3/mL	
	5 min	2.7 L	1.376 µS/cm	0.736 mg/L	0.9/mL	0.0/mL	
	8 min	4.2 L	1.016 µS/cm	0.549 mg/L	1.5/mL	0.0/mL	
	10 min	5.2 L	0.895 µS/cm	0.449 mg/L	0.5/mL	0.0/mL	
	12 min	6.2 L	0.818 µS/cm	0.425 mg/L	0.6/mL	0.0/mL	
	15 min	7.7 L	0.741 µS/cm	0.377 mg/L	0.3/mL	0.0/mL	
	18 min	9.2 L	0.715 µS/cm	0.339 mg/L	0.5/mL	0.0/mL	
	20 min	10.2 L	0.652 µS/cm	0.260 mg/L	1.1/mL	0.1/mL	
	Background		0.431 µS/cm	0.047 mg/L	0.7/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

			TEST VALUE				
FILTER ID	SAMPLING TIME	FLOW VOLUME AT FLOW RATE 0.5 L/MIN	CONDUCTIVITY	TOC	PARTICLES ≥10 µM	PARTICLES ≥25 µM	DIFFUSIVE FLOW
171	0 min	0.2 L	18.350 µS/cm	>1 mg/L	4.2/mL	0.5/mL	11.90 mL/min
	2 min	1.2 L	4.300 µS/cm	>1 mg/L	0.8/mL	0.1/mL	
	5 min	2.7 L	1.578 µS/cm	0.787 mg/L	0.3/mL	0.1/mL	
	8 min	4.2 L	1.035 µS/cm	0.594 mg/L	0.9/mL	0.1/mL	
	10 min	5.2 L	0.888 µS/cm	0.516 mg/L	0.7/mL	0.1/mL	
	12 min	6.2 L	0.776 µS/cm	0.460 mg/L	0.5/mL	0.1/mL	
	15 min	7.7 L	0.689 µS/cm	0.395 mg/L	1.3/mL	0.0/mL	
	18 min	9.2 L	0.642 µS/cm	0.352 mg/L	1.5/mL	0.1/mL	
	20 min	10.2 L	0.591 µS/cm	0.308 mg/L	1.1/mL	0.2/mL	
	Blank control samples		0.431 µS/cm	0.047 mg/L	0.7/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min
220	0 min	0.2 L	13.660 µS/cm	>1 mg/L	1.1/mL	0.1/mL	11.70 mL/min
	2 min	1.2 L	3.080 µS/cm	>1 mg/L	1.3/mL	0.3/mL	
	5 min	2.7 L	1.497 µS/cm	0.704 mg/L	0.4/mL	0.0/mL	
	8 min	4.2 L	0.945 µS/cm	0.518 mg/L	0.3/mL	0.0/mL	
	10 min	5.2 L	0.776 µS/cm	0.456 mg/L	0.4/mL	0.1/mL	
	12 min	6.2 L	0.714 µS/cm	0.405 mg/L	0.3/mL	0.1/mL	
	15 min	7.7 L	0.637 µS/cm	0.352 mg/L	0.7/mL	0.1/mL	
	18 min	9.2 L	0.647 µS/cm	0.318 mg/L	1.5/mL	0.0/mL	
	20 min	10.2 L	0.568 µS/cm	0.246 mg/L	0.2/mL	0.0/mL	
	Blank control samples		0.431 µS/cm	0.047 mg/L	0.7/mL	0.0/mL	
	SPEC		≤1.3 µS/cm	≤0.5 mg/L	≤25/mL	≤3/mL	≤25 mL/min

USP <87> BIOLOGICAL REACTIVITY TESTS, IN VITRO (POST-GAMMA STERILIZATION)

Cytotoxicity testing assesses the potential of a given material for having a toxic effect on living cells.

Test method: Each component of the Pharmsteri II filter was gamma sterilized at 50 kGy and tested by a certified and independent third-party laboratory in accordance with USP <87> Biological Reactivity Tests, in vitro. For detailed information, please contact Entegris.

Results: Five test article samples scored a grade of 0 for biological reactivity after 48 hours. The negative and positive controls confirmed system suitability. The test samples were deemed to meet USP <87> criteria and not considered cytotoxic, Table 16.

Table 16. Cytotoxicity test results

PROJECT NUMBER	SPONSOR	TEST ARTICLE	TEST	24 HOURS	48 HOURS
				Final grade	Final grade
		Medium	MEM	0	0
		Negative Control	MEM	0	0
		Positive control	MEM	4	4
21-03756-G1	Entegris	Resin	MEM	0	0
21-03754-G1	Entegris	PES membrane	MEM	0	0
21-03753-G1	Entegris	Lamination/Edge strip	MEM	0	0
21-03747-G1	Entegris	Nonwoven support	MEM	0	0
1526234	Entegris	O-ring	MEM	0	0

USP <88> BIOLOGICAL REACTIVITY TESTS, IN VIVO, CLASS VI TEST (POST-GAMMA STERILIZATION)

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

Test method: Test articles were gamma sterilized at 50 kGy before testing. The post-gamma sterilized test article was exposed at a surface area (cm^2) to extraction solution volume (mL) ratio of 6. Extract medium that included USP 0.9% sodium chloride injection, cotton seed 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. And animals were observed for a biological response. Test article implantation into the paravertebral muscles of rabbits was observed for seven days for signs of irritation or infection.

Results: Pharmsteri II filters meet criteria established per USP guidelines USP <88> Biological Reactivity Tests, In Vivo, Class VI Plastics, Table 17. For detailed information, please contact Entegris.

Table 17. USP <88> test result

USP <88> TESTING ITEM	TEST RESULT
Intracutaneous reactivity test	Pass
Systemic injection test	Pass
Intramuscular implantation test	Pass

USP <85> BACTERIAL ENDOTOXIN TESTS, EP 2.6.14, JP

Endotoxin are lipopolysaccharide complexes found in gram-negative bacterial cell walls. They can cause fever in humans. The bacterial endotoxin test is a test to detect or quantify endotoxins from gram-negative bacteria using amoebocyte lysate from the horseshoe crab (*Limulus poly-phemus* or *Tachypleus tridentatus*).[6]

Test method: The testing was performed per USP <85> method.[6] The test article fluid path was soaked with sterile water for injection (WFI) and incubated at 37°C (98.6°F) for one hour. A positive product control was prepared using the test article extract and the endotoxin standard. Sterile WFI and LAL (limulus amebocyte lysate) reagent water (endotoxin-free) were used as negative controls. LAL reagent was added to all test and control samples, which were then incubated and read via a plate reader.

Results: Based on the positive control, negative control and positive product control data, the system was suitable, and the product did not interfere with the test system. The endotoxin level was determined to be below the limit of 0.25 EU/mL.

EXTRACTABLES

An extractable study was performed by an independent laboratory following BioPhorum Operations Group (BPOG) recommended protocol.[7]

Test method: A total of 16 filters from three different manufacturing lots were gamma sterilized at 50 kGy and provided to an independent laboratory to generate the BPOG E&L profile. These 16 filters were divided into two lots of filters and were extracted with 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 7 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 analytical strategy for establishing an extractable profile of Pharmsteri II filters.

Result: Based on the aggregate results pertaining to the organic extractables and the trace inorganic elements testing, a representative extractable profile for the Pharmsteri II filter has been established for the conditions of use as described above. For more detailed information, please contact Entegris.

CAPSULE BURST TEST

Test method: The specification for burst test is to have burst pressure ≥120 psi. 10 capsule filters from each of three lots (N = 30) were tested for burst pressure and the burst test function was performed. Pressure was increased until the capsule burst.

Test Result: All filters burst at the shell, with none bursting at the welding locations. The burst pressure for 30 capsule filters ranges from 292 psi to 375 psi, meeting the required burst pressure >120 psi.

MANUFACTURING PROCESS VALIDATION

Design validation was executed to demonstrate product adherence to functional requirements. All filters tested were exposed to a nominal gamma radiation dose of 50 kGy, 5 kGy higher than the specification listed in the data sheet.

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

Test Method: Process parameters where variation may impact product quality were identified and challenged. Ranges in process parameters were challenged in the operational qualification (OQ), product was run using the high and low ends of the accepted process ranges of 13 pieces of equipment. Nonvariable parameters were set at nominal.

Filter parts injection, pleating condition, seaming, trimming, parts bonding, end capping, heat bonding, flushing condition, etc. were conducted on units manufactured from the high/low settings to verify products are integral and meet acceptance criteria.

Following the OQ, product qualification (PQ) testing was executed. Filter parts injection, resin mixture, membrane lamination, pleating, seaming, trimming, potting, bonding at different parts, flushing, integrity test, and drying were tested on manufacturing equipment and manual operations to verify products are integral and meet acceptance criteria.

Results: OQ and PQ testing confirmed Entegris' manufacturing process can consistently and reliably manufacture Pharmsteri II filters that meet product specifications.

PACKAGING VALIDATION

Product packaging was tested per the ISTA 2A-2011, testing for packaged products. Standard ISTA 2A is designed to provide a standard set of tests to verify the performance of individual packaged products weighing 68 kg (150 lb) or less in relation to the risks involved during the distribution cycles. ISTA 2 Series tests include at least one element of a 3 Series type test in addition to basic elements of a 1 Series type test. Entegris chose the ISTA 2A Series because the packing format most closely aligns with how the Pharmsteri II filter is packaged and shipped and is representative of the majority of stresses that Pharmsteri II filter packaging would experience. In addition, Entegris has an established history of using the ISTA 2A Series test standard for shipping and packaging validation.

The packaged product was exposed to the conditions shown in Table 18.

Table 18. Product packaging testing

Test	Condition
Laboratory ambient	24.1°C (75.4°F), 56% RH, 6 hours
Controlled temperature and humidity	38°C (100.4°F), 85% RH, 72 hours
Stacking test	2195.2 N for 1 hour
Sinusoidal vibration at constant frequency	4.8 Hz/Amplitude 25 mm, 14,200 cycles
Random vibration test	Four frequencies with different orientation at different test duration
Drop test	10 drops at different orientations

Test method: Following exposure to the conditions above, the Pharmsteri II filter was tested for:

a. Whether the outer and inner packaging boxes of the products were damaged

b. Whether the packaging bag and vacuum packaging were damaged or leaky

c. Whether there was mechanical damage to the appearance of the product

In addition, all capsule filters were subjected to a flow test to measure flow rate and differential pressure and diffusive flow for integrity.

Results: Two packaging configurations were tested. One with eight filters in one big box, Figure 5, and the other with one filter in one box, Figure 6. No damage was found in any outer or inner packages. Outer packaging pouch and inner vacuum package were integral. No cosmetic or mechanical defect observed. All acceptance criteria were met. As listed below, for the eight filters in one box format, testing demonstrated that the final packaging protects the product during shipping. All capsules passed flux, differential pressure, and diffusive flow test.

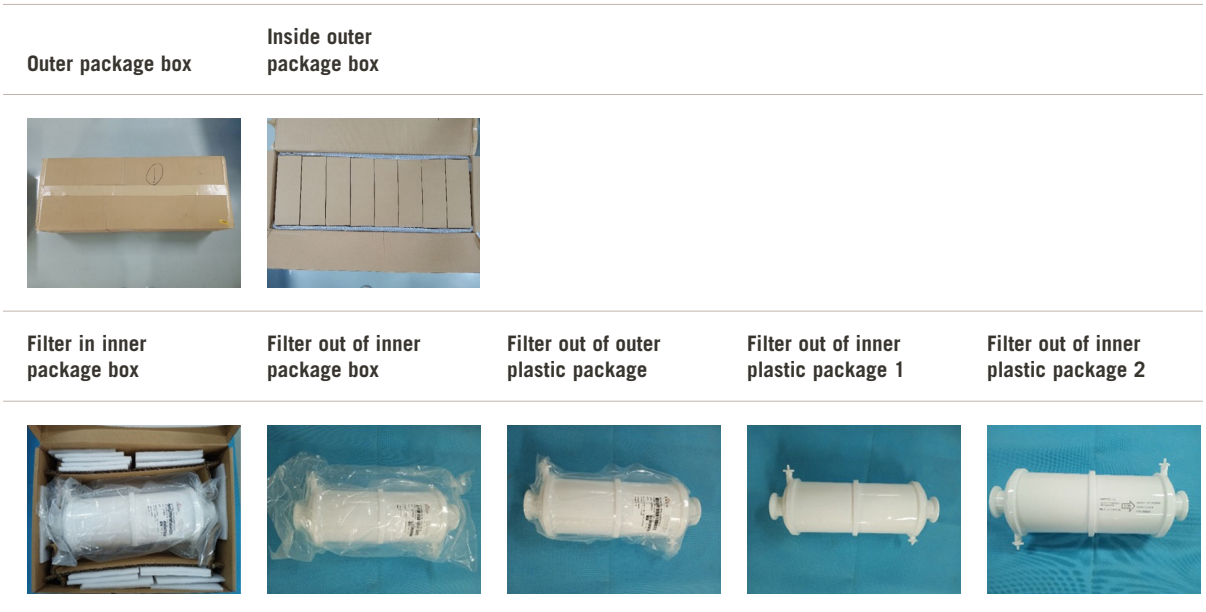


Figure 5. Eight filters in one package format.

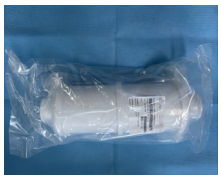
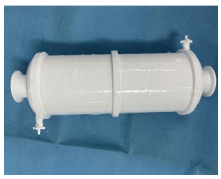
Outer package box				
				
Open box	**Filter with outer plastic package**	**Filter with inner vacuum plastic package**	**Filter without packaging material**	
				

Figure 6. One filter in one package format.

References

[1] USP <87> Biological reactivity tests, in vitro USP <87> Biological Reactivity Tests, In Vitro

[2] USP <88> Biological reactivity tests, in vivo USP <88> Biological Reactivity Tests, In Vivo

[3] USP<645> Water Conductivity

[4] USP <643> Total Organic Carbon

[5] USP <788> Particulate Matter in Injections

[6] USP <85> Bacterial Endotoxins Test

[7] Biophorum best practices guide for extractables testing of polymeric single-use components used in biopharmaceutical manufacturing Best-practices-guide-for-extractables-testing-April-2020.pdf (biophorum.com)

Technical Information

The full version of this document including USP <87>, USP <88>, and BPOG extractables reports are available upon request with an NDA in place. Please contact Entegris for more information.

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