LifeASSURE™ PDA Series Filter Cartridge Validation Guide

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LifeASSURE™ PDA Series Filter Cartridge Validation Guide

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I. INTRODUCTION

A. PRODUCT INTRODUCTION

This Guide contains validation data and regulatory support information pertinent to LifeASSURE™ PDA series 0.2 micron rated filter cartridges. It contains information that supports the safety, efficacy and regulatory compliance of LifeASSURE PDA series filter cartridge in pharmaceutical, biological and bioprocessing filtration applications.

The LifeASSURE PDA series 0.2 micron rated filter cartridges are used in critical process stages where microbially-rated 0.2 micron sterile or final filtration is required. The filter cartridges meet the FDA's definition of an 0.2 micron sterilizing grade filter as described in the FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, Good Manufacturing Practice - September, 2004.

The filter cartridges are qualified for quantitative retention of *Brevundimonas diminuta* (*B. diminuta)* at a minimum challenge of 10^7 organisms /cm² of effective filter surface area. Bacterial challenge studies were conducted in accordance with ASTM method F838-05. This Validation Guide has been prepared specifically for manufacturers requiring product documentation as part of their process validation. It includes the following test data to support published performance claims:

- Cartridge construction
- *B. diminuta* retention and correlation to non-destructive integrity testing
- Water flow
- Thermal stress
- Total Non-Volatile Gravimetric Extractables
- Effluent cleanliness
- *Limulus* Amebocyte Lysate (LAL) Testing
- Conductivity and Total Organic Carbon (TOC)

In addition to product performance test results, the following safety and regulatory support information is provided:

- Class VI USP Biological Test for Plastics and Elution Test Results
- ISO Certification
- Material Safety Data Sheet
- Animal Derived Component Statement

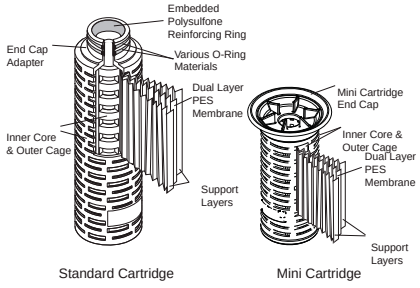
LifeASSURE PDA series 0.2 micron rated filter cartridges are manufactured and tested in accordance with procedures documented in 3M Purificiation's Drug Master File (DMF) No. 19073 on record with the U.S. Food and Drug Administration. Further technical data and product information can be found in LifeASSURE PDA series literature (70-0201-8687-3).

3M would be pleased to supply you with any additional information you require. Further information may be obtained by contacting: Scientific Applications Support Services (SASS) at:
3M Purification Inc., 400 Research Parkway, Meriden, CT 06450, U.S.A. Tel. (800) 243-6894, (203) 237-5541.

B. CARTRIDGE CONSTRUCTION

Membrane:

LifeASSURE PDA series 0.2 micron rated membrane filter cartridges are made from a proprietary polyethersulfone (PES) membrane. Two (2) layers of filter media are used providing assurance of the highest possible reliability.



Membrane Inner & Outer Support Layers:

Polyethersulfone membrane is pleated with an upstream support layer of polypropylene to provide access of influent fluid, and dual layers downstream to support flow of effluent fluid. These layers also provide support and protection of the filter membrane.

Cartridge Hardware Components:

Inner filter core and outer protective cage are molded polypropylene. Plastic o-ring adapters contain a polysulfone ring for dimensional stability that is fully encapsulated in polypropylene. End caps and flange seal are polypropylene. All filter cartridge components are assembled by thermal bonding.

LifeASSURE™ PDA Series Filter Cartridge Construction			
	Cartridges	Mini-Cartridges	
	5" to 40" Length	2.5" Length	5" Length
Filter Rating	0.2 micron		
Inner Core, Outer Cage, End-Caps, Capsule Head & Sump	Polypropylene		
Membrane	Polyethersulfone		
Media Support Layer	Polypropylene		
Encapsulated Adapter Support Ring	Polysulfone	N/A	
Filtration Surface Area m^2 (ft^2)	5": 0.35 (3.8) 10": 0.78 (8.4)*	0.12 (1.26)	0.26 (2.84)

*Multiply surface area of 10" cartridge for 20", 30", and 40" cartridges

C. PART NUMBER DESCRIPTION

LifeASSURE™ PDA Series Filter Cartridge Ordering Guide

Grade Designation	Configuration	Height (inches)	End Modification	O-Ring Material
PDA020 0.2 micron	F	01 – 10 02 – 20 03 – 30 04 – 40 50 – 5	B – 226 O-ring & Spear C – 222 O-ring & Spear F – 222 O-ring & Flat Cap J – 226 O-ring & Flat Cap	A - Silicone B – Fluorocarbon C – EPR D – Nitrile K – PTFE Encapsulated Fluorocarbon

LifeASSURE PDA Series Mini-Cartridge Ordering Guide

Grade Designation	Configuration	Height (inches)	End Modification	Package Quantity
PDA020 0.2 micron	M	01 – 2.5 02 – 5.0	AN - Flange Seal	01 – 1 Pack

D. PRODUCT OPERATING PARAMETERS

Recommended operating conditions for LifeASSURE PDA Series filter cartridges and Mini-Cartridges:

	Cartridges & Mini-Cartridges
Maximum Operating Temperature:	80 °C (176 °F)
Maximum Differential Pressure:	Forward - 5.5 bar (80 psid) @ 25 °C (77 °F); 1.7 bar (25 psid) @ 80 °C (176 °F) Reverse - 2.4 bar (35 psid) @ 25 °C (77 °F)
Sterilization:	
In situ Steam:	Up to 135 °C (275 °F)
Autoclave:	Up to 126 °C (259 °F)

II. PERFORMANCE

A. VALIDATION OF BACTERIAL RETENTION AND CORRELATION WITH NON-DESTRUCTIVE INTEGRITY TESTS

The validation of bacterial *B. diminuta* retention for LifeASSURE™ PDA series 0.2 micron rated pharmaceutical grade cartridges was performed in accordance with American Society of Testing and Materials (ASTM) method F838-05. Using this test methodology, LifeASSURE PDA series 0.2 micron rated pharmaceutical grade filters retained in excess of 1×10^7 CFU of *B. diminuta* (ATCC 19146) per cm^2 of effective filter surface area.

The correlation between a non-destructive integrity test and assurance of microorganism retention is critical for filters used in sterile filtration applications. The LifeASSURE PDA series filter validation study establishes the relationship between non-destructive integrity tests and bacterial retention and serves as the basis for establishing pre- and post-use integrity testing of production filters. In pharmaceutical manufacturing, integrity testing is recommended before and after the filtration process to ensure filter integrity.

Protocol for Correlation of Forward Diffusive Flow with Bacteria Retention (10" cartridge):

LifeASSURE PDA series 0.2 micron rated pharmaceutical grade filters were taken from multiple production lots. Cartridges were subjected to a forward flow diffusion integrity test and were bacteria challenge tested in accordance with ASTM F838-05 to challenge levels in excess of 1×10^7 CFU / cm^2 (*B. diminuta*). Each 10" test filter was initially wetted with water prior to challenge. The filter was then subjected to a diffusive flow integrity test using 40 psig of clean air. Diffusive flow rate (cc/min) in the forward flow direction was determined once a stable flow rate was observed.

Results (10" cartridge):

LifeASSURE PDA series 0.2 micron rated pharmaceutical grade filters with forward flow diffusion values of less than or equal to 45.3 cc/min successfully passed the bacterial challenge validation test. Thus, any wetted LifeASSURE PDA series 0.2 micron rated filter cartridge yielding a forward flow diffusion value of less than or equal to 38.0 cc/min per 10" element at a 40 psig test pressure can be used with confidence.

Table 1. 10" Cartridge Bacterial Retention Correlation

Lot Number/Serial Number	Diffusion @40 psig (cc/min)	Sterile Effluent
05N015-404	26.4	YES
05N026-027	26.4	YES
05N021-128	26.4	YES
05N021-132	26.8	YES
05N026-029	27.0	YES
05N026-017	27.2	YES
05N015-407	27.4	YES
05N026-021	27.4	YES
05N021-036	27.5	YES
05N026-025	28.0	YES
05N021-048	29.1	YES
05N015-430	29.2	YES
05N021-043	29.5	YES
05N021-035	29.7	YES
05N015-444	30.1	YES
05N021-041	30.2	YES
05N021-034	30.3	YES
05N015-441	30.4	YES
05N015-446	30.4	YES
05N021-039	30.4	YES
05N026-022	31.0	YES
04N024-005	31.2	YES
05N015-402	31.5	YES
05N026-026	31.5	YES
05N021-042	31.6	YES
05N015-411	31.8	YES
05N026-031	32.0	YES
05N015-436	32.6	YES
05N015-423	33.0	YES
04N024-002	33.9	YES
04N024-011	34.0	YES
04N024-017	34.2	YES
05N026-092	34.8	YES
04N024-007	36.2	YES
05N021-061	38.2	YES
05N026-094	38.6	YES
05N024-009	45.3	YES
05N015-416	45.8	NO
05N024-015	54.6	YES
04N023-003	65.2	NO
05N015-499	79.2	NO

Protocol for Correlation of Forward Diffusive Flow with Bacteria (5” Capsule):

LifeASSURE PDA series 0.20 micron rated 5” Capsules were taken from multiple production lots. Capsules were subjected to a forward flow diffusion integrity test and were bacterial challenge tested in accordance with ASTM F838-83 to challenge levels in excess of 1 x 107 CFU/cm2. Each test filter was initially wetted with water prior to challenge. The filter was then subjected to a diffusive integrity test using 40 psig of clean air. Diffusive flow rate (cc/min) in the forward flow direction was determined once a stable flow rate was observed.

Results (5” Capsule):

LifeASSURE PDA series 0.20 micron rated 5” capsule filters with diffusion values of less than or equal to 16.5 cc/min success fully passed the bacterial challenge validation test (Table 2). Thus, any wetted LifeASSURE PDA series 0.20 micron rated 5- inch Capsules yielding a forward flow diffusion value of less than or equal to 15.0 cc/min at a 40 psig test pressure can be used with confidence.

Table 2. 5” Capsule Microbial Retention Correlation

Lot Number/Serial Number	Diffusion @40 psig (cc/min)	Sterile Effluent
05N021-028	8.5	YES
05N021-033	9.0	YES
05N026-027	9.2	YES
05N026-002	9.6	YES
05N026-005	9.7	YES
05N026-020	9.9	YES
05N021-030	10.0	YES
05N021-037	10.2	YES
05N015-224	10.4	YES
05N021-021	10.6	YES
05N021-038	10.8	YES
05N021-036	10.9	YES
05N015-206	11.0	YES
05N015-240	11.2	YES
05N015-232	12.0	YES
05N021-017	12.8	YES
05N015-219	13.0	YES
05N015-255	13.5	YES
05N015-252	14.0	YES
05N015-257	16.5	YES
05N015-190	20.1	YES
05N026-013	20.1	NO
05N021-008	24.8	YES
05N021-010	36.8	NO

Capsule data was generated using a 5" capsule fabricated from a 5" module. The design of the of the 2.5"& 5" cartridge share the same subunit technology, thus the 5" capsule data applies to the 2.5" & 5" mini-cartridges.

Table 3. Summary of LifeASSURE™ PDA Series Filter Integrity Test Parameters

Filter Type	Rating (micron)	Minimum Bubble Point (psig)	Forward Flow Test Pressure (psig)	Maximum Forward Flow/ Diffusion (cc/min)
PDA020 40" Cartridge	0.2	45.0	40.0	137.0
PDA020 30" Cartridge	0.2	45.0	40.0	104.0
PDA020 20" Cartridge	0.2	45.0	40.0	71.0
PDA020 10" Cartridge	0.2	45.0	40.0	38.0
PDA020 5" Cartridge	0.2	45.0	40.0	17.2
PDA020 5" Mini-Cartridge	0.2	45.0	40.0	15.0
PDA020 2.5" Mini-Cartridge	0.2	45.0	40.0	6.7

Maximum Forward Flow Diffusion values for 10- 40 inch cartridges is not linear. Diffusion values were determined using a Root Mean Square calculation.

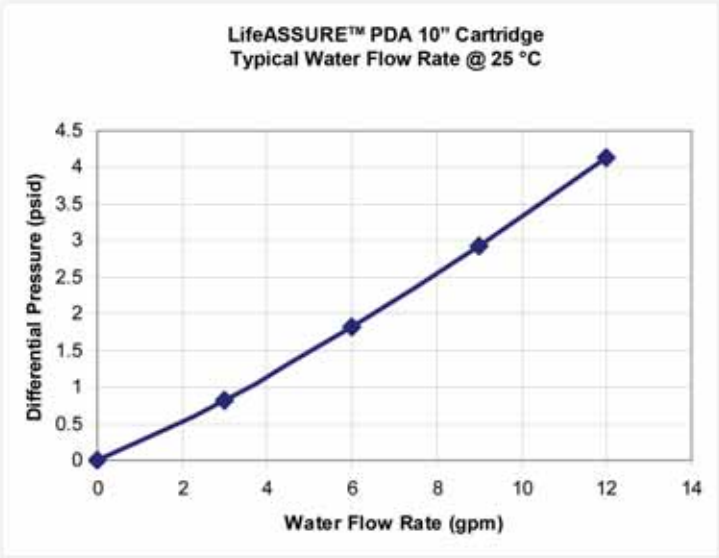
B. WATER FLOW RATE

Protocol 10" LifeASSURE PDA Series Filter Cartridge:

LifeASSURE PDA series 10" filter cartridges were inserted into a 10" filter housing. Particle-free, 25 °C water was passed through the filter at controlled flow rates of 3.0, 6.0, 9.0, and 12.0 gpm. Differential pressure across the filter at the various flow rates was measured with a calibrated pressure transducer and recorded.

Results 10" LifeASSURE PDA Series Filter Cartridge:

A standard curve was developed for the typical water flow rate for a 10" cartridge.

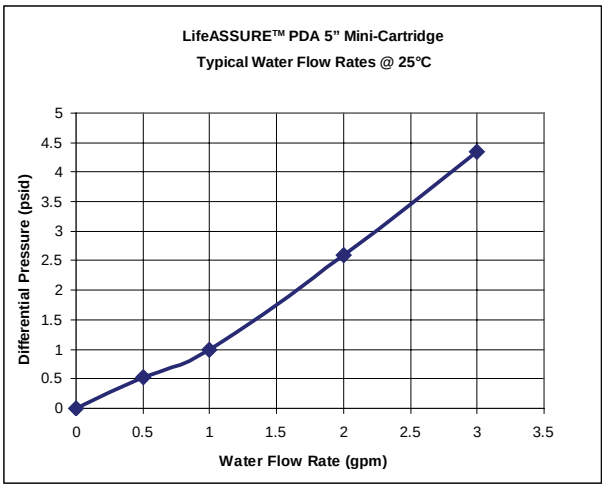


Protocol 5" LifeASSURE PDA Series Mini-Cartridge:

LifeASSURE PDA series 5" Mini-Cartridge filters were inserted into a Mini-Cartridge filter housing. Particle-free, 25 °C water was passed through the filter at controlled flow rates of 0.5, 1.0, 2.0, and 3.0 gpm. Differential pressure across the filter, at the various flow rates was measured with a calibrated pressure transducer and recorded

Results 5" LifeASSURE PDA Series Mini-Cartridge:

A standard curve was developed for the typical water flow rate of a 5" Mini-Cartridge.

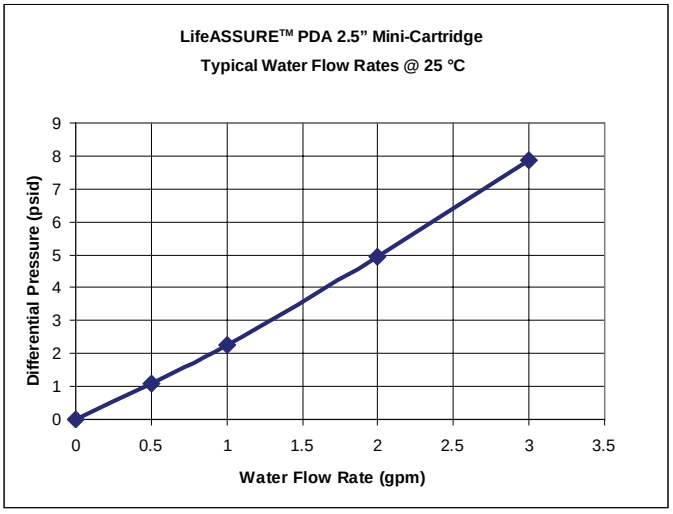


Protocol 2.5" LifeASSURE PDA Series Mini-Cartridge:

LifeASSURE PDA series 2.5" Mini-Cartridges were inserted into a Mini-Cartridge filter housing. Filters were placed in a fluid stream of particle-free, 25 °C water that passed through the filter at controlled flow rates of 0.5, 1.0, 2.0, and 3.0 gpm. Differential pressure across the filter, at the various flow rates was measured with a calibrated pressure transducer and recorded.

Results 2.5" LifeASSURE PDA Series Mini-Cartridge:

A standard curve was developed for the typical water flow rate of a 2.5" Mini-Cartridge.



C. THERMAL STRESS – CARTRIDGE STEAM STERILIZATION

LifeASSURE PDA series 0.2 micron rated pharmaceutical grade filters are designed to perform in demanding process conditions. The materials of construction and design for the cartridge provide an durable envelope that can be *in situ* steam sterilized (or autoclaved) repeatedly without loss of integrity (LifeASSURE PDA series 0.2 micron rated capsules cannot be *in situ* steam sterilized).

Protocol 10" Cartridge Filters:

Water wetted 10" cartridges were installed in filter housings. The assemblies were then steam sterilized *in situ* at 135 °C for a total of 20 sterilization cycles (30 minutes per cycle). Between cycles, the filter housings' temperature was allowed to drop below 60 °C. At the end of the 20th cycle, each filter was tested for integrity via forward flow diffusion and tested for microbial retention at challenge levels in excess of 1.0×10^7 CFU/cm² *B. diminuta* using standard methods.

Results:

The results demonstrate the robustness of the LifeASSURE PDA series 0.2 micron rated cartridge filters to repeated steam sterilization cycles. The LifeASSURE PDA series 0.2 micron rated filters should be considered equally resilient to autoclave sterilization. For temperatures of up to 135 °C liquid cycle (slow exhaust), autoclave sterilizations are recommended.

Table 4. 10" Cartridge Integrity Test and Bacterial Challenge Results After 20 Steam Cycles @ 135° C

Lot Number/Serial Number	Water Wet Diffusive Flow @ 40 psi (cc/min)	Sterile Effluent Flow Challenge
05N015-402	28.9	Yes
05N015-411	28.3	Yes
05N015-423	29.6	Yes
05N021-035	24.5	Yes
05N021-036	26.8	Yes
05N021-048	25.4	Yes
05N026-022	27.1	Yes
05N026-026	28.5	Yes
05N026-031	29.9	Yes

Protocol 2.5" and 5" Mini-Cartridge Filters:

Water wetted 2.5" or 5" mini-cartridges were installed in filter housings. The assemblies were then steam sterilized *in situ* at 135 °C for a total of 20 sterilization cycles (30 minutes per cycle). Between cycles, the filter housings' temperature was allowed to drop below 60 °C. At the end of the 20th cycle, each filter was tested for integrity via forward flow diffusion.

Results:

The results demonstrate the robustness of the LifeASSURE™ PDA series 0.2 micron rated mini-cartridge filters to repeated steam sterilization. The LifeASSURE PDA series 0.2 micron rated filters should be considered equally resilient to autoclave sterilization. For temperatures of up to 135 °C liquid cycle (slow exhaust), autoclave sterilizations are recommended.

Table 5. 2.5" Mini-Cartridge Integrity Test Results After 20 Steam Cycles @ 135° C

2.5" Mini-Cartridge Lot Number/Serial Number	Water Wet Diffusive Flow @ 40 psi (cc/min)
05N015-0152	4.0
05N015-0154	3.6
05N015-0160	3.6

Table 6. 5" Mini-Cartridge Integrity Test Results After 20 Steam Cycles @ 135 °C

5" Mini-Cartridge Lot Number/Serial Number	Water Wet Diffusive Flow @ 40 psi (cc/min)
05N015-0165	10.0
05N015-0168	9.9
05N015-0175	10.1

III. EFFLUENT QUALITY

A. TOTAL NON-VOLATILE GRAVIMETRIC EXTRACTABLES

Protocol (10" cartridge):

10" LifeASSURE PDA series cartridge filters (O-rings removed) were autoclaved at 126 °C, flushed with 20 liters purified water, and submerged in 1.4 liters of distilled water held in 2 liter graduated cylinders until all of the air from within them was displaced. The graduated cylinder's contents were magnetically stirred at modest rpm for 24 hours. The filter was removed from the water and the water drained from the filter was allowed to return into the graduated cylinder.

Protocol (drying and weighing extraction residue):

The volume of the extract water was reduced to 40 ml on a hot plate. The 40 ml of concentrated extract was quantitatively transferred into a tared (± 0.1 mg), desiccated, aluminum weighing pan. The contents of the weighing pan were brought to dryness on a hot plate. The weighing pan was dried in a convection oven for 30 minutes at 105 °C and was then desiccated for an additional 30 minutes. Finally, the weighing pan was weighed to determine gross weight (± 0.1 mg). Total non-volatile gravimetric extractables from the test filters were equal to the difference between the weighing pan's gross and tare weights, in milligrams.

Results:

Total gravimetric extractable values for LifeASSURE PDA series 0.2 micron rated cartridges taken from multiple production lots are detailed in the following tables. The average extractable level from 10" cartridge filters was 17 mg.

Table 7. 10" Cartridge - TGNVE

10" Cartridge Lot Number/Serial Number	TGNVE mg
05N015-401	17
05N015-414	24
05N015-432	20
05N021-044	16
05N021-047	14
05N021-062	21
05N026-072	18
05N026-109	12
05N026-111	12

B. EFFLUENT CLEANLINESS AND NON-FIBER RELEASING

LifeASSURE PDA series 0.2 micron rated cartridge filters are designed to contribute minimal particulate to the effluent stream.

Protocol:

LifeASSURE PDA series 0.2 micron rated 10" cartridge filters were pre-flushed with 15 liters deionized water (4-5 liter flush for 5" Mini-Cartridges). Four liters of effluent (1liter for 5" Mini-Cartridges) from each cartridge was collected and placed in a laminar flow hood for vacuum filtration. Each effluent sample was vacuum filtered through a 47 mm 0.8 micron gridded black membrane disc. Each membrane disc was examined microscopically under 125x magnification and the particles counted and measured at two size ranges (> 10 micron and > 25 micron).

Results:

The effluent from LifeASSURE PDA series 0.2 micron rated cartridges tested met, with adequate safety margin, the current USP 34 limits under Particulate Matter in Injections <788> with effluent counts determined microscopically.

Analysis of fiber counts document conformance with the requirements for a non-fiber releasing filter per Title 21 of the U.S. CFR parts 211.72 and 210.3 (b) (6). The following table details the particle counts determined microscopically for the LifeASSURE PDA series 0.2 micron rated filters.

Table 8. 10" Cartridge Effluent Particle Counts

Cartridge ID	Particulate Size	
	> 10 micron Particle/ml	> 25 micron Particle/ml
05N015-403	0.13	0.01
05N015-434	0.07	0.02
05N021-137	0.10	0.03
05N021-144	0.15	0.06
05N026-104	0.10	0.03
05N026-118	0.12	0.02
Average	0.11	0.03

Table 9. 5" Cartridge Effluent Particle Counts

Capsule ID	Particulate	
	> 10 µm Particle/ml	> 25 µm Particle/ml
05N015-188	0.06	0.01
05N015-233	0.04	0.01
05N021-005	0.06	0.01
05N021-016	0.06	0.02
05N026-007	0.02	0.01
05N026-025	0.05	0.01
Average	0.05	0.01

C. *LIMULUS* AMEBOCYTE LYSATE (LAL) TESTING

LifeASSURE PDA series 0.2 micron rated cartridge filter effluent is designed to meet with adequate safety margin, the specification for endotoxin as stated in the current United States Pharmacopoeia (USP 34).

Protocol:

Autoclaved LifeASSURE PDA series filters were rinsed with LAL Reagent Water (LRW) and filtrate samples were collected at the 3.5 Liter mark. Without further dilution and using only depyrogenated glassware and endotoxin-free plasticware, the samples were tested in duplicate for endotoxin using an Associates of Cape Cod (ACC) gel clot method. The method makes use of 0.03 EU/ml sensitivity lysate and Control Standard Endotoxin. 3M's procedure is consistent with ACC's recommendations for optimal performance of the method and uses the following controls: 1) endotoxin standard series, 2) positive product control, 3) LRW negative control, and 4) endotoxin spike control. For more details, see the "USP 34 Bacterial Endotoxin Test" and ACC's technical brief entitled "LAL Pyrotell® for the Detection and Quantification of Gram-Negative Bacterial Endotoxins," April, 1990.

Results:

The table below provides endotoxin results from cartridge filters spanning multiple manufacturing lots. All product met USP 34 requirements for Sterile Water for Injection.

Table 10. 10" Cartridge LAL Test

Lot Number/Serial Number	Endotoxin Concentration at Effluent Volume of 3500 ml (EU/ml)	Oxidizable Substances at Effluent Volume of 3500 ml
05N015-403	0.06	negative
05N015-434	0.06	negative
05N021-137	<0.03	negative
05N021-144	<0.03	negative
05N026-104	0.12	negative
05N026-118	<0.03	negative

D. CONDUCTIVITY AND TOTAL ORGANIC CARBON (TOC) COMPLIANCE WITH USP 34 SPECIFICATION FOR PURIFIED WATER:

Protocol:

Sample 10" cartridges were flushed with deionized water at a flow rate of 6 lpm and effluent samples were collected at 5 L, 10 L, 15 L, and 20 L. Effluent samples were analyzed for conductivity and TOC according to USP 34 procedures.

Results:

The results for three (3) lots of 10" LifeASSURE PDA series filters tested show compliance with current USP 34 specifications for Pure Water conductivity and Total Organic Carbon following a 20 liter flush volume.

Table 11. 10" Cartridge Total Organic Carbon

	TOC (ppm)				Conductivity (uS/cm)			
	Flush Volume (liters)				Flush Volume (liters)			
10" Cartridge Lot Number/Serial Number	5	10	15	20	5	10	15	20
05N015-406	1.34	0.76	0.52	0.33	0.94	0.62	0.59	0.66
05N021-058	0.79	0.32	0.24	0.18	0.73	0.66	0.70	0.74
05N026-101	0.98	0.35	0.21	0.2	0.84	0.78	0.80	0.79

IV. BIOLOGICAL SAFETY TESTS

Based upon testing results provided by Toxikon Corporation, all of the materials of construction incorporated into the LifeASSURE PDA series 0.2 micron rated cartridge filters meet the requirements of:

A. ISO MEM Elution Test (Page 15)

B. Class VI Biological Test for Plastics, (Page 16)

A. ISO MEM Elution Test

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TEST RESULT CERTIFICATE

Sponsor	Cuno, Inc.	**Technical Initiation**	06/04/03
Address	400 Research Pkwy Meriden, CT 06450	**Technical Completion**	06/06/03
Contact	Kim Buckland	**Report Date**	06/12/03
P.O. Number	77971	**Project Number**	03-2695-G1

Test Article	BioASSURE 10", PES, 0.2 Micron Cartridge	**Ratio**	3 cm^2 per 1 mL
Lot # / Part #	03-N002-01	**Vehicle**	MEM complete
Study	MEM Elution Test - ISO	**Extraction Conditions**	37°C for 24 hours
Comments	None		

REFERENCE: This study was conducted based on the procedure described in Biological Evaluation of Medical Devices-Part 5: Tests for *In Vitro* Cytotoxicity, EN/ISO 10993-5, 1999, Biological Evaluation of Medical Devices-Part 12: Sample Preparation and Reference Materials, EN/ISO 10993-12, 1997.

GENERAL PROCEDURE: The biological reactivity of a mammalian monolayer, L929 mouse fibroblast cell culture, in response to the test article extract was determined. Extracts were prepared at 37±1°C for 24 hours in a humidified atmosphere containing 5±1% carbon dioxide. Positive control (natural rubber) and negative control (negative control plastic) articles were prepared to verify the proper functioning of the test system. The test article or control article extracts were used to replace the maintenance medium of the cell culture. All cultures were incubated in triplicate for 48 hours, at 37±1°C, in a humidified atmosphere containing 5±1% carbon dioxide. Biological reactivity (cellular degeneration and malformation) was rated on a scale from Grade 0 (No Reactivity) to Grade 4 (Severe Reactivity). The test article met the requirements of the test if none of the cultures exposed to the test article showed greater than a Mild Reactivity (Grade 2).

RESULTS: No signs of reactivity (Grade 0) were exhibited by the cell cultures exposed to the test article extract or the negative control article extract at the 48 hour observations. Severe signs of reactivity (Grade 4) were observed for the positive control article extract at the 48 hour observation.

CONCLUSION: The test article is considered non-cytotoxic and meets the requirements of the Elution Test, EN/ISO 10993-5.

AUTHORIZED PERSONNEL:

Leigh Waugh-Cohen, B.A.
Study Director

Lakshmi Jayaraman, B.S.
Quality Assurance

B. Biological Test for Plastics, Class VI

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TEST RESULT CERTIFICATE

Sponsor	CUNO, Inc.	**Technical Initiation**	06/11/03
Address	400 Research Parkway Meriden, CT 06450	**Technical Completion**	06/18/03
Contact	Kim Buckland	**Report Date**	07/07/03
P.O. Number	77971	**Project Number**	03-2695-G2

Test Article	BioASSURE 10", PES, 0.2 micron Cartridge	**Ratio**	4 gm per 20 mL
Lot #/Part #	03-N002-01	**Vehicles**	0.9% USP Sodium Chloride for Injection (NaCl), Cottonseed Oil (CSO), 1:20 Alcohol in NaCl (EtOH), Polyethylene Glycol 400 (PEG)
Study	Biological Test for Plastics Class VI (4 Extracts)	**Extraction Conditions**	121±2°C for 1 hour

REFERENCE: USP 26, NF 21, 2003, <88> Biological Reactivity tests, *In Vivo*.

GENERAL PROCEDURE: The extraction conditions were performed as stated above. The test article extracts and corresponding blanks were injected systemically and intracutaneously in mice and rabbits, respectively. The injections were in the amounts and routes set forth by USP 26; including the further dilution of the extracts prepared with PEG. The animals were observed for signs of toxicity and skin reactivity for up to 72 hours post treatment. In addition, the test article was implanted into the paravertebral muscles of rabbits for 7 days and observed for signs of hemorrhage, inflammation, necrosis, discoloration, encapsulation, and infection.

RESULTS: None of the mice injected with the test article extracts exhibited any signs of toxicity in the Systemic Injection Test. In addition, none of the rabbits injected intracutaneously with the test article extracts exhibited any signs of erythema, edema or clinical toxicity. In both the Systemic and Intracutaneous Tests the controls were normal through 72 hours. Also, the implant sites exhibited no significant signs of hemorrhage, inflammation, necrosis, discoloration, encapsulation, or infection compared with the control sites.

CONCLUSION: The test article meets the requirements of USP 26, NF 21, 2003 for the Biological Test for Plastics, Class VI-121 °C.

AUTHORIZED PERSONNEL:

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Please note: The tradename "BioASSURE" is now "LifeASSURE" CUNO Incorporated is now 3M Purification Inc.

I. APPENDICES

A. ISO Certificate

CERTIFICATE

TUV Rheinland of North America, Inc.
1300 Massachusetts Avenue, Boxborough, MA 01719

TÜVRheinland®

Hereby certifies that

3M Purification Inc.

400 Research Parkway
Meriden, CT 06450

250 South Road
Enfield, CT 06082

32 River Road
Stafford Springs, CT 06076

has established and maintains a quality management system for the

Design and Manufacture of Products for Filtration and Ultrafiltration Products and Systems and other Media Platforms for the Potable Water, Fluid Processing and Healthcare Markets

An audit was performed and documented in Report No 9519.
Proof has been furnished that the requirements according to

ISO 9001:2008

are fulfilled.
Further clarification regarding the scope of this certificate and the applicability of ISO 9001:2008 requirements may be obtained by contacting TRNA.

Certificate Registration No.

74 300 9519

Certificate Validity Date:
August 10, 2011

Certificate Expiration Date:
August 9, 2014

ANAB ACCREDITED

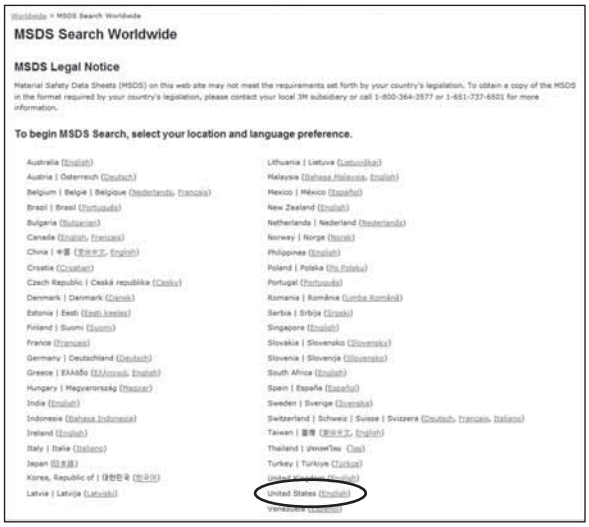
Certification of Management Systems

Revised 12/20/2011
Certification Decision Date: 07/28/2011

C. Material Safety Data Sheet (MSDS)

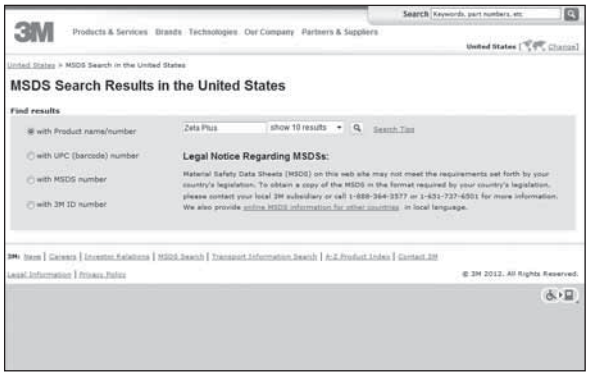
The products in this document are covered by one or more Material Safety Data Sheets (MSDS). To view the MSDS online, pleas follow the three steps outlined below. To request and MSDS relating to these products, call 203-238-8965. For emergencies, call 800-364-3577 or 651-737-6501 (24 hours).

Product Name	MSDS Number
LifeASSURE	25-0277-1
LifeAssure(TM) PDA Capsules	29-9710-4



Step 1: Go to www.3M.com/MSDS

Step 2: Select "United States" regardless of your home country.



Step 3: Use the search engine to find MSDS using one of the following methods:

a. Search "with Product name/number" or "with MSDS number", click the appropriate radio button and enter the keyword or number from the list above. Be sure to type exactly as it is shown here.

b. Search "with 3M ID number," click the radio button and type the appropriate 3M ID number (example: 70-0202-3655-3).

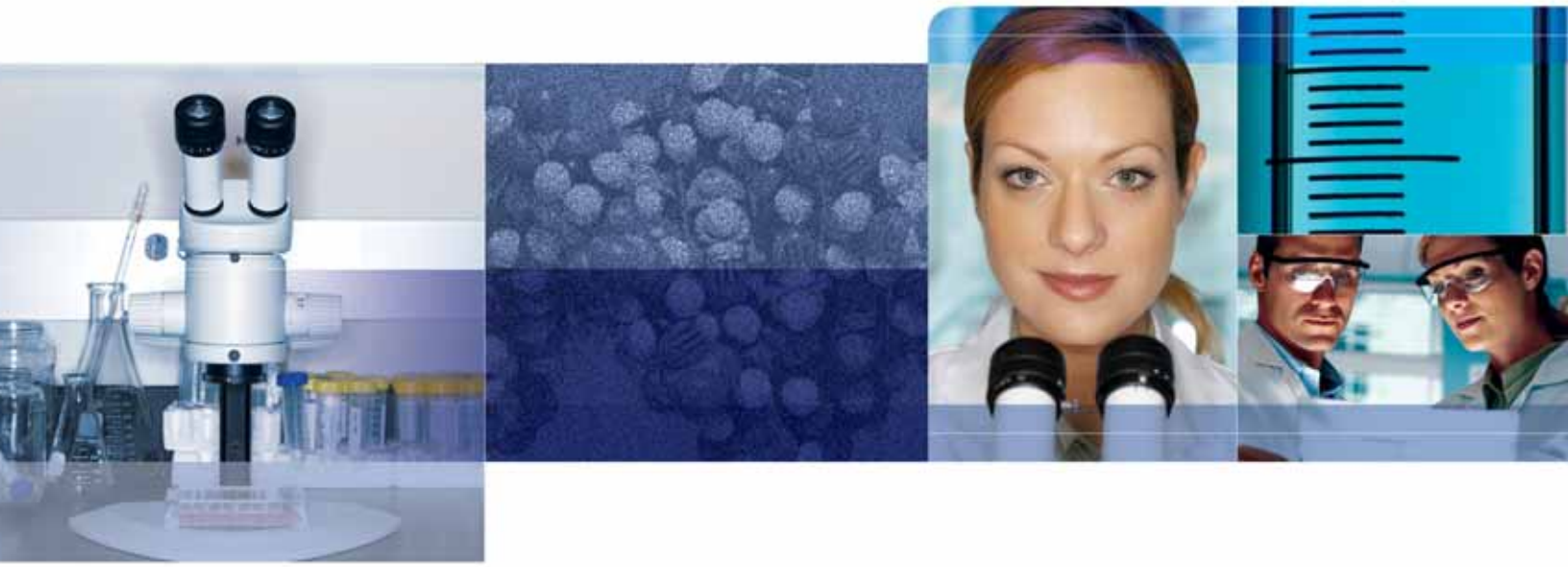
D. ANIMAL DERIVED COMPONENT STATEMENT

3M understands the continued public interest and the increased regulatory scrutiny concerning the transmission of bovine spongiform encephalopathy (BSE) and other transmissible spongiform encephalopathies (TSE). In order to address these issues, the following statement is offered:

In order to assess the BSE/TSE risk associated with the LifeASSURE™ PDA series filter media product, we have contacted our suppliers of raw materials and performed an evaluation of our production processes to determine if any of the materials used are of animal origin. The result of our survey and inquiries of our raw material suppliers has revealed that the polypropylene resins used to mold parts may contain tallow derivatives and certain o-rings could contain a stearic acid that is used as an activator in the vulcanization process. We can state, however, that these parts which use tallow derivatives and stearic acid are processed at conditions conforming to the requirements of the European Agency for the Evaluation of Medicinal Products EMEA/410/01 rev. 3 and are thought unlikely to be infectious, per said regulation.

Based on this, the likelihood of BSE or other TSE prions being present in 3M filter products is very low. Therefore, the exposure risk to your product using 3M filters is also minimal. Should you have any questions, please do not hesitate to contact us.

3M Purification Inc. Corporate Worldwide Quality Assurance



Important Notice

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