PALL Life Sciences

Validation Guide

USTR 2661(2)

T-Series TFF Cassettes with Delta Membrane

For use with Centramate™ and Centrasette™ TFF Systems

*Filtration. Separation. Solution.*SM

Contents

1. Purpose of this Document

This document provides validation support information for Pall's T-Series tangential flow filtration (TFF) cassettes with Delta membrane, and includes summary data to support testing conducted for biological safety, extractables, chemical compatibility, physical and performance attributes, as well as usage conditions (such as temperature limits, chemical limits, cleaning, flushing, integrity testing, and operating methods).

The data contained in this guide is generated under standard conditions as specified. The methods and information contained in this guide are designed to provide the user with guideline for validation of T-Series TFF cassettes with Delta membrane under actual conditions of use.

Pall Life Sciences offers technical support to customers to develop, troubleshoot, and validate TFF procedures.

1.1 Validating Filtration Processes — General Concepts

TFF membrane cassettes play an important role in purifying, concentrating, and separating biopharmaceutical solutions and products. Typical applications include concentrating human plasma fractions, downstream processing of enzyme and protein solutions, and harvesting mammalian or bacterial cells. Hence, the validation of TFF processes utilizing membrane cassettes is an essential part of ensuring the manufacture of safe and efficacious products.

The U.S. Food and Drug Administration defines validation as “establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes” [Current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals, 21 CFR 210.3]. With respect to a TFF process, validation involves providing assurance that the filtration process operates reproducibly and consistently.

For any given process, a Functional Design Specification must be written based on the requirements of the process and data generated at the pilot scale. For a TFF process utilizing the T-Series cassettes with Delta membrane, this will include developing operational protocols within performance limits outlined in this validation guide and based on the individual cassette operating instructions and the Care and Use manuals supplied with the cassettes.

A process system can then be designed and built to allow direct scale-up to meet specifications established at pilot or bench scale. Because TFF membrane cassettes are incorporated into complex systems, three stages of system validation are followed: Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

1.2 Installation Qualification (IQ)

Performing the IQ checks that the cassettes selected for the process are the ones supplied and installed in the system, and that specified installation procedures such as torque settings have been adhered to. Additionally, it is confirmed that all required documentation has been received (operating instructions and certificates of conformance) with the cassettes.

1.3 Operational Qualification (OQ)

During OQ, validation personnel test and document the range and operational limits of the filtration process with cassettes in place. OQ does not have to be conducted in the customer process manufacturing area. Validation personnel normally simulate worst-case production conditions for these studies, using water or another surrogate process fluid, to deliberately trigger alarm conditions. As part of the OQ, validation personnel also verify and document procedures such as flushing and sanitizing that are associated with the operation of the membrane cassettes.

1.4 Performance Qualification (PQ)

PQ involves testing the cassette filtration process during production of the final product under actual operating conditions, including installation, sanitizing, conditioning, concentration, diafiltration, product recovery, cleaning, etc. Critical elements of PQ include verification of chemical compatibility and retention characteristics. Since validating a process ensures the process accomplishes what is intended, PQ provides the most meaningful process validation data (which will be confirmed by ongoing performance data collected during system operation) because the data is derived from the process itself, utilizing the intended operating conditions. PQ may not necessarily provide data on the operation of the system at the design limits (alarm conditions), as the process may never reach these limits.

Manufacturers of regulated products must develop and submit protocols, qualification documents, and validation documents for their specific product to be granted approval to manufacture and market their product.

2. Product Specifications

To help prepare IQ documentation, this section provides information on the materials of construction, physical characteristics, and basic performance of T-Series TFF cassettes with Delta membrane.

2.1 Packaging

Membrane cassettes are individually packaged in heat-sealed inner foil and outer clear plastic bags with the following information printed on the cassette edge (Figure 1):

- Company name
- Membrane type
- Nominal molecular weight cutoff (NMWC)
- Cassette format
- Membrane area
- Part number
- Serial number

Cassettes are shipped in a box containing two silicone gaskets in a plastic bag, Certificate of Test, T-Series Membrane Care and Use Procedures (USD 2662) and MSDS documents (where appropriate).

Figure 1

Example of Information Printed on the Side of Cassettes

2.2 Part Numbers

Part numbers give specific information about the cassette. For example, the part number DC010T12 represents a T-Series Centramate screen channel cassette with Delta 10 kD membrane with a 0.1 m^2 (1.1 ft^2) area (Figure 2).

The part number for a cassette can be interpreted to identify specific information about the cassette characteristics.

Figure 2
Part Number Code

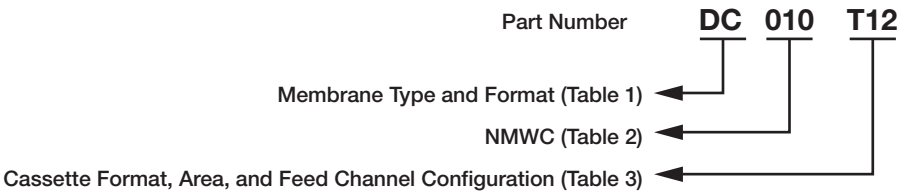


Table 1
Identification Code for Membrane Type

Part Number (Digits 1 – 2)	Membrane Type
DC	Delta

Table 2
Identification Codes for NMCO

Part Number (Digits 3 – 5)	NMWC
010	10 kD
030	30 kD

Table 3
Identification Codes for Cassette Format and Feed Channel Configuration

Part Number (Digits 6 – 8)	Cassette Format, Feed Channel Configuration	Membrane Area (Nominal)
T01	Centramate Screen Channel	93 cm^2 (0.1 ft^2)
T02	Centramate Screen Channel	186 cm^2 (0.2 ft^2)
T12	Centramate Screen Channel	0.1m^2 (1.1 ft^2)
T06	Centrasette Screen Channel	0.5 m^2 (5.4 ft^2)
T26	Centrasette Screen Channel	2.5 m^2 (27 ft^2)

2.3 Serial Numbers

Unique serial numbers enable the tracking of the following cassette information:

- Date of manufacture
- Components used in manufacture
- Water permeability of membrane lot used in construction
- Air integrity (Forward Flow) test results at 4 barg (58 psig)
- Membrane marker retention
- Manufacturing plant location

From the serial number and production records, components can be traced back to their source.

2.4 Materials of Construction

2.4.1 Membrane

Delta membranes are cast from cellulose resins. The membrane is cast on a polypropylene substrate that imparts strength and rigidity to the finished membrane product. The membrane then undergoes regeneration. The nominal thickness is 220 µm, including the backing. Materials meet requirements of USP Class VI @ 70 °C.

2.4.2 Screens

Screens are constructed of polypropylene with nominal thicknesses of 315 and 525 µm. Material meets requirements of USP Class VI @ 70 °C.

2.4.3 Encapsulant

The encapsulant is polyurethane with a white pigment — TiO_2.

2.4.4 Permeate Seals

Permeate seals are made from platinum cured silicone, USP Class VI @ 70 °C.

2.4.5 Gaskets

Gaskets are constructed from USP Class VI @ 70 °C medical grade, platinum cured silicone. They have a nominal thickness of 1.6 mm (0.063 in.).

2.5 Dimensions

Pall membrane cassettes are manufactured in a range of formats and membrane areas (Table 4). This allows the ability to directly scale up or down depending on requirements.

Figure 3

Cassette Screen Channel Configuration

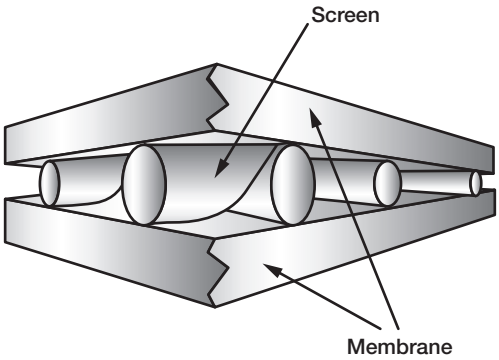


Table 4

Physical Dimensions of T-Series TFF Cassettes with Delta Membrane (Nominal)

Cassette Format	Centramate	Centramate	Centramate	Centrasette	Centrasette
Part Code	T01	T02	T12	T06	T26
Area	93 cm^2 (0.1 ft^2)	186 cm^2 (0.2 ft^2)	0.1 m^2 (1.1 ft^2)	0.5 m^2 (5.4 ft^2)	2.5 m^2 (27 ft^2)
Weight — kg (lb)*	0.019 (0.042)	0.029 (0.064)	0.17 (0.37)	0.54 (1.19)	2.56 (5.63)
Thickness — cm (in.)	0.178 (0.07)	0.305 (0.12)	1.6 (0.6)	1.6 (0.6)	7.4 (2.9)
Length — cm (in.)	21 (8.25)	21 (8.25)	21 (8.25)	21 (8.25)	21 (8.25)
Width — cm (in.)	5.6 (2.2)	5.6 (2.2)	5.6 (2.2)	17.8 (7)	17.8 (7)
Flow Path length — cm (in (port center to center)	17 (6.7)	17 (6.7)	17 (6.7)	17 (6.7)	17 (6.7)
Flow path width — cm (in.)	3.2 (1.3)	3.2 (1.3)	3.2 (1.3)	16 (6.3)	16 (6.3)
Port diameter feed — cm (in	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)
Number of feed ports	1	1	1	5	5
Port diameter retentate — cm (in.)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)
Number of retentate ports	1	1	1	5	5
Port diameter permeate — cm (in.)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)
Number of permeate ports	2	2	2	8	8

** Approximate weight of a cassette as shipped in a bag (no outer packaging). The cassette is wetted with a storage solution and drained. Weights may vary due to different amounts of storage solution remaining in the cassette.*

2.6 Operating Pressures and Temperatures

Membrane cassettes have operating limits for pressure, temperature, pressure drop (feed pressure minus retentate pressure), and pH (Table 5).

Table 5

Cassette Operating Limits of Pressure, Temperature, and pH for T-Series Cassettes with Delta Membrane (All Formats)

Maximum Recommended Operating Pressure**	Maximum TMP	Temperature Range	pH Range
6 barg (87 psig) @ 23 °C 4 barg (58 psig) @ 55 °C	4 barg (58 psig) @ 55 ºC	4 to 55 ºC	2 to 13 @ 4 barg (58 psig) @ 50 ºC

*** Torque value must be set to the recommended level to avoid leaks.*

2.7 Normalized Water Permeability (NWP) Ranges

NWP is a measure of the membrane's hydraulic resistance. Water quality, temperature, and pressure affect the NWP. At a minimum, the water used to measure NWP should be distilled, deionized (DI), 0.2 µm filtered, or preferably, pharmaceutical grade (USP Water for Injection, hereafter called WFI). The presence of biological organisms, organic materials, or minerals in the water may affect NWP.

2.7.1 Typical NWP Performance for Delta Membranes Used in T-Series Cassettes

The NWP is measured in stirred cells with 43 mm disc membrane samples stamped out from the beginning, middle, and end of each production lot of membrane (Table 6).

Table 6

Typical NWP Performance For Delta Membranes Used in T-Series Cassettes

Membrane	NWP on Disc Membrane	
NMWC	LMH/psig @ 25 °C	LMH/barg @ 25 °C
10 kD	5 – 6	72 – 87
30 kD	8 – 13	120 – 196

2.8 Membrane Solute Passage Specifications

Solute passage measurements are not made on finished cassettes because of the invasive nature of the test. However, if needed, a solute passage test can be performed on a cassette to characterize the passage characteristics. The passage data will vary from disc data because of hydrodynamic differences between the formats; for example, pressure drops in the permeate channel. Because the test is invasive, cassettes exposed to a foreign substance would not be reused in many applications (i.e., pharmaceutical processes). To diagnose a specific problem, a cassette can be cut open and pieces of membrane removed for testing. Contact Pall for support if this process is required.

2.9 Test Solute Concentrations and Detection Methods

Table 7 lists the concentration of solutes and the detection method used to test membranes for passage.

Table 7

Concentration of Solute and Detection Method Used to Test Membranes

NMCO	Test Solute	Concentration (%)	Detection Method	Solvent
10 kD	Ovalbumin	0.1	UV @ 280 Nm	PBS
10 kD	BSA	0.2	UV @ 280 Nm	PBS
30 kD	BSA	0.2	UV @ 280 Nm	0.01M PBS
30 kD	Mixed Dextrans	Mixed	Refractive Index	Cascada™ Water System

2.10 Membrane Integrity—Forward Flow Test Values

The membrane integrity test measures air forward flow rates at specified pressures to determine the integrity of membranes. The air forward flow is a measure of air diffusion through the liquid in the membrane pores, air flow through empty pores, plus air leakage around seals. The test identifies gross defects in the cassette membrane or membrane seals. Membrane forward flow integrity test values are given in Table 8 for the different cassette formats.

Use only dry filtered air or nitrogen from cylinders (instrument-quality) when using integrity analyzers incorporating mass flow meters. Fluctuations in house air and nitrogen supplies as well as changes in temperature can cause inconsistent results. Fully wet-out the membrane in a cassette prior to performing the membrane integrity test or high forward flow values may be obtained. The procedures for wetting out cassettes and measuring forward flow are described in the Care and Use Procedures (USD 2662).

Table 8

Membrane Integrity Test — Forward Flow Limits

Membrane NMWC	Test Pressure	Allowable Air (Forward Flow) Rate per unit area of membrane (*, **)
10 kD	4 barg (58 psig)	< 500 sccm/m^2 (< 50 sccm/ft^2)
30 kD	4 barg (58 psig)	< 500 sccm/m^2 (< 50 sccm/ft^2)

** Nitrogen can be used in place of air.*

*** sccm = standard cubic centimeters per minute.*

2.11 Shelf Life of New and Used Cassettes

The recommended shelf life of new, unused, or unopened cassettes stored in sodium diacetate is expected to be at least 30 months from date of manufacture. Shelf life studies are ongoing. To achieve satisfactory performance, it is recommended that the cassettes be stored unopened in the original packaging at 4 to 25 °C and protected from direct light. Shelf life studies are ongoing. Users should test the membrane integrity prior to use.

The useful life of cassettes that are properly conditioned, used, cleaned, stored, and maintained is often more than 30 months. However, it is not possible to specify a shelf life or useful life of a cassette that has been used or removed from the original packaging. The actual useful life for a cassette will depend on the character and complexity of the product to which it is exposed, composition of process fluids, process temperatures, operating pressures, and cleaning regimen. Delta cassettes can be stored in 0.1 N NaOH at 23 °C for 30 months. Nevertheless, customers should validate reuse and the useful life of a cassette in their process. Pall Life Sciences makes no claims of warranty or guarantee of performance related to reuse of cassettes. Consult the Care and Use Procedures (USD 2662) for recommended storage conditions.

2.12 Cleaning Agent Compatibility

2.12.1 Compatibility with 0.25 N Sodium Hydroxide 50 °C

Sodium hydroxide is an effective and commonly used agent in biological applications for cleaning, sanitizing, and depyrogenating membrane cassettes.

To evaluate the chemical resistance of T-Series cassettes with Delta membrane to this mixture, a study was performed in which new T-Series Centrasette cassettes with Delta 10 kD membrane first underwent recommended sanitization flush (request Pall USD 2662) then were characterized to determine water permeability, air integrity and pressure drop. A solution of 0.25 N NaOH at 50 to 55 °C was circulated through the cassettes for 2 hours after which time the cassettes were flushed with water at room temperature. This process was repeated for 10 cycles or a total of 20 hours contact time. Cassettes were characterized after the fifth and tenth cycles.

Results

After 10 cycles (20-hour exposure time) with 0.25 N NaOH at 50 to 55 °C, cassettes tested were within specification.

Table 9

Compatability with 0.25 N NaOH at 50 °C (10 x 2-hour Cycles)

Serial No./ Format	NWP LMH/psig @ 10 psig			DP @ 5 L/min/m² (0.5 L/min/ft²)			Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²		
Delta T26, 10 kD	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles
37092043	5.7	6.1	6.7	9	8.9	8.2	16.4	25.5	4.8
37092046	6.4	6.0	6.7	9	8.8	7.5	15.5	21.8	11.3

2.12.2 Compatibility with 0.1 N Phosphoric Acid

During the cleaning process, cassettes are often exposed to a range of pH conditions at elevated temperature and pressure in order to remove traces of remaining product and fouling agents.

To evaluate the effect of these conditions on T-series cassettes with Delta membrane, studies were performed on T-Series Centrasette cassettes with Delta 10 kD membrane (Part No. DC010T06) under simulated test conditions. For this study, cassettes tested for low pH were subjected to 10, two-hour cycles in 0.1 N phosphoric acid at 50 to 55 °C and 4 barg (58 psig) feed pressure. A summary of the test procedures and results are given below.

Table 10

Compatibility with 0.1 N Phosphoric Acid at 50 °C (10 x 2-hour Cycles)

Serial No./ Format	NWP LMH/psig @ 10 psig			DP @ 5 L/min/m² (0.5 L/min/ft²)			Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²		
Delta T26, 10 kD	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles
37092097R	7.08	7.20	7.00	6.2	5.9	6.1	9.0	8.6	9.2
37092102R	6.20	6.70	6.50	8.4	10.6	8.4	5.1	5.2	4.3

2.13 General Chemical Compatibility

Chemical compatibility of membrane cassettes can be described in terms of changes in physical characteristics as a result of continuous contact with a chemical solution for several hours. Changes can affect dimensions, hardness, swelling, integrity of internal seals, and membrane integrity. Changes can also be described in terms of functional characteristics of the membrane (such as water permeability and retention characteristics).

Table 11 illustrates the chemical compatibility of T-Series TFF cassettes with Delta membrane at 23 °C (unless otherwise noted) with respect to physical characteristics. The Membrane Chemical Compatibility Chart should be used only as a guide. Cassettes should be tested in the appropriate solvent and product under actual operating conditions and for an appropriate time to determine compatibility for the specific application. Membrane porosity, consequently both water permeability and retention characteristics, may be affected. Physical changes to the cassette may be permanent or reversible. To determine if changes are permanent, flush and then soak the cassette in water for one to two days and then test the sample again. Changes in water permeability and solute retention may be due to physical changes in the membrane.

Table 11

Membrane Chemical Compatibility Chart

Reagent	Compatible*
Acetic Acid (5%)	✔
Alconox◆ (1%)	✔
Citric acid (1%)	✔
Ethanol (20%)	✔
Glycerine (20%)	✔
Phosphoric acid (0.1 N)	✔
Sodium dodecyl sulfate (0.01 M)	✔
Sodium hydroxide (0.25 N @ 25 °C)	✔
Terg-a-zyme◆ (1%)	✔

** Data for cassette membrane and components at 20 °C, 24-hour exposure, unless otherwise noted. There may be changes in porosity and/or selectivity of membrane.*

3. Validation Procedures

This section describes the procedures Pall used to validate specific chemical and physical characteristics of T-Series TFF cassettes with Delta membrane.

3.1 High and Low Temperature Operational Testing at Maximum Recommended Operating Pressure

T-Series Centrasette cassettes with Delta 10 kD membrane (Part No. DC010T12) were subjected to low and high operating temperature cycling in water to determine the effects on air forward flow integrity test (IT), pressure drop (DP) and normalized water permeability (NWP) values.

Cassettes were prepared and conditioned to a point where customers would begin operating, i.e., tested for release, preserved with Delta membrane preservative. Cassettes were then sanitized and flushed per recommended flush protocol for new cassette conditioning, characterized for CFF, DP, IT, NWP, dimensional and subjected to 10 x 2-hour cycles at 6 barg (87 psig) feed, 4 °C cycles. Cassettes were tested at ambient temperature at cycles 1, 2, 5, and 10. Separate cassettes were used for each test regime.

3.1.1 Low Temperature Testing at Feed Pressure of 6 barg (87 psig)

Test Conditions: water at 4 °C; feed pressure of 6 barg (87 psig); 10 x 2-hour cycles

3.1.1.1 Procedure

1. Perform Pall recommended preconditioning flush.
2. Characterize the cassettes to establish initial values of IT, DP, and NWP.
3. Install the cassettes in the holder.
4. Feed solution: DI water ambient.
5. Open all valves (feed, retentate and permeate).
6. Increase the pump speed and slowly close the retentate valve.
7. Adjust pump speed, retentate valve, and permeate valve as necessary
   to maintain a feed pressure of 6 barg (87 psig). Neither retentate nor permeate should be dead ended. Permeate pressure should never exceed and always be less than retentate pressure.
8. Chill the solution to 4 °C. Cycle time commences when the DI water temperature reaches < 4 °C.
9. Recirculate for 2 hours. Maintain water condition.
10. Characterize for NWP, CFF, DP, IT. Record values as first cycle.
11. Repeat “Cycle initiation“ nine more times. Characterize on the cycles 1, 2, 5 and 10.

3.1.1.2 Results

Two (2) T-Series Centrasette cassettes (T12) with Delta 10 kD membrane were subjected to low operating temperature cycling. After circulation in water for 10 x 2-hour cycles at 4 °C, all cassettes were within normal operating parameters for air integrity, pressure drop, and normalized water permeability.

Table 12

Low-Operating Temperature Study

Cassette and Serial Number	NWP @ 690 mbarg (10 psig) (LMH/psig)			DP @ 5 L/min/m² (0.5 L/min/ft²)			Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²		
Delta T12, 10 kD	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles
36339024R	7.0	6.5	6.0	8.4	8.5	9.9	6.4	6.4	4.5
36341055R	8.0	7.4	7.4	9.2	10.1	10.2	9.1	9.1	12.7

sccm = standard cubic centimeters per minute

3.1.2 High Temperature Testing at Feed Pressure of 4 barg (58 psig)

Test Conditions: water at 55 to 60 °C; feed pressure of 4 barg (58 psig); 10 x 2-hour cycles

3.1.2.1 Procedure

1. Perform Pall recommended preconditioning flush.
2. Characterize the cassettes to establish initial values of IT, DP, and NWP.
3. Install the cassettes in the holder.
4. Feed solution: DI water ambient.
5. Open all valves (feed, retentate and permeate).

6. Increase the pump speed and slowly close the retentate valve.
7. Adjust pump speed, retentate valve, and permeate valve to obtain a feed pressure of 6 barg (87 psig). Neither retentate nor permeate should be dead ended. Permeate pressure should never exceed and always be less than retentate pressure.
8. Heat the solution to 55 °C.
9. Recirculate for 2 hours. Recirculation time commences when DI water reaches 55 °C. Direct both permeate and retentate streams back to the feed tank.
10. Characterize for NWP, CFF, DP, IT. Record values as first cycle.
11. Repeat “Cycle initiation“ nine more times. Characterize on the cycles 1, 2, 5 and 10.

3.1.2.2 Results

Two (2) T-Series Centrasette cassettes (T06) with Delta 10 kD membrane were subjected to high operating temperature cycling. After circulation in water for 10 x 2-hour cycles at 55 °C, all cassettes were within normal operating parameters for air integrity, pressure drop, and normalized water permeability.

Table 13

Compatibility with 55 °C at a Feed Pressure of 4 barg (58 psig), (10 x 2-hour Cycles)

Serial No./ Format	NWP LMH/psig @ 10 psig			DP @ 5 L/min/m² (0.5 L/min/ft²)			Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²		
Delta T06, 10 kD	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles
37052005R	7.1	7.0	7.2	8.4	8.5	9.9	7.2	5.9	5.9
37052006R	6.40	6.45	6.30	7.4	6.8	7.2	6.1	5.8	5.0

3.2 Maximum Pressure Test at Ambient Temperature

To confirm cassette performance at maximum operating pressure, two (2) T-Series Centrasette cassettes with Delta 10 kD membrane (Part No. DC010T06) were subjected to 10 x 2-hour cycles at a feed pressure of 6 barg (87 psig) and ambient temperature.

3.2.1 Procedure

1. Perform Pall recommended preconditioning flush.
2. Characterize the cassettes to establish initial values of IT, DP, and NWP.
3. Install the cassettes in the holder.
4. Feed solution: DI water ambient.
5. Open all valves (feed, retentate and permeate).
6. Increase the pump speed and slowly close the retentate valve.
7. Adjust pump speed, retentate valve, and permeate valve as necessary to maintain a feed pressure of 6 barg (87 psig). Neither retentate nor permeate should be dead ended. Permeate pressure should never exceed and always be less than retentate pressure.
8. Recirculate for 2 hours. Direct both permeate and retentate streams back to the feed tank.
9. Characterize for NWP, CFF, DP, and IT at cycles 1, 2, 5 and 10.

3.2.2 Results

Two (2) T-Series Centrasette cassettes (T06) with Delta 10 kD membrane were subjected to a feed pressure of 6 barg (87 psig) at ambient temperature. After circulation in water for 10 x 2-hour cycles, all cassettes were within normal operating parameters for air integrity, pressure drop, and normalized water permeability.

Table 14

Compatibility with Feed Pressure of 6 barg (87 psig) at Ambient Temperature (10 x 2-hour Cycles)

Serial No./ Format	DP @ 5 L/min/m² (0.5 L/min/ft²)			NWP LMH/psig @ 10 psig			Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²		
Delta T06, 10 kD	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles	Initial	After 5 cycles	After 10 cycles
37072066R	9.5	8.3	8.3	6.7	6.5	6.9	6.3	5.9	13.0
37052005R	8.0	7.8	7.9	6.2	6.6	6.9	5.9	6.3	6.1

3.3 Chemical Compatibility

3.3.1 Introduction

Cassettes may be exposed to a number of chemicals, primarily during sanitization and cleaning procedures. To evaluate the effect of commonly used chemicals on cassette performance, cassettes were exposed to chemicals under conditions that simulated typical worst-case use. The criteria used to evaluate the performance of the cassettes after exposure to chemicals were water permeability, cassette integrity test, pressure drop, and physical appearance of the polyurethane encapsulant.

3.3.2 Scope

Three different solutions under various conditions were chosen as representative of commonly used cleaning agents. The solutions and exposure conditions were:

1. 0.1 N NaOH at 23 °C for 12 months
2. 0.1 N H_3PO_4 at 23 °C for 12 months
3. 20% EtOH at 23 °C for 12 months

A typical cleaning regimen is less than three hours. Cleaning with acids such as phosphoric acid is used less frequently, for shorter periods (1 to 1.5 hours) and often in addition to a caustic cleaning. Therefore, the exposure time in this study is equivalent to about one cleaning cycle/day (4 to 5 days per week) for one year.

3.3.3 Summary of Method

T-Series cassettes with Delta membrane were used for each test solution. Cassettes were characterized in water for air integrity, pressure drop, and normalized water permeability.

The cassettes were installed in a holder and the test solution circulated through the cassette for 15 minutes. Cassettes were then removed from the holder and immersed in a container containing the test solution. The container was sealed and stored at the required temperature. After a specified time, the cassettes were removed from the container, installed in a holder, flushed with 0.2 µm filtered DI water and re-characterized according to the test protocol.

Table 15

Compatibility with 0.1 N NaOH (23 °C)

Cassette and Serial Number	NWP @ 10 psig (LMH/psig)	
Delta T06, 10 kD	Initial	After 12 months
209164001	6.3	6.9
209164002	6.3	6

	DP @ 5 L/min/m² (0.5 L/min/ft²)	
Delta T06, 10 kD	Initial	After 12 months
209164001	9.6	15
209164002	9.5	14.6

	Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²	
Delta T06, 10 kD	Initial	After 12 months
209164001	3.7	23.8
209164002	1.5	23

Table 16

Compatibility with 0.1N H_3PO_4 (23 °C)

Cassette and Serial Number	NWP @ 10 psig (LMH/psig)	
Delta T06, 10 kD	Initial	After 12 months
37113046R	6.8	9.25
37127060R	4.55	5.54

	DP @ 5 L/min/m² (0.5 L/min/ft²)	
Delta T06, 10 kD	Initial	After 12 months
37113046R	11.2	8.5
37127060R	9.5	5.4

	Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²	
Delta T06, 10 kD	Initial	After 12 months
37113046R	25.1	28.8
37127060R	13.0	17.8

Table 17

Compatibility with 20% Ethanol (23 °C)

Cassette and Serial Number	NWP @ 10 psig (LMH/psig)	
Delta T06, 10 kD	Initial	After 12 months
36207048R	7.1	8.6
36207049R	6.7	8.8

Table 17 *Continued*
Compatibility with 25% Ethanol (23 °C)

Cassette and Serial Number	DP @ 5 L/min/m² (0.5 L/min/ft²)	
Delta T06, 10 kD	Initial	After 12 months
36207048R	7.5	7.3
36207049R	7.5	7.8

	Air Forward Flow IT @ 4 barg (58 psig) sccm/ft²	
Delta T06, 10 kD	Initial	After 12 months
36207048R	3.7	33.5
36207049R	3.3	8.2

3.3.4 Results

Three solutions were chosen as representative of commonly used cleaning agents. The solutions and their exposure conditions were: 1. 0.1 N NaOH at 23 °C for 28 days; 2. 0.1 N H_3PO_4 at 23 °C for 12 months; 3. 20% EtOH at 23 °C for 12 months. After exposure to these chemical solutions at the specified temperature and period, all cassettes tested were within normal operating parameters for IT, DP, and NWP. No significant changes in performance were observed between the initial measured values and those measured after soaking in the test solution for the specified period.

3.4 Cassette Flushing Procedure to Remove Storage Agent

A preconditioning procedure was developed to remove storage agents and reduce total organic carbon (TOC) levels from new and stored T-Series cassettes prior to use in a TFF process. The procedure includes the following steps:

3.4.1 Install Cassettes

Details of the preconditioning procedure are given in Section 6.1.

1. Flush with DI water to waste (flush out bulk storage agent).

2. Sanitization with 0.25 N NaOH at 40 to 45 °C.

3. Flush with DI water to waste (flush out caustic).

4 to 6. Water recirculation for 30 minutes (3 cycles).

7. Final water flush to drain.

To evaluate the effectiveness of this flushing/sanitization procedure, two (2) T-Series cassettes with Delta 10 kD membrane were preconditioned using this procedure. Samples of the flush or recirculated solution taken from the retentate and permeate at the end of each step were analyzed for TOC. The results are given in Table 18.

Table 18
TOC Results from Cassette Flushing Study

Serial No.	TOC (PPM) / Total PPM Retentate + Permeate
209010004F	0.9392
209010006F	0.9944

TOC of flushing water was < 0.1 PPM

3.4.2 Results

Using the preconditioning procedure outlined in Section 6.1, the TOC levels in both retentate and permeate streams were under 1 PPM at the final flush.

3.5 Extractables Test

3.5.1 Introduction

The purpose of this test is to quantify and characterize the non-volatile residue (NVR) materials that may be extracted from T-series cassettes with Delta membrane into aqueous products after the cassettes have first been subjected to a proper preconditioning protocol.

3.5.2 Summary of Method

Cassettes were subjected to a preconditioning flush followed by 2 x 24-hour extraction cycles. Two cassettes underwent the extraction process using DI water at 50 °C as the recirculated solution. The extracted material was analyzed by gas chromatography (GC), TOC, NVR, high performance liquid chromatography (HPLC), Fourier Transform Infrared spectroscopy (FTRIS) and gas chromatography/mass spectroscopy (GC/MS). The cassettes tested contained approximately 0.1 m^2 (1.1 ft^2) of a cellulose filter membrane supported by sheath core sheet also interleaved between polypropylene screens incorporating silicone seals. The repeating layers of membrane, support and screen spacer are encapsulated with a polyurethane sealant. Centramate and Centrasette cassettes are constructed from the same raw materials and by the same procedure. Therefore, the type of extractables determined for one format can be considered representative of all formats.

Test Results

The predominant extractable found in all of the cassettes was glycerine.

Figure 4

Second 16-hour Extraction (Serial Number 209041004F)

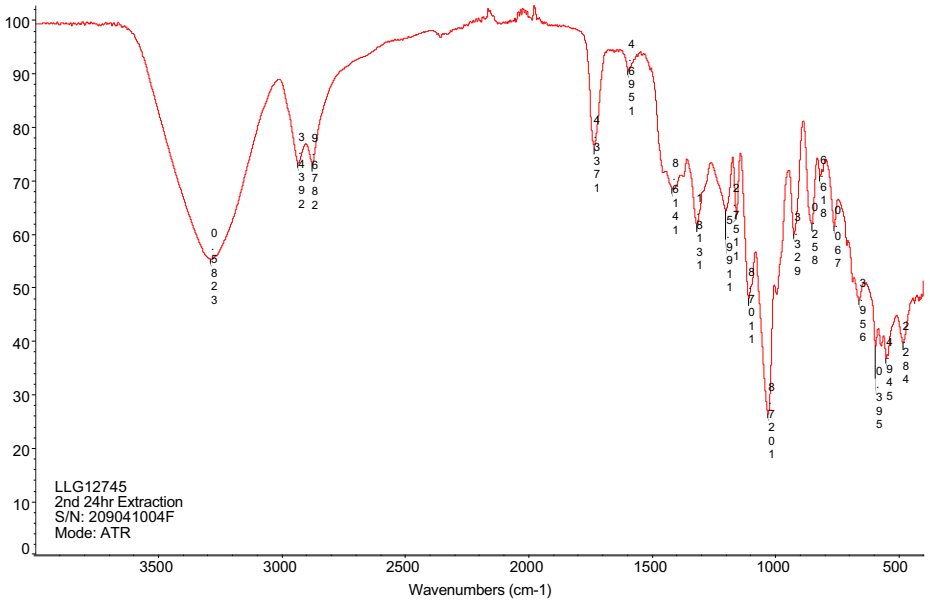
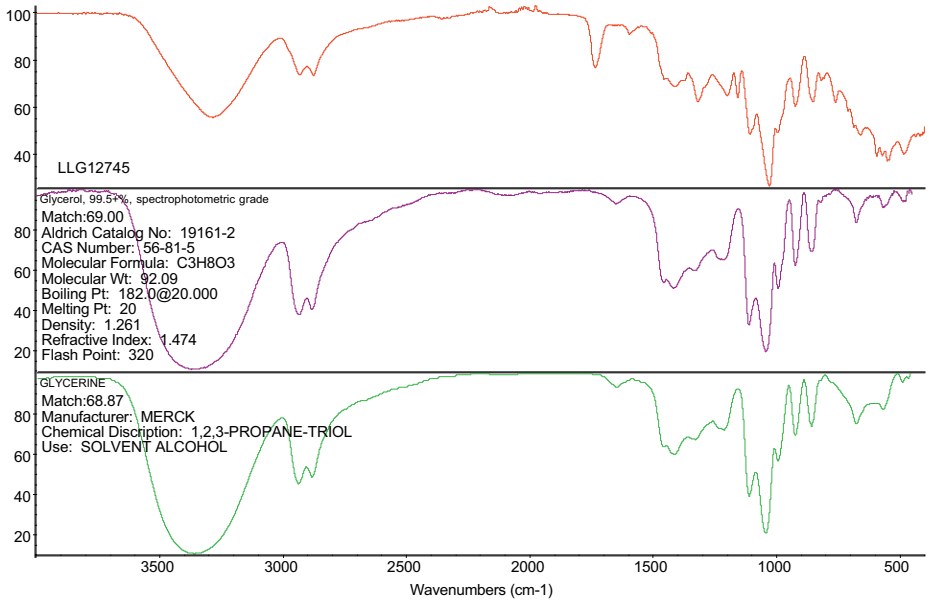


Figure 5
Library Match



3.6 Sanitization — Endotoxin Removal — New Cassette Flush Procedure

Endotoxin – a high molecular weight lipopolysaccharide – is associated with the cell wall of gram-negative bacteria. As part of normal functioning and during cell autolysis, bacteria release endotoxin into their environment. Unpurified endotoxin contains lipids, carbohydrates, and protein. Aggregated forms of endotoxin have molecular weights ranging from about 30,000 to 1,000,000 daltons. Active subunits can occur with molecular weights as small as 10,000 daltons. Endotoxin is pyrogenic, that is, it can cause fever in humans and animals, so it is imperative that pharmaceutical products, especially injectables, are endotoxin-free. Endotoxin can be detected by the Limulus Amoebocyte Lysate (LAL) procedure. The lower detection limit is based on the method and sensitivity of the lysate being used. 1 EU (endotoxin unit) = 100 picograms endotoxin.

3.6.1 Introduction

Cassettes are not supplied sterile, and Pall does not claim that cassettes are endotoxin-free. Therefore, they should be flushed and sanitized prior to use. To evaluate initial endotoxin levels and the effectiveness of the recommended flushing procedure, the following study was performed.

3.7 Sanitization — Endotoxin Challenge Procedure

3.7.1 Introduction

Membrane cassettes are typically cleaned and reused many times. There is a risk of contamination with endotoxin from previous samples, or from bacterial growth during storage. Therefore, endotoxin levels should be reduced in the cassette after use and prior to use with a new sample. The following study was performed to show the effectiveness of a typical cleaning procedure with 0.25 N NaOH as recommended in Pall USD 2662. This study also applies to the standard flushing and sanitization protocol recommended for preconditioning of cassettes (Section 6.1).

3.7.2 Summary of Method

Two (2) T-Series Centramate cassettes with Delta 10 kD membrane (Part No. DC010T12) which had been previously preconditioned using the standard procedure outlined in Section 6.1 were installed in a Centramate holder. The cassettes were then challenged by recirculating 2 L of a solution containing ~1350 EU/mL endotoxin for one hour through the cassettes. The total feed flow was 5 L/min/m^2 (0.5 L/min/ft^2); adjust the retentate valve to achieve a flow distribution of 85% through the retentate and 15% through the permeate; ~4.25 L/min/m^2 (~0.425 L/min/ft^2) retentate flow, 0.75 L/min/m^2 (0.075 L/min/ft^2) permeate flow.

Following recirculation with the challenge solution, the cassettes were subjected to Pall recommended flush.

Step 1. Flush with DI water to waste.

Step 2. Sanitize with 0.25 N NaOH at 40 to 45 °C for 30 minutes.

Step 3. Flush with DI water to waste (flush out caustic).

Step 4 to 6. Water recirculation for 30 minutes (3 cycles).

Step 7. Final flush with DI water to drain.

During Step 7, the cassette retentate and permeate streams were sampled for endotoxin evaluation.

3.7.3 Results

Cassettes were stacked during challenge for uniformity in contamination. Results at each flush stage are total of permeate and retentate. Detection Limit = 0.005 EU/mL.

Table 19

Results of Endotoxin Removal for the Challenge Procedure

Serial No.	36352063	36352036
Challenge	1379 EU/mL	1379 EU/mL
Recommended preconditioning flush. Accumulated volume L/m^2	Retentate / Permeate	Retentate / Permeate
	Total Endotoxin EU/mL	Total Endotoxin EU/mL
Initial flush to waste	40	5.95
Flush post 0.25 N NaOH recirculation	0.087	0.187
First water recirculation	0.133	0.021
Second water recirculation	0.174	0.013
Third water recirculation	0.038	0.006
Final flush	0.02	0.005

3.7.4 Conclusions

The flushing, sanitization and cleaning procedures recommended by Pall Life Sciences effectively reduce endotoxin levels. Using the recommended sanitization/cleaning described above on a cassette spiked with 2 L of solution containing 1379 EU/mL, reduced the endotoxin level in the final flush to 0.02 EU/mL.

3.8 Particle Release from T-Series Cassettes

Cassettes are manufactured from components that are considered non-fiber releasing and as such are not tested for particle release in manufacturing. It is further assumed that any particles released by the cassette into the product would be removed further downstream in the process at or before final filtration. A study was performed to evaluate the typical level of particles that may be attributed to the cassette after the cassette has been properly preconditioned.

Criteria was set for maximum particle release using the procedure described below. This criteria is recommended in USP <788> Particle Matter in Injections.

Table 20

Criteria for Maximum Particle Release After Standard Preconditioning Flush

Particle Size Range (µm)	Specification Particles/mL
> 25	< 3
10 – 25	< 25

To evaluate the level of particles that might come from a T-series cassette with Delta membrane following a standard preconditioning procedure, the following test was performed.

Two (2) T-Series Centramate cassettes with Delta 10 kD membrane (Part No. DC010T12) were flushed following the standard preconditioning sanitization flush protocol.

Step 1. Water flush to waste.

Step 2. Sanitize with 0.25 N NaOH at 40 to 45 °C for 30 minutes.

Step 3. Water flush to waste (flush out caustic).

Step 4 to 6. Water recirculation for 30 minutes (3 cycles).

Step 7. Final water flush to drain.

After the preconditioning, the system was configured to flush to drain. The feed pump was adjusted to provide 5 L/m^2 (0.5 L/ft^2) through the retentate at a retentate pressure of 0.5 barg (7 psig). The cassette flow ration was 25% through the permeate, and 75% through the retentate. Twenty (20) liters of water were pumped through the cassette. At the end of the flush, samples of retentate and permeate were collected and analyzed.

Table 21

Particle Count of Flush Solution after Preconditioning

	Optical Particle Counts (Counts/mL)						
Sample ID	2-5 µm	5-10 µm	10-15 µm	15-25 µm	25-50 µm	> 50 µm	Fibers
Blank Feed	0.07	0.10	0.00	0.00	0.00	0.00	0.00
Blank Retentate	0.30	0.57	0.19	0.38	0.08	0.02	0.02
Blank Permeate	0.52	1.40	1.11	2.40	0.31	0.09	0.06
Cass 46R Feed	0.91	0.22	0.16	0.09	0.02	0.01	0.00
Cass 46R Retentate	0.91	1.11	0.64	0.70	0.51	0.05	0.01
Cass 46R Permeate	0.26	0.19	0.13	0.22	0.06	0.03	0.01
Cass 44R Feed	0.59	1.11	0.38	0.49	0.07	0.02	0.01
Cass 44R Retentate	1.04	0.57	0.38	0.28	0.08	0.03	0.01
Cass 44R Permeate	0.20	0.60	0.22	0.42	0.08	0.01	0.01

3.8.1 Results

Following the standard protocol recommended for preconditioning, T-Series Centramate cassettes were flushed with 0.2 µm filtered DI water and samples from the retentate and permeate streams were collected. One-liter (1 L) samples were drawn down on a filter and analyzed. All of the samples analyzed had less than 1 particle/mL in the particle size ranges evaluated.

4. Quality Assurance (QA)

Membranes and cassettes are produced in conformance with the Pall Corporation manufacturing documentation. Cassette components meet current standards for USP Class VI, 70 °C Biological Reactivity Tests for Plastics.

4.1 Quality Control Measures

Raw materials used in production are logged in for traceability and quarantined upon receipt. After inspection by the Quality Control Department, approved raw materials are issued to the warehouse for storage. The membrane is manufactured in Pall's Hauppauge, NY, facility, and the cassettes are manufactured in Pall's Puerto Rico facility. In Pall's Hauppauge, NY, manufacturing plant, multiple samples from the beginning, middle, and end of each lot of membrane are tested for quality. Tests include water permeability and the retention/passage characteristics of selected solute molecules applicable to the specific NMWC or pore size of the membrane. As required, membrane is removed from inventory, inspected, and sent to the assembly area. In Pall's Puerto Rico manufacturing site, cassettes are produced according to an assembly procedure from approved lots of membrane and other raw materials, which are recorded on a lot control card. The finished cassette is visually inspected, stamped with the cassette identification, and released from assembly to quality control with the accompanying lot card. Quality control inspects each cassette and lot card for completeness. The cassettes are integrity tested, then flushed with a Delta membrane preservative solution and integrity is tested.

4.1.1 Labels

Each cassette is first sealed in a foil bag and then in a plastic bag, then packed in a carton box using foam corners to protect the cassette. Labels affixed to the cradle, box and bag describe the contents (Figure 6). The label identifies the cassette format and contains the part number and the serial number. This information should match the information printed on the side of the cassette (Figure 1).

Figure 6

Example of Box Label

4.1.2 Quality Assurance Certificates

A quality assurance certificate is packaged with each TFF cassette (Figure 7).

Figure 7

Example of a Certificate of Test

PALL Pall Corporation

Certificate of Quality

We hereby certify that

Pall®: **DELTA 10K T-SERIES CENTRAMATE™**
T01 0.01m² / 0.1ft² FILTER

Part Number: **DC010T01**

Serial Number: **209211001F**

Membrane Lot Number: **UF12593**

was manufactured in a controlled environment.

Materials of Construction

Conformance to Regulatory Requirements
This product may be used in conjunction with current good manufacturing practices as per Title 21 of the **Code of Federal Regulations** (CFR) parts 210 and 211.72.

This product does not contain materials of construction that are considered TSE or BSE risk materials according to current legislation and guidelines (reference European CPMP EMEA/410/01 Rev.2 and **Code of Federal Regulations**, Title 9 Part 94.18).

Bio Safety Data
The fluid path components have met the specifications for biological tests listed in the current revision of the **United States Pharmacopeia** (USP) for Class VI plastics. Contact Pall for further information regarding materials of construction.

Product Quality

Membrane Quality
Representative membrane samples from this manufacturing lot underwent the following tests and the lot was released by Quality Control when it was verified that their respective criteria were met:
- Water Permeability
- Solute Marker Passage

Integrity
This product successfully passed a final installation integrity test based on an air diffusion / forward flow test that ensures membrane and seal integrity.

Pressure Drop
This product was tested for pressure drop and conforms to the current specification

Recommended Storage Conditions
This Pall cassette can be expected to perform within specifications if stored and handled in a manner consistent with the parameters below:
- The cassette is stored unopened in the original packaging at 4-25ºC, and in a dry environment.
- The cassette is protected from direct sunlight, radiation or weather conditions.
- Care is taken to avoid physical damage while handling.
- Thermal shock is avoided.

In addition to the above tests, this product met manufacturing inspection standards and requirements for full traceability in an ISO 9001 certified facility. **These products are not supplied sterile**. Users should test the membrane integrity prior to use. Consider only unopened, undamaged packages for use. Further information is available by contacting Pall.

Augie Antomattei, Quality Manager, Pall Puerto R

31/July/2009

Date of Manufacture

CoQ0021E rev 01

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Filtration. Separation. Solution.SM

5. Biosafety Evaluation and Test Procedures

5.1 Introduction

The purpose of the biological evaluations and tests was to evaluate the biological suitability of the materials of construction of the T-Series cassettes with Delta membrane. Tests were performed by an outside contract laboratory in order to evaluate the suitability of the materials of construction of the T-Series cassettes with Delta membrane in terms of biological safety. Tests performed included the Biological Reactivity Tests, *in vivo*, for Plastics (hereafter called the Biological Reactivity Tests), as described in the United States Pharmacopoeia, Chapter <88>; as well as the Hemolysis Test, and the L929 MEM- Cytotoxicity Test (hereafter called the cytotoxicity test).

In addition, a test was also performed to measure the level of oxidizable substances and endotoxin found in a cassette after an appropriate cleaning and flushing procedure had been performed.

5.2 Summary of Test Procedures

The Biological Reactivity Tests described in the United States Pharmacopoeia include injection of extracts of plastic materials, as well as implantation of the material itself into animal tissue. Four extracting media are listed which simulate parenteral solutions and body fluids. These include: (1) sodium chloride injection, (2) 1-in-20 solution of alcohol in sodium chloride injection, (3) polyethylene glycol 400, and (4) vegetable oil (sesame or cottonseed oil). Extracts are prepared at one of three standard conditions: 50 °C for 72 hours, 70 °C for 24 hours, or 121 °C for one hour. Since T-Series cassettes with Delta membrane have a recommended operating temperature limit of 50 °C, cassette components were extracted at 70 °C to provide for the most stringent test condition not resulting in physical changes in the plastic itself.

An acute systemic injection test was performed to evaluate the potential of a single injection of an extract to produce systemic toxicity. Sodium chloride injection and 1-in-20 solution of alcohol in sodium chloride injection extracts were injected intravenously. Vegetable oil extract and polyethylene glycol 400 extract were injected intraperitoneally.

An intracutaneous test was performed to evaluate the potential of a single injection of an extract to produce tissue irritation. The four specified extracts were used.

Implantation was also performed in order to subject the materials of construction to the most stringent conditions included in the United States Pharmacopoeia. Each of the components of the filter cassette was implanted separately.

The hemolysis test and cytotoxicity test were conducted to determine the potential toxicity resulting from contact of the materials of construction with blood or tissue. The hemolysis test determines the degree of red blood cell lysis caused by contact of the test material. Using cell culture techniques, the cytotoxicity test determines the lysis of cells and the inhibition of cell growth caused by extracts of the test materials.

5.2.1 Results

All T-Series cassettes with Delta membrane components passed the requirements of the Biological Reactivity Tests, and thus meet the requirements in USP Class VI-70 °C Plastics. Additionally, test samples meet the requirements of the hemolysis test and cytotoxicity test.

The tests were conducted by:

STS division of Ethox International
7500 W. Henrietta Road
Rush, NY 14543

Results from the following tests are included in the appendices.

- USP XXI Biological Test for Plastics, *in vivo, Class VI*
- L-929-MEM Cytotoxicity Test
- Hemolysis Test-Direct Contact with Rabbit Blood

5.3 Materials of Construction Conformance Summary

- Polypropylene screen — Meets 21 CFR, part 177.1630, USP Class VI-70 °C Plastics.
- Polyurethane encapsulant — Meets 21 CFR, part 175.103, 175.300, 177.2600, USP Class VI-70 °C Plastics.
- Silicone permeate seals — Meets 21 CFR, part 175.103, 175.300, 177.2600, USP Class VI-70 °C Plastics.
- Silicone gaskets — Platinum cured, medical grade, Meets 21 CFR, part 177.2600, USP Class VI-70 °C Plastics.
- Glycerine — CP/USP grade, plant origin, (added as humectant; removed with flushing).
- Delta membrane — Meets 21 CFR, part 177.1630, USP Class VI-70 °C Plastics.

6. Method Details

6.1 Procedure for Flushing Cassettes (Preconditioning)

This procedure is recommended for flushing and preconditioning cassettes before use with product. It has been found effective to significantly remove storage agents and extractables while keeping water usage to under 110 L/m^2 (10 L/ft^2).

6.1.1 Initial Flush

Volume: DI water 10 L/m^2 (0.9 L/ft^2)

Temperature: Ambient

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.

6.1.2 Caustic Recirculation: 0.25 N

Volume: Appropriate volume to accommodate hold up. Use 5 L/m^2 (0.5 L/ft^2) as a guide.

Temperature: 40 to 45 °C

Time: 30 minutes

1. Adjust the pump flow rate so that 2 L/min/m^2 (0.2 L/min/ft^2) flows through the retentate.
2. Set the retentate valve to produce 0.1 barg (2 psig) backpressure.
3. Set the permeate valve open 100%.
4. Direct both streams to the feed tank.

6.1.3 Post Caustic Cycle Flush

Volume: DI water 30 L/m^2 (3 L/ft^2)

Temperature: Ambient

1. Adjust the pump flow rate and backpressure to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.

6.1.4 First Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to the feed tank.

6.1.5 Second Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.

6.1.6 Third Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.

6.1.7 Final Flush

Volume: DI water 40 L/m^2 (4 L/ft^2)

Temperature: Ambient

1. Adjust the pump flow rate and the retentate valve to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.

6.2 Procedure for Determination of Extractables from T-Series Cassettes with Delta Membrane

Note: *The preconditioning of cassettes (6.1) is performed prior to the extraction study and analysis for NVR.*

6.2.1 Equipment

- Centrasette holder and gauges
- TOC analyzer: Dohrmann-(ACL-TOC-1); M/N: Phoenix 8000; S/N: 9338001; Calibrate per use
- TOC standard: 1000 PPM; Alfa Aesar: L/N: 72-071688F1; Stock # 42562; Expires: June 20, 2012
- Balance: (ACL-B-1); Calibration due: July 28, 2009
- Stop watch: (ACL-SW-8); Calibration due: September 7, 2009

- HPLC: (ACL-HPLC-2); Calibrate per use
- GC/MS: (ACL-GCMS-1); Calibrate per use
- GC Column: DB-1; Agilent: 60 m x 0.25 mm x 0.25 um; P/N: 122-1062; S/N:US7519724H
- Pipettman:

  (ACL-PM-4); Calibration due: April 20, 2009

  (ACL-PM-6); Calibration due: April 20, 2009

  FTIR: (ACL-IR-1); Calibration due: March 24, 2009
- Graduated Cylinder:

  (ACL-GC-167); Calibration due: January 24, 2017

  (ACL-GC-55); Calibration due: December 18, 2012

  (ACL-GC-166); Calibration due: January 24, 2017
- Thermometer: (ACL-DT-8); Calibration due: September 26, 2009
- Sodium Hydroxide: J.T. Baker; L/N: C33P01; Expires: December 5, 2011
- pH Meter: (ACL-PH-3); Calibrate per use
- pH 5: BDH; L/N: 2802083; Expires January 2010
- pH 4: J.T. Baker; L/N: G45504; Expires November 30, 2010
- pH 7: J.T. Baker; L/N: G43524; Expires November 30, 2010
- Water: Mallinckdrodt; HPLC Grade; L/N: G30010; Expires July 31, 2009

6.2.2 Reagents

- Purity of Reagents: HPLC grade or high-grade chemicals
- Purity of Water: HPLC grade or having a resistivity of at least 17.8 MS-cm
- Purity of Mobile Phase: HPLC or high grade

6.2.3 Preparation of Apparatus and Materials

1. Thoroughly clean the glassware and the liquid contact surfaces of the pumps, tubing, and holder. Where appropriate, a TOC measurement of a DI water rinse is used to assure cleanliness. Clean the porcelain crucibles by heating in furnace at 500 °C or higher for approximately 30 minutes and allow cooling in a desiccator.
2. Prepare sanitizing solution of 0.1 N NaOH/200 PPM sodium hypochlorite by dissolving 16.8 grams of NaOH in 3 liters of DI water, adding 16 mL of 5.25% sodium hypochlorite (commercial bleach), and bringing the total volume to 4 liters. Filter the solution through a 0.2 µm filter.

6.2.4 Extraction Procedure

The following extraction procedure will be run in DI water at 45 to 50 ºC. A sample blank is run first. The blank consists of using a flushing gasket in place of a cassette. Extractions performed in duplicate.

6.2.5 Holder Sanitization Process

6.2.5.1 Initial Flush

Volume: DI water ~100 L

Temperature: Ambient

Time: 25 minutes

1. Clean a set of cut-out gaskets with DI water and install the set in the pre-cleaned cassette holder.
2. Adjust the pump flow rate to achieve a flow distribution of 50% flow through the retentate and 50% flow through the permeate, ~ 2 L/min/m^2 (~ 0.2 L/min/ft^2) through the retentate and 2 L/min/m^2 (0.2 L/min/ft^2) through the permeate.
3. Direct both streams to waste.

6.2.5.2 Sanitization

Volume: 0.5 N NaOH 4 L in pre-cleaned glass container

Temperature: 40 ºC

Time: 40 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 50% flow through the retentate and 50% flow through the permeate, ~ 2 L/min/m^2 (~ 0.2 L/min/ft^2) through the retentate and 2 L/min/m^2 (0.2 L/min/ft^2) through the permeate.
2. Stop pump and drain the system.

6.2.5.3 Post Sanitization Water Flush

Volume: DI water ~100 L

Temperature: Ambient

Time: 25 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 50% flow through the retentate and 50% flow through the permeate, ~ 2 L/min/m^2 (~ 0.2 L/min/ft^2) through retentate and 2 L/min/m^2 (0.2 L/min/ft^2) through the permeate.
2. Direct both streams to waste.

6.2.5.4 pH Check

Volume: DI water 4 L in pre-cleaned glass container

Temperature: Ambient

1. Adjust the pump flow rate to achieve a flow distribution of 50% flow through the retentate and 50% flow through the permeate, ~ 2 L/min/m^2 (~ 0.2 L/min/ft^2) through retentate and 2 L/min/m^2 (0.2 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Recirculate for 10 minutes.
4. Collect samples from both reservoirs for pH.
5. Criteria < 8.
6. Criteria not met? Repeat Steps 3 and 4.

6.2.5.5 16-hour Recirculation

Volume: DI water 4 L in pre-cleaned glass container

Temperature: 50 ºC

Time: 16 hours (maintain record of time and temperature)

1. Adjust the pump flow rate to achieve a flow distribution of 50% flow through the retentate and 50% flow through the permeate, ~ 2 L/min/m^2 (~ 0.2 L/min/ft^2) through the retentate and 2 L/min/m^2 (0.2 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Increase temperature to 50 ºC.
4. Isolate all tubing and feed container to prevent cross contamination by covering container with PTFE film.

On completion of 16 hours, remove pump feed tube from the feed tank, continue to pump for 1 minute, stop pump and remove retentate and permeate tubing from the feed tank. Pour the 4 L solution from the feed tank into pre-cleaned glass jars; seal and label with the solvent name.

6.2.5.6 Perform NVR Evaluation Per GLSM002 rev 03b

- Section 10
- Quantitive determination of NVR
- Criteria < 2 mg/4 L

6.2.5.7 Perform TOC Evaluation Per GLSM019 rev 03

- Criteria < 400 ppb

Both criteria met? Continue per section 6.2.6 Negative Control.

Criteria not met? Repeat steps 6.2.5.3 through 6.2.5.6.

6.2.6 Negative Control

6.2.6.1 Place in Holder

Place blank in holder. Use 2 x 1/16" (1.6 mm) silicone gaskets.

Use a manual holder clamp with an applied torque of 70 in-lbs. For T06 use 350 in-lbs.

Note: *Flow rates will be based on the size of the cassette used in the extraction.*

6.2.6.2 Initial DI Water Flush: Sample for Analysis

Volume: DI water 10 L/m^2 (0.9 L/ft^2)

Temperature: Ambient (record)

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.6.3 0.25 N Caustic Recirculation

Volume: Appropriate volume to accommodate hold up. Use 5 L/m^2 (0.5 L/ft^2) as a guide.

Temperature: 40 to 45 ºC

Time: 30 minutes

1. Adjust the pump flow rate so that 2 L/min/m^2 (0.2 L/min/ft^2) flows through retentate.
2. Set retentate valve to produce 0.1 barg (2 psig) backpressure.
3. Set the permeate valve open 100%.
4. Direct both streams to the feed tank.

6.2.6.4 Post Caustic Cycle Flush

Volume: DI water 30 L/m^2 (3 L/ft^2)

Temperature: Ambient

1. Adjust the pump flow rate and backpressure to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.6.5 First Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.6.6 Second Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.6.7 Third Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.6.8 Flush

Volume: DI water 40 L/m^2 (4 L/ft^2)

Temperature: Ambient

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.6.9 5-hour Recirculation

Feed: Pre-cleaned glass container

Volume: DI water 10 L/m^2 (0.9 L/ft^2)

Temperature: 50 ºC

Time: 5 hours (maintain record of time and temperature)

1. Remove cassette and drain system.
2. Replace cassette. Tighten the bolts to a torque of 350 in-lbs. Use same silicone gaskets used in step 6.2.6.7. Ensure the gaskets have been rinsed with DI water.
3. Adjust the pump flow rate to achieve a flow distribution of 90% flow through the retentate and 10% flow through the permeate, ~ 0.9 L/min/m^2 (~ 0.09 L/min/ft^2) through the retentate and 0.1 L/min/m^2 (0.01 L/min/ft^2) through the permeate.
4. Direct both streams back to the feed tank.
5. Bring solution temperature to 50 ºC.
6. Isolate all tubing and feed container to prevent cross contamination by covering container with PTFE film.

On completion of 5 hours, remove pump feed tube from the feed tank, continue to pump for 1 minute, stop pump and remove retentate and permeate tubing from the feed tank. Pour the solution from the feed tank into pre-cleaned glass jars, seal and label with the solvent name, job #, cassette serial # and the wording, “First 5-hour extraction.” Record volume.

6.2.6.10 Perform NVR Evaluation Per GLSM 002 rev 03b

- Section 10
- Quantitative determination of NVR

6.2.6.11 Perform TOC Evaluation Per GLSM019 rev 03

6.2.6.12 Perform FTIR per GLSM29 rev 01

6.2.6.13 GC per GLSM 057 Rev 00A

6.2.6.14 GC/MS per GLSM079 Rev 00

6.2.6.15 HPLC per GLSM 075 Rev 00A

6.2.7 Cassette Recommended Sanitization Flush

6.2.7.1 Place in Holder

Use 2 x 1/16" silicone gaskets cleaned with DI water.

Manual or auto torque holders may be used.

With a manual holder, tighten the sealing bolts to a torque of 70 in-lbs. For T06 use 350 in-lbs.

6.2.7.2 Initial DI Water Flush – Sample for TOC

Delta membrane preservative (sodium diacetate, triethyl citrate, ethanol, glycerine).

Volume: DI water 10 L/m^2 (0.9 L/ft^2)

Temperature: Ambient (record)

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.7.3 0.25 N Caustic Recirculation

Volume: Appropriate volume to accommodate hold up. Use 5 L/m^2 (0.5 L/ft^2) as a guide.

Temperature: 40 to 45 ºC

Time: 30 minutes

1. Set pump so that 2 L/min/m^2 (0.2 L/min/ft^2) flows through the retentate.
2. Set retentate valve to produce 0.1 barg (2 psig) backpressure.
3. Set permeate valve open 100%.
4. Direct both streams back to the feed tank.

6.2.7.4 Post Caustic Cycle Flush

Volume: DI water 30 L/m^2 (3 L/ft^2)

Temperature: Ambient

1. Adjust the pump flow rate and backpressure to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.7.5 First Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.7.6 Second Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.7.7 Third Water Recirculation

Volume: DI water 8 L/m^2 (0.7 L/ft^2)

Temperature: Ambient

Time: 30 minutes

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams back to the feed tank.
3. Use the PTFE containers to sample the feed, retentate and permeate for analysis.

6.2.7.8 Flush

Volume: DI water 40 L/m^2 (4 L/ft^2)

Temperature: Ambient

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.

6.2.7.9 First 24-hour Recirculation

Volume: DI water 10 L/m^2 (0.9 L/ft^2) in pre-cleaned glass container

Temperature: Ambient

Time: 24 hours (maintain record of time and temperature)

1. Remove cassette, drain system.
2. Replace cassette. Tighten the sealing bolts to a torque of 350 in-lbs. Use same silicone gaskets used in Step 6.2.7.8. Ensure the gaskets have been rinsed with DI water.
3. Adjust flow for 324 LMH permeate fully open, 0.7 barg (10 psig) on retentate.
4. Isolate all tubing and feed container to prevent cross contamination by covering container with PTFE film.

On completion of 24 hours, remove pump feed tube from the feed tank, continue to pump for 1 minute, stop pump and remove retentate and permeate tubing from the feed tank. Pour the solution from the feed tank into pre-cleaned glass jars, seal and label with the solvent name.

6.2.7.10 Flush Cassette

Use PTFE containers to sample for TOC; label the feed, retentate and permeate sample with cassette serial #, section, and step description.

Volume: DI water 10 L/m^2 (0.9 L/ft^2) 0.2 µm

Temperature: Ambient (record)

1. Adjust the pump flow rate to achieve a flow distribution of 25% flow through the retentate and 75% flow through the permeate, 1 L/min/m^2 (0.1 L/min/ft^2) through the retentate and 3 L/min/m^2 (0.3 L/min/ft^2) through the permeate.
2. Direct both streams to waste.
3. Remove cassette from the holder and package in foil pouch, and refrigerate until commencement of second 24-hour recirculation.
4. Second 24-hour recirculation should commence no later than 18 hours post completion of the first 24-hour recirculation.

6.3 Procedure for Determination of NVR

1. Take an aliquot of the extraction solution (e.g., 1000 mL) and evaporate on a rotary evaporator using a clean 1000 mL glass and round-bottom flask. Adjust and maintain the temperature of the water bath to 80 °C. Evaporate the aliquot to less than 25 mL.
2. Weigh crucibles to the nearest 0.0002 g. Repeat until constant weight is obtained (± 0.0002 g). Store in a desiccator. See Section 6: Method Details.
3. Quantitatively transfer the concentrated extract to the tared crucible contained in the desiccator. If residue remains in the round-bottom flask, add a few drops of fresh DI water, swirl, and add to crucible. If more than a few drops are needed, note the volume used.
4. Carefully place the crucibles in an oven (circulating air type) maintained at 60 to 80 °C. Evaporate the extract to dryness. Remove the crucibles from the oven after evaporation of the water, return to a desiccator, cover, and allow to cool to room temperature.
5. Weigh the crucibles to the nearest 0.0001 g and record the weight.
6. Calculate the NVR for the volume evaporated as follows:

   NVRV (mg) = CR (mg) - CC (mg)

   Where NVRV = NVR for volume evaporated in mg; CR = constant weight of crucible; and, residue CC = constant weight of crucible 7.
7. Calculate the total NVR for both the control and each sample.

   NVRT (mg) = NVRV (mg) x VI/VE

   Where NVRT (mg) = total NVR in mg; VI = initial solvent volume used for extraction; VE = volume of solvent taken from final volume for evaporation 8.
8. Calculate the net NVR for each sample as follows.

   Net NVR (mg) = NVRS - NVRC

   Where NVRS = total NVR of the sample in mg; NVRC = total NVR of the control in mg.

6.3.1 Determining Chemical Compatibility of Common Cleaning Agents

The following protocol was used to determine the chemical compatibility of T-Series screen channel cassettes with Delta membrane in the following solutions:

Compatibility Study Procedure

1. Characterize cassettes for IT, DP, and NWP.
2. Prepare test solution.
3. Install cassettes(s) in holder. Set system up for recirculation of retentate and permeate.
4. Open feed retentate and permeate valves 100%.
5. Adjust the pump flow rate and the retentate valve to achieve a feed pressure of ~1.4 barg (20 psig), and a retentate pressure of ~0.7 to 1.0 barg (10 to 15 psig).
6. Recirculate for 15 minutes.
7. Remove the cassette from the holder, put in a plastic bag and seal it.
8. Store the cassettes at specified temperature and time period.
9. Remove cassettes after 14 or 28 days.
10. Install the cassette in a holder/TFF system.
11. Fill reservoir with water.
12. Flush the cassette with 0.2 µm filtered DI water for at least 20 minutes.
13. Characterize the cassette(s) for IT, DP, and NWP.

7. Detection Methods

7.1 Detection Methods for Cleaning and Storage Agents

7.1.1 Sodium Hydroxide

Residual sodium hydroxide can be determined by measuring the pH of effluent from the cassette and comparing the pH to that of the influent. When the two match, the residual sodium hydroxide has been removed. The pH is a direct measure of the hydroxyl ion concentration and can be used to calculate residual hydroxyl ion concentration (Table 22).

Table 22

Relationship of pH to Hydroxyl Ion Molar Concentration

pH	Hydroxyl Ion Molar Concentration
7	1×10^{7}
8	1×10^{6}
9	1×10^{5}
10	1×10^{4}
11	1×10^{3}
12	1×10^{2}
13	1×10^{1}
14	1.0

See Section 7.2: Detection Methods for Storage Agents.

7.1.2 Glycerine

The following steps describe the size exclusion chromatography method for determination of glycerine concentration. The sensitivity of the method is 1 PPM.

1. Prepare 100 PPM, 10 PPM, and 1 PPM glycerine standards.
2. Inject 50 µL of the glycerine standards on a size exclusion chromatography column (TOSO Haas, G3000PWXL) connected to an HPLC system (Hewlett Packard, Model #1050) using a refractive index detector (mobile phase: H_2O). Identify the glycerine peak and calculate the peak area for each standard. Prepare a standard curve of peak area versus glycerine concentration.
3. Inject 50 µL of each of the retentate and permeate samples collected. Identify the glycerine peak found in each of the retentate and permeate samples. Measure the peak area and determine glycerine concentrations from the standard curve.

7.2 Endotoxin Assay Procedure — ThermoMax Chromogenic Assay

This section describes the test procedure for detecting endotoxin in solution using Limulus Amoebocyte Lysate reagent incorporated into the ThermoMax Chromogenic (Endochrome◆ K) Assay.

7.2.1 Introduction

Recent advances in computer technology have made kinetic quantitation the method of choice for simultaneous measurement of endotoxin in multiple samples. This procedure provides a standard method for the use of the Molecular Devices ThermoMax microtiter plate reader with endotoxin standards in detecting and quantitating endotoxin in control and unknown samples.

USP Class VI References

STS, a division of Ethox International
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Rush, NY 14543
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Table 23

Component	Test Description	Report #
Polyurethane	1. Muscle implantation	T06-1445
	2. Hemolysis test (saline extraction method)	T06-1446
	3. MEM elution cytotoxicity test (ISO method)	T06-1447
	4. Systematic injection test (USP Method)	T06-1444
	5. Intracutaneous (intradermal) reactivity test (USP Method)	T06-1443
Sheath core fiber	1. Muscle implantation T06-1455	T06-1455
	2. Hemolysis test (saline extraction method)	T06-1456
	3. MEM elution cytotoxicity test (ISO method)	T06-1457
	4. Systematic injection test (USP method)	T06-1454
	5. Intracutaneous (intradermal) reactivity test (USP Method)	T06-1453
Silicone 200026	1. 7 Day muscle implantation with macrospic evaluation	T03-0245
	2. Hemolysis test (saline extraction method)	T03-0258
	3. Intracutaneous (intradermal) reactivity test (USP method)	T03-0256
	4. MEM elution cytotoxicity test (ISO method)	T03-0259
	5. Systematic injection test (USP method)	T03-0257
Delta 10K membrane	1. Muscle implantation	T05- 4172
	2. Hemolysis test (saline extraction method)	T05- 4174
	3. MEM elution cytotoxicity test (ISO method)	T05- 4173
	4. Systematic injection test (USP Method)	T05- 4171
	5. Intracutaneous (intradermal) reactivity test (USP method)	T05- 4170
Polypropylene mesh	1. Muscle implantation	T06-1393
	2. Hemolysis test (saline extraction method)	T06-1394
	3. MEM elution cytotoxicity test (ISO method)	T06-1395
	4. Systematic injection test (USP method)	T06-1392
	5. Intracutaneous (intradermal) reactivity test (USP method)	T06-1391

8. Glossary

Access Pall's Tangential Flow Filtration (TFF) Glossary online at www.pall.com/biopharm.

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