BIOTECH

Validation Guide

USTR 3485

Pall Profile® II Filters

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Contents

1 Introduction

Pall's Profile II filters have been designed as highly efficient, absolute-rated, and continuously graded depth filters with excellent chemical compatibility, long service life, and high flow rates. Filter cartridge (AB-style) end caps, core, and media are comprised of polypropylene (PP). The PP depth filter media of Profile II filters is made of melt blown fibers where the pore size variation is achieved by varying the fiber diameter, while maintaining uniform density. Based on that approach the pore sizes continuously vary from coarser pore sizes in the outer section to finer pore sizes in the inner section of the filter element (Figure 1). Throughout the inner section, the pore size is constant and provides reliable, absolute-rated filtration for every particle larger than the rated size. Profile II AB-style filters are available with absolute ratings from 0.3 – 120 µm (referring to the inner section of the filter). The absolute rating in µm is determined in liquids by the modified Oklahoma State University (OSU) F2 filter performance test in single-pass mode providing a beta (β) ratio as β 5000 (99.98% removal efficiency). In addition to β 5000 values, β 1000 (99.9% removal efficiency), β 100 (99% removal efficiency) and β 10 (90% removal efficiency) values are shown in Table 2.

Profile II AB-style cartridges are manufactured with pure polypropylene end caps which are melt sealed to the filter media. Profile II filters are manufactured without the aid of binders or surfactants, do not employ a side seam and are available as 'P' (pharmaceutical grade) option.

Figure 1

Profile II filter (schematic)

This report summarizes the tests conducted to qualify the performance of Profile II filter cartridges under a range of standard test conditions.

The qualification program included:

- Particulate retention testing
- Steam life tests
- Determination of water flow characteristics
- Extractables testing
- Biological reactivity tests
- Testing for Pall's certificate of test for pharmaceutical grade filters (P-certificate)

The units of pressure quoted in this document are bar or millibar (mbar) and pounds force per square inch (psi). The following formula can be used to convert these units of pressure to Pascals (Pa):

- 1 bar = 1000 mbar = 1 x 10^5 Pa
- 1 psi = 6.89476 x 10^3 Pa = 0.069 bar = 68.95 mbar

Profile II filter cartridges supported by this validation guide are listed in Table 1.

Table 1

Overview of Profile II AB-style filter cartridges

Code	Nominal Length	Code	Removal Rating*	Code	Cartridge Style	Code	Filter Grade	Code***	O-Ring Option
1	254 mm (10 in.)	003	< 0.5 µm	7	Double 226 O-ring with bayonet lock and fin end	P	Pharmaceutical**	H4	Silicone
2	508 mm (20 in.)	005	0.5 µm					J	Ethylene propylene
3	762 mm (30 in.)	007	0.7 µm						
4	1016 mm (40 in.)	010	1 µm						
		020	2 µm						
		030	3 µm						
		050	5 µm						
		070	7 µm						
		100	10 µm						
		150	15 µm						
		200	20 µm						
		300	30 µm						
		400	40 µm						
		700	-						
		900	-						
		1200	-						

**The removal rating is the value in microns at which the modified OSU-F2 test gives a Beta value of ≥ 5000.*

***Pall pharmaceutical-grade filters are designed for use in conformance with Code of Federal Regulations Title 21 Food and Drugs, Part 210: Current Good Manufacturing Practice (cGMP) in Manufacturing, Processing, Packing, or Holding of Drugs (21CFR210), and CFR Title 21 Food and Drugs, Part 211: cGMP for Finished Pharmaceuticals (21CFR211.72) including batch release certificates and full traceability.*

****Other materials available on request*

Please see below for an example AB-style filter cartridge part number ‘AB1Y0037PH4’. This informs you about the information contained within the part number and how to interpret that information:

- 254 mm (10 in.) AB-style (AB1) Profile II filter (Y) providing a 0.3 µm removal rating (003), equipped with a double 226 O-ring with bayonet lock and fin end (7), pharmaceutical grade (P) and O-ring material consists of silicone (H4).

2 Particulate Retention Testing

Removal performance of a particle retaining filter is determined by performing a particulate retention test. A beta rating system is used to measure and predict the particulate retention performance of a filter under specified test conditions. Beta ratios are determined under laboratory testing using the modified OSU-F2 test (developed at Oklahoma State University as a filter performance test) in single-pass mode. This test utilizes a defined test dust in a liquid dispersion as the test system. Particles are counted upstream in the influent and downstream in the effluent of the tested filter in dependence of particle size (Figure 2).

For data in the 0.5 to 30 µm range, a standardized siliceous contaminant, Air Cleaner (AC) Fine Test Dust, was prepared as a stable suspension in water. This suspension was pumped at 10 L/min through a single 254 mm (10 in.) test cartridge. The test system was equipped with two particle counters each with a range of 1 to 100 µm. One counter, upstream of the filter, recorded the influent particle levels, and the other downstream similarly recorded the effluent particle levels. Each counter can be preset at minimum five particle diameters. These counts were used to determine the efficiencies at the selected diameters. The data was plotted to obtain efficiencies at intermediate diameters, and in addition, was extrapolated to yield efficiency values down to <0.5 µm.

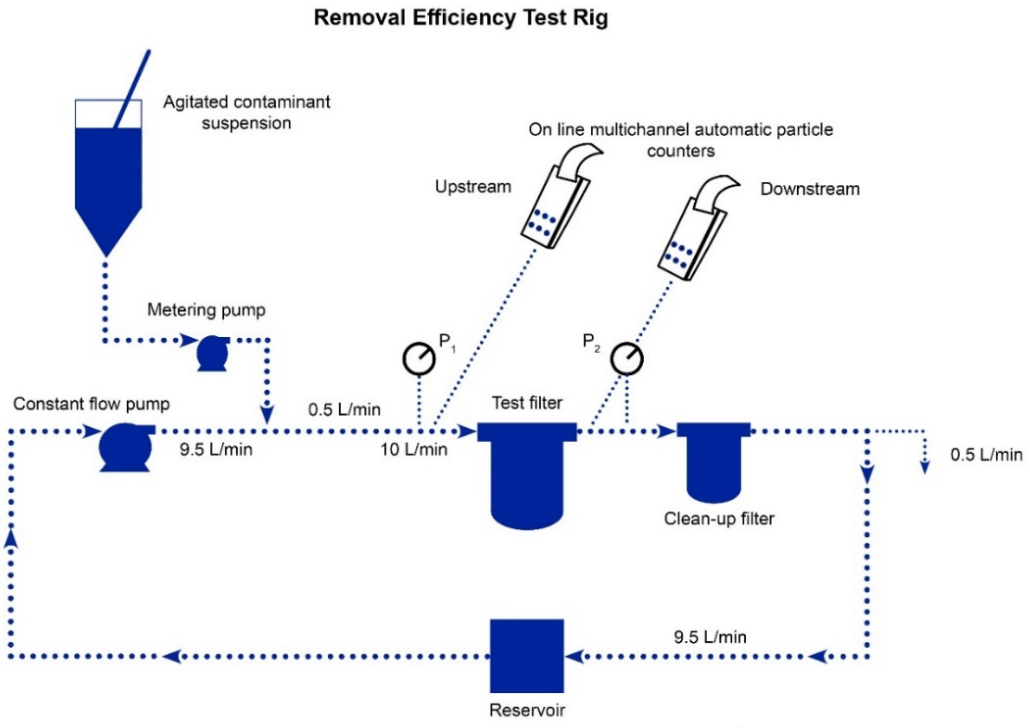
For data in the 40 to 120 µm range, a similar test set-up was used with AC Coarse Test Dust as the contaminant suspended in military standard MIL-H-5606 oil with a viscosity of 12 centipoise at 37 °C. This viscous oil kept the larger particles in suspension. The oil test flow rate was 10 L/min. It should be noted that precise evaluation of the 99.9% removal efficiency for Profile II filter grade 900 and 1200 is not possible with this test procedure (Table 2).

The beta ratio is defined as follows:

$$\beta = \frac{Number\ of\ particles\ of\ a\ given\ size\ and\ larger\ in\ the\ influent}{Number\ of\ particles\ of\ a\ given\ size\ and\ larger\ in\ the\ effluent}$$

Figure 2

Modified OSU-F2 test in single-pass mode of Profile II filters



The following table (Table 2) summarizes test results regarding the absolute particulate removal rating (β 5000 = 99.98% removal efficiency). In addition to β 5000 values, β 1000 = 99.9%, β 100 = 99% and β 10 = 90% removal efficiency in liquids (in µm), determined by the modified OSU-F2 test, are shown for Profile II AB-style filters.

Table 2

Profile II AB-style filter grades and particulate removal ratings (β ratio) in liquids

Code	β 5000 (99.98%) (µm)	β 1000 (99.9%) (µm)	β 100 (99%) (µm)	β 10 (90%) (µm)
003	<0.5*	<0.5*	<0.5*	<0.5*
005	0.5*	<0.5*	<0.5*	<0.5*
007	0.7*	<0.5*	<0.5*	<0.5*
010	1.0	0.5*	<0.5*	<0.5*
020	2.0	1.5	1.0	<1.0*
030	3.0	2.5	1.8	<1.0*
050	5.0	4.0	3.0	2.0
070	7.0	6.0	5.0	3.5
100	10.0	9.0	7.5	6.5
150	15.0	13.0	10.0	8.0
200	20.0	18.0	14.0	10.0
300	30.0	26.0	18.0	14.0
400	40.0	35.0	30.0	20.0
700	**	70.0	50.0	32.0
900	**	90.0*	78.0*	50.0
1200	**	120*	100.0*	60.0

**Extrapolated value*

***Evaluation of the absolute removal efficiency for these coarse grades is not possible with the test procedures utilized.*

3 Steam Life Tests

Profile II AB-style filters can be sterilized by *in-situ* steaming. The maximum differential pressure during *in-situ* steaming is 300 mbar (4.4 psi) in forward direction. The maximum cumulative steaming exposure time is 10 hours at up to 125 °C.

The physical test conditions for *in-situ* steaming of Profile II filters can be considered as worst case for any sterilization process by steam and therefore include autoclave process conditions with the same temperature and cumulative exposure time.

4 Determination of Water Flow Characteristics

Tests were performed to determine the typical differential pressure (DP) across Profile II AB-style filter cartridges at set water flow rates.

Pre-filtered deionized water was pumped through the filters in the normal flow direction (out-to-in). Pressure readings from transducers on the upstream and downstream sides of the test assembly were monitored to calculate the DP at set water flow rates.

Further flow measurements for AB-style filter cartridges were taken with the test assembly with no filter cartridge installed, so that the pressure losses caused by piping/housing could be measured and then subtracted from the filter assembly results. The results were corrected for a standard temperature of 20 °C.

The water flow characteristics for Profile II AB-style filter cartridges (254 mm [10 in.]) are shown for filter codes 003 – 050 (Figure 3), filter codes 070 – 1200 (Figure 4) and are summarized in Table 3. To calculate the expected flow rate for fluids other than water, multiply the DP by the fluid viscosity (cP).

Figure 3

Water flow/differential pressure characteristics for Profile II AB-style filters (codes 003 – 050)

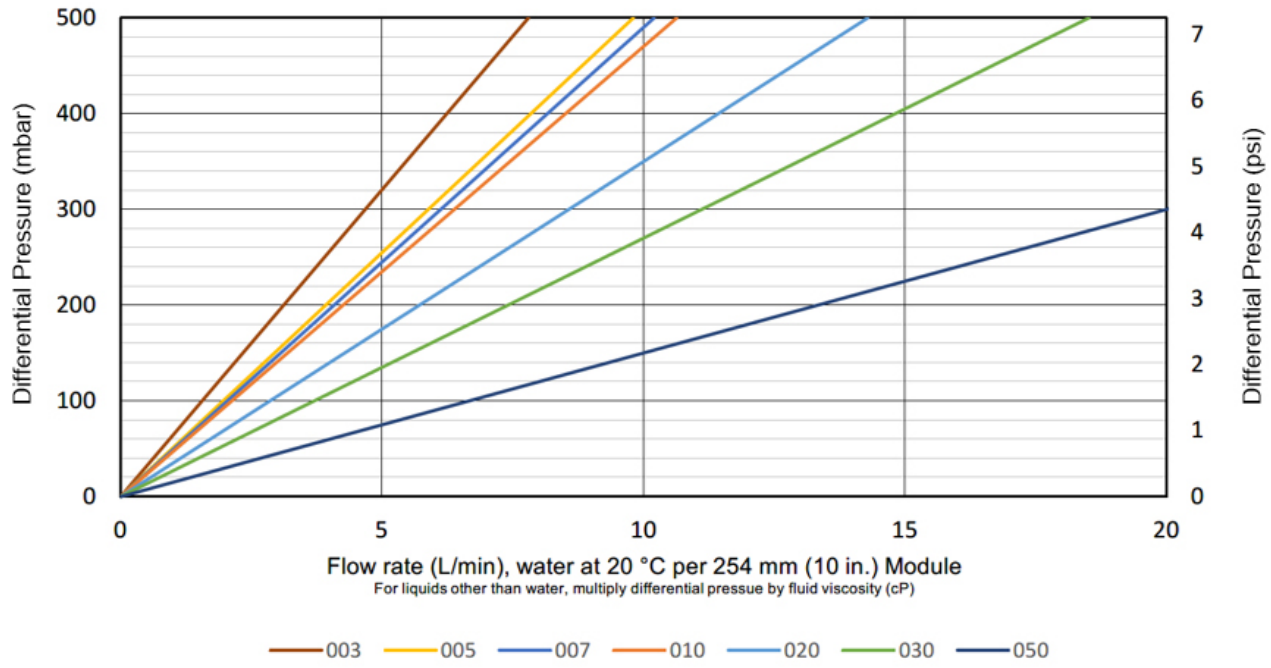


Figure 4

Water flow/differential pressure characteristics for Profile II AB-style filters (codes 070 – 1200)

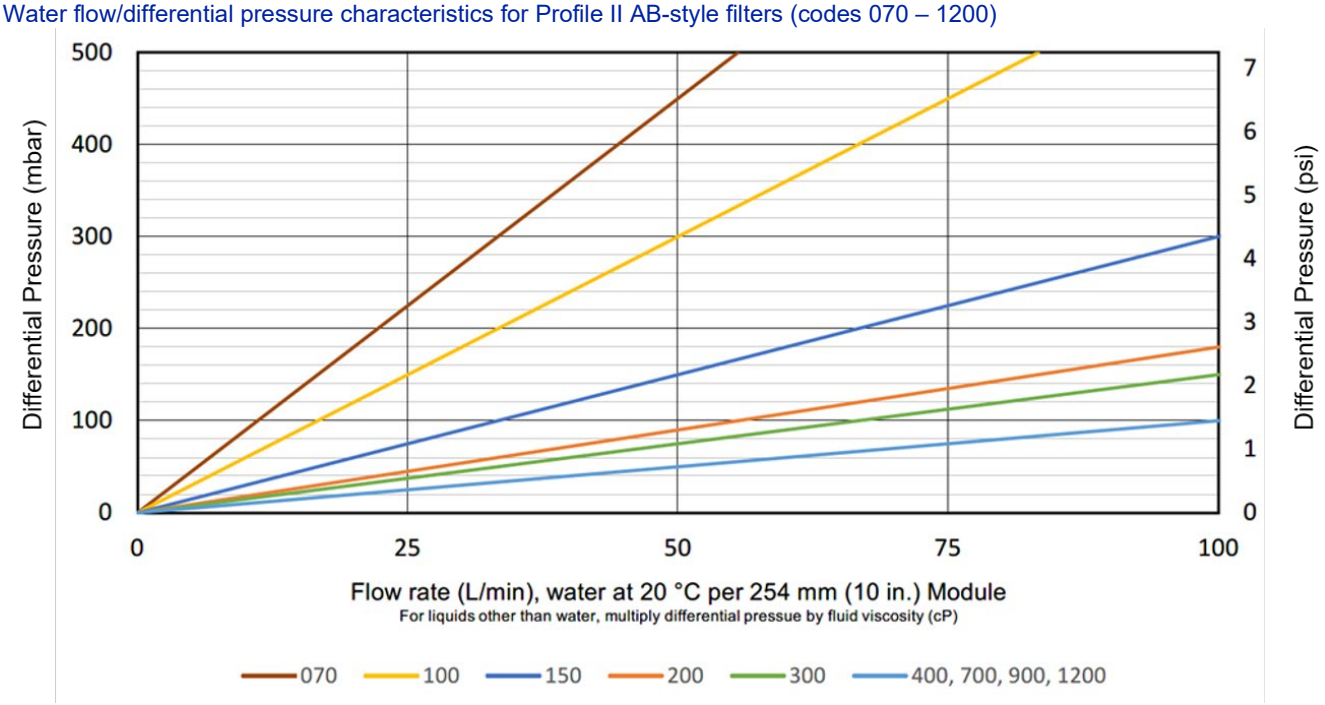


Table 3

Water flow/differential pressure overview for Profile II AB-style 254 mm (10 in.) filters (code 003 – 1200) at 100 mbar DP

Code	Flow Rate (L/min)
003	1.6
005	2.0
007	2.0
010	2.1
020	2.9
030	3.7
050	6.7
070	11.1
100	16.7
150	33.3
200	55.6
300	66.7
400	>100.0*
700	>100.0*
900	>100.0*
1200	>100.0*

**Determined typical aqueous DP per 254 mm (10 in.) module is <1.0 mbar/Lmin^{-1}*

5 Extractables Testing

Extractable testing of Profile II filters was performed to assess extractables deriving from melt-blown filter media and from injection-molded hardware parts. The amount of extractables is driven by the total available surface area of a given material to be extracted. Melt-blown filter media present a much higher surface contact area than injection-molded hardware parts.

Representative filters of AB1Y0057P were tested post sterilization by autoclaving (125 °C for 60 minutes) or by gamma-irradiation (50 kGy). No flushing was performed on sterilized filters prior to extraction.

5.1 Extraction Procedure for Filter Cartridges and Analysis of Extractables

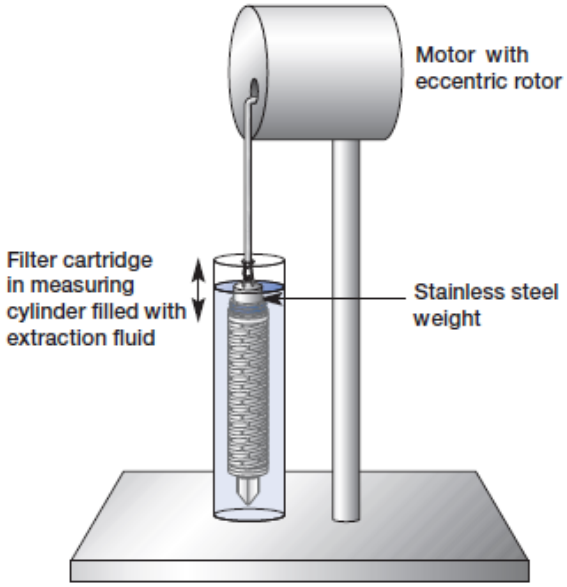
Dynamic extraction tests were performed at 40 °C in water, 50% ethanol/water and 95% ethanol/water. The test filters were immersed in 1500 mL of the respective extraction fluid in a clean graduated cylinder, as shown in Figure 5. For 24 hours, the filter was gently moved up and down. This movement created flow through the filter media as a result of pressure that was created each time the element was partially lifted out of the liquid.

Following the extraction period, a measured volume of the extraction liquid was evaporated to dryness and the non-volatile residue (NVR) were determined gravimetrically. A correction was made to the NVR value to account for the total extraction volume used.

The extractables were analyzed by Fourier Transform Infrared Spectroscopy (FTIR).

Figure 5

Filter extraction apparatus for filter cartridges



5.2 Results

NVR results for autoclaved Profile II filters (AB1Y0057PH4, lots ID2628 and ID6350) are shown in Table 4 and for gamma-irradiated Profile II filters (AB1Y0057PH4, lots ID2628 and ID6350) in Table 5. Reported NVR values are after negative control subtraction.

Table 4

NVR results for autoclaved Profile II filters (AB1Y0057PH4)

Solvent	NVR (mg)		
	ID2628	ID6350	Average Value
Water	< 0.5	< 0.5	< 0.5
50% ethanol/water	2.07	2.78	2.43
95% ethanol/water	117.75	59.25	88.5

Table 5

NVR results for gamma-irradiated Profile II filters (AB1Y0057PH4)

Solvent	NVR (mg)		
	ID2628	ID6350	Average Value
Water	0.60	0.60	0.60
50% ethanol/water	12.38	14.83	13.6
95% ethanol/water	105.56	122.44	114.0

The FTIR spectra of NVR from the filters indicated the presence of oligomers and polymer additives associated with polypropylene which is consistent with the materials of construction of the filters.

Extractables studies performed in accordance with the BioPhorum[1] protocol at 40 °C for 24 h with 50% ethanol/water can be provided upon request where extractables were analyzed by:

- Liquid Chromatography / Photodiode Array / Mass Spectrometry (LC/PDA/MS) for non-volatile, semi-volatile, and heat-sensitive compounds including fatty acids, antioxidants, and degradation products;
- Gas Chromatography / Mass Spectrometry (GC/MS) for characterization of volatile and semi-volatile compounds;
- Inductively Coupled Plasma / Mass Spectrometry (ICP/MS) for elemental analysis.

6 Biological Reactivity Tests

Biological suitability is expected to be evaluated for all materials of construction of pharmaceutical grade filters. The materials of construction of Profile II filters are listed in Table 6.

Table 6

Materials of construction (Profile II filters)

Component	Material
Media	Polypropylene
Core & endcaps	Polypropylene
O-rings	Silicone elastomer for ´H4´or ethylene propylene for ´J´ option

Tests were performed according to the requirements for biological reactivity, *in vivo*, under United States Pharmacopeia (USP) <88> (for Class VI – 121 °C plastics) and *in vitro*, under USP <87>. Filter media (melt-blown) and filter hardware (injection-molded) were either autoclaved (125 °C for 60 min) or gamma-irradiated (50 kGy) and subjected to the following tests according to USP requirements:

- USP <88>
    - Acute systemic toxicity tests (injection)
    - Intracutaneous tests
    - Implantation tests
- USP <87>
    - Minimum essential medium (MEM) elution cytotoxicity tests

No biological response was observed in any of the tests performed. Therefore, the materials used in Profile II AB-style filters met all the requirements of the USP Biological Reactivity Tests (*in vivo*) for Class VI-121 °C Plastics (USP <88>) and *in vitro* (USP <87>).

7 Testing for Pall's Certificate of Test for Pharmaceutical Grade Filters (P-Certificate)

All lots of Pall pharmaceutical (P)-grade filters undergo a certain set of quality control tests as part of the manufacturing lot release testing. Manufactured filter lots met all applicable lot release tests and thus the criteria for Pall's certificate of test for pharmaceutical-grade filters. These tests include:

- Fabrication integrity & effluent quality
- Cleanliness (particulates)
- Total organic carbon (TOC) and water conductivity

[1]Ding *et al.*, "Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing", *Pharmaceutical Engineering*, Vol 34, No 6, p.1-11, Nov/Dec 2014

- pH
- Endotoxins

The following table summarize the tests performed on two different filter lots of AB1Y0057PH4 (ID2628 & ID6350) and one filter lot for AB1Y1007PH4 (ID2630). The effluent quality is assessed on samples of filter effluents according to the specified limits for the single filter media as defined in Table 7, which are listed on certificate of tests.

Table 7

Result summary of quality control testing certified in certificate of test for Profile II filters

	Filter			
	AB1Y0057PH4		AB1Y1007PH4	
Test Type	**ID2628**	**ID6350**	**ID2630**	**Description**
Fabrication Integrity & Effluent Quality	Pass	Pass	Pass	Filter element samples from the appropriate manufacturing lot are tested for fabrication integrity and underwent the following effluent quality tests. The lot is released by quality control when it was verified that the following and respective criteria are met.
Cleanliness (Particulates)	Pass	Pass	Pass	Meets with adequate safety margin after flushing, current limits under USP <788> Particulate Matter in Injections, with effluent counts determined microscopically. Counts serve to document conformance with the requirements for a non-fiber-releasing filter per Title 21 of the U.S. Code of Federal Regulations (CFR) parts 211.72 and 210.3 (b)(6).
Total Organic Carbon (TOC) and Water Conductivity	Pass	Pass	Pass	Meets internal specifications after flushing, when tested in accordance with USP <643> Total Organic Carbon and USP <645> Water Conductivity. Total Organic Carbon: Upstream versus downstream differential not to exceed 500 ppb Water Conductivity: ≤ 1.3 µS/cm @ 25 °C.
pH	Pass	Pass	Pass	Meets internal specifications after flushing, upstream versus downstream differential not to exceed ± 0.5 pH units, when tested in accordance with USP <791> pH.
Endotoxins	Pass	Pass	Pass	Meets current requirements under USP Water for Injection, < 0.25 EU/mL, when an aliquot from a soak solution is tested using Limulus Amoebocyte Lysate (LAL) reagent in accordance with USP <85> Bacterial Endotoxins Test.

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