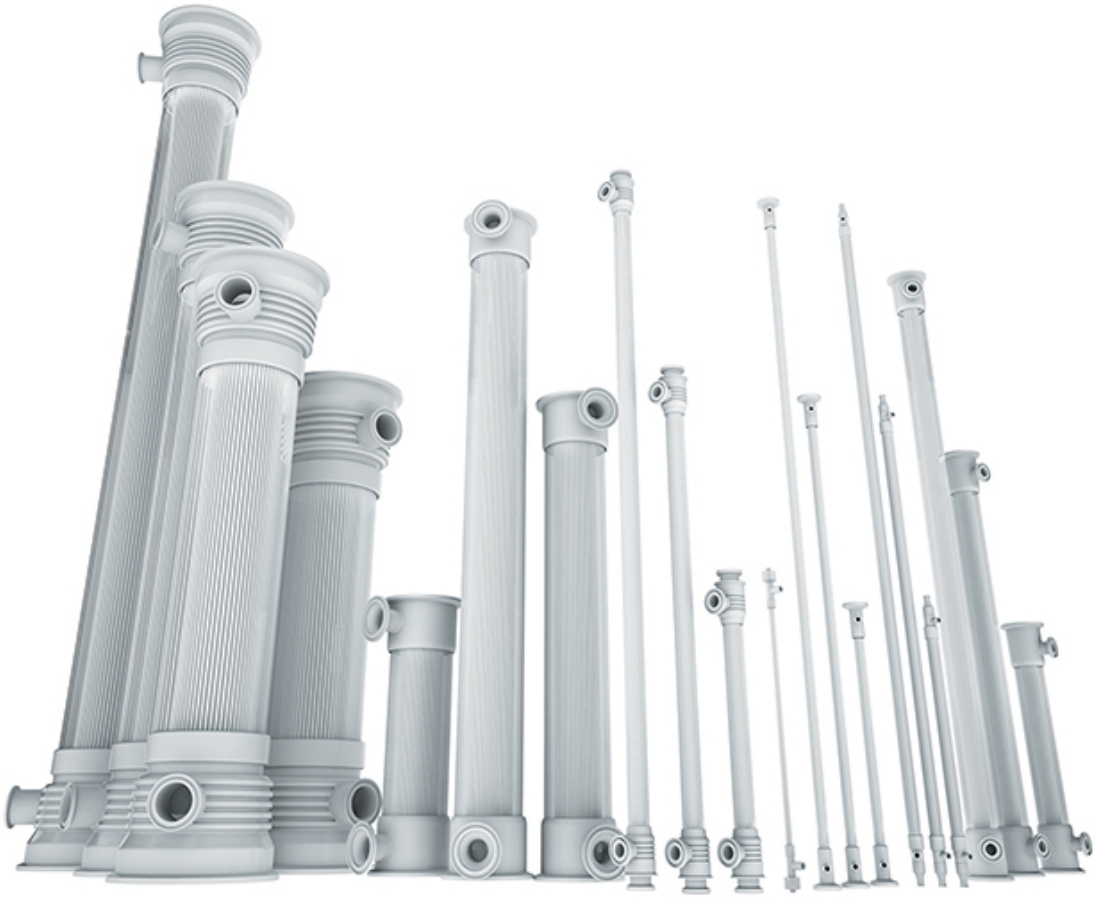
Spectrum® mPES Hollow Fiber Filter Modules

Regulatory Support File



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Abbreviations

CFU	Colony Forming Units
CHO	Chinese Hamster Ovary
EU	Endotoxin Units
kD	Kilodalton
kGy	Kilogray
LMH	Liters / Meters^2 / hour
ME	Mixed Ester
MF	Microfiltration
mPES	modified Polyethersulfone
MW	Molecular Weight
MWCO	Molecular Weight Cut Off
nMWCO	nominal Molecular Weight Cut Off
NWP	Normalized Water Permeability
ProConnex®	Items: Flow Paths, modules, bags or bottles, tubing sets, fittings kits
PS	Polysulfone
PVDF	Polyvinylidene Fluoride
SAL	Sterility Assurance Level
TFF	Tangential Flow Filtration
TMP	Transmembrane Pressure
TRM	Total Recirculation Mode
UF	Ultrafiltration
VLP	Virus Like Particle

1. Introduction

1.1 Purpose of this Regulatory Support File

This Regulatory Support File presents product information for Spectrum® mPES Hollow Fiber Filter Modules from Repligen Corporation. As an engineer, scientist, or manufacturer, you may need this information to guide your validation activities, including process development, writing validation protocols, and scaling up systems.

If you are new to tangential flow filtration, reading this validation guide will help you learn about Spectrum® Hollow Fiber Filter Modules and the procedures required to use them successfully.

When you purchase a Spectrum® mPES Hollow Fiber Filter Module, you receive user instructions as well as product quality and performance data. This product quality and performance data, combined with the information in this validation guide (and the data collected from your process) provide much of the information you need to validate your process in an effective and efficient manner.

1.2 Where to get help

If you need to know more about tangential flow filtration and filter module validation, contact the technical support team at Repligen. The technical support team includes scientists and engineers that can:

a. Answer your technical questions.
b. Assist in the in the selection and design of filtration systems.
c. Provide user training programs.

Specifically, Repligen provides the following support:

- Process optimization and filtration testing
- Integrity testing
- Validation protocol development
- Troubleshooting
- Periodic checks to ensure continued efficiency of filtration system
- Operator training

To obtain support, contact your local Repligen sales representative or our customer support team. Customer support information is located on page 2.

2. Quality documentation

2.1 Quality policy

2.1.1 Repligen Corporation– A higher standard

Repligen Corporation has over 50 years of experience providing filtration products that meet the quality required in bioprocessing applications. Repligen is one of the few suppliers of OEM Hollow Fiber Filtration products. We can satisfy the quality needs of customers with particular application requirements. Full compliance with regulatory requirements and meeting customer needs are the driving forces for Repligen higher standard of quality.

2.1.2 Complying with quality regulations

Since product quality is essential to our customers' success, Repligen makes quality assurance a top priority. Repligen is an ISO 9001 certified company and has an established (QMS) Quality Management System.

2.1.3 Product certification

Repligen supplies certificates of quality for released manufacturing lots (Figure 1). Upon advanced request, you can receive certificates of quality for individual Spectrum® mPES Hollow Fiber Filter Modules. Certificates of quality are substantiated with data appropriate to each filter type.

This information typically includes:

- Technical specifications
- USP Class VI compliance or supplier certification
- Integrity testing—destructive and non-destructive
- Filter rating (pore size) verification testing or supplier certifications

Substantiation data is maintained on file for 5 years or as required by customers and OEM applications.

2.1.4 Animal byproduct free

Our mPES fiber is manufactured from synthetic or manufactured materials and does not contain any raw materials produced from or substances derived of animal origin. Moreover, Repligen uses materials for filter module production that do not use ingredients of animal origin or are compliant with EMEA 410/01 guidelines. Our products do not come in contact with animal product during storage and transportation.

2.1.5 ISO and USP Class VI statements

ISO Statement: Product is manufactured in compliance with Repligen ISO 9001 certified Quality Management System.

USP Class VI Statement: All flow path materials meet USP Class VI biosafety requirements.

Figure 1. Example of Certificate of Quality (CoQ) included with each module

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Certificate of Quality

This is to certify that the Hollow Fiber Module indicated by the affixed label complies with the following descriptions and specifications:

Affix Label Here

10kD
0.5mm, mPES

Product – Hollow Fiber Module

Product is manufactured in compliance with Repligen's ISO 9001:2015 certified quality management system.
The modules and materials have lot traceability and are manufactured in ISO Class 7 cleanroom.

All fluid path materials of construction meet USP Class VI biosafety requirements and do not contain any substances derived from animal products (BSE/TSE free) and are compliant with EMA 410/01 guidelines.

The materials of construction are as follows:

Housing	Polysulfone
Potting Material	Polyurethane & May Contain UV Epoxy (fluid path)
Filtration Filter Media	Modified Polyethersulfone (mPES)

The fiber lot(s) used in the module was sample tested to verify product claims.

% Pore Passage (Vitamin B^{12})	> 90%
% Pore Retention (PVP K-17)	> 30%
Water flux ($L/m^2/h/psi$)	≥ 5

Each filter module is integrity tested for acceptance in accordance with Quality Control procedures.
Each filter membrane surface area is true within ±10% of the surface area labeled on the filter.

Each module with part numbers ending in 'S' is exposed to gamma radiation after final packaging and is certified to be sterile in accordance with the VD_{max} method, ANSI/AAMI/ISO 11137-1 and ANSI/AAMI/ISO 11137-2. Not applicable for modules with part number ending in 'N'.

Shelf Life: Intended for Single Use within three (3) years for gamma irradiated and five (5) years for non-irradiated, from the date of manufacture. The month and year of manufacture is indicated after the first dash of the labeled lot number.
Origin of Manufacture: U.S.A.

Issued by Quality Assurance

Electronically produced and valid without a signature

Please note that it is incumbent upon the end user to validate that this product is suitable for the intended use in their application.

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* CoQ example is for a 10 kD 0.5 mm Spectrum® mPES Hollow Fiber Filter Module.

3. Product design and performance

This chapter describes the design, construction, and performance of Spectrum® mPES Hollow Fiber Filter Modules. The information includes:

Product design

- Overview of product design
- Materials of construction
- Design of the hollow fibers

Product performance

- Applications
- Normalized water permeability
- Scalability
- Operating parameters and limits

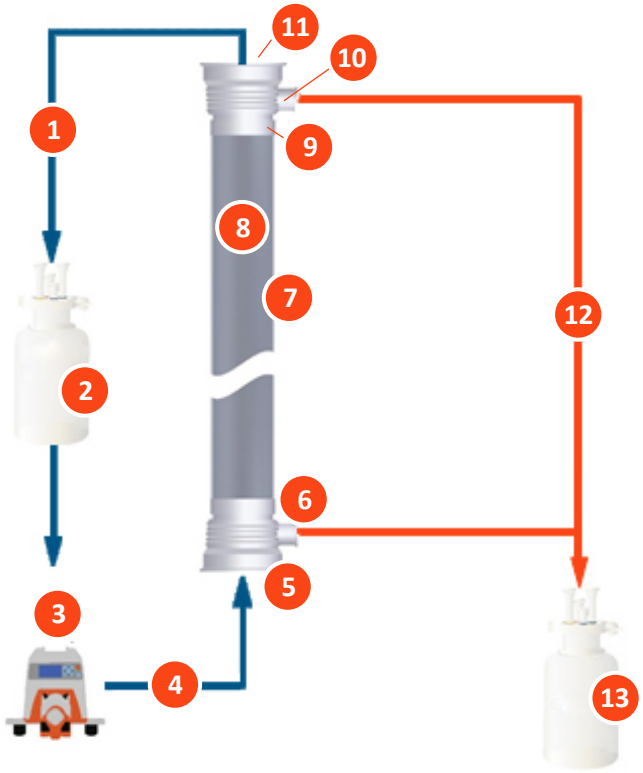
3.1 Product design

3.1.1 Overview of product design

Spectrum® Hollow Fiber Filter Modules consist of hollow fibers encapsulated in a housing (Figure 2). The housing has end fittings and each end fitting includes two ports. In total, the ports include a Feed port, a Retentate port, and two Permeate ports. The ports use various types and sizes of adaptors and connectors.

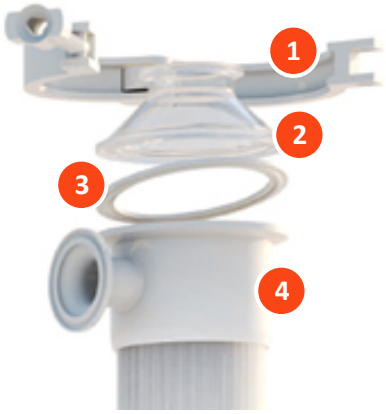
The hollow fibers run the length of the housing, connecting the Feed and Retentate ports. During use, you pump your interim product fluid into the Feed port under pressure. Most of the fluid flows through the hollow fibers and out of the Retentate port. Some fractional volume of the fluid flows through the walls of the hollow fibers into the housing shell and out of the Permeate ports.

Figure 2. Spectrum® Hollow Fiber Filter Module main components and example configuration



1. The retentate (fluid and components that do not pass through the wall of the hollow fibers) is returned to the Feed reservoir.
2. Feed reservoir
3. Pump
4. Fluid pumped into the Feed port
5. Feed port
6. Permeate port 2
7. Filter housing
8. Hollow fibers inside housing
9. End fitting
10. Permeate port 1
11. Retentate port
12. Components that pass through the hollow fiber membrane flow from the permeate ports for collection.
13. Collection reservoir

Figure 3. Connection components for larger Spectrum® Hollow Fiber Filter Modules



1. Clamp
2. Adaptor
3. Gasket
4. End fitting

Note: *Large filter modules can use different size adaptors to connect to filtration systems.*

3.1.2 Materials of construction

The materials of construction for Spectrum® mPES Hollow Fiber Filter Modules are listed in Table 1. Materials used in the construction of the wetted parts meet USP Class VI requirements. The filter module design and material durability enables Spectrum® mPES Hollow Fiber Filter Modules to operate at a maximum pressure of 30 psi (Figure 4).

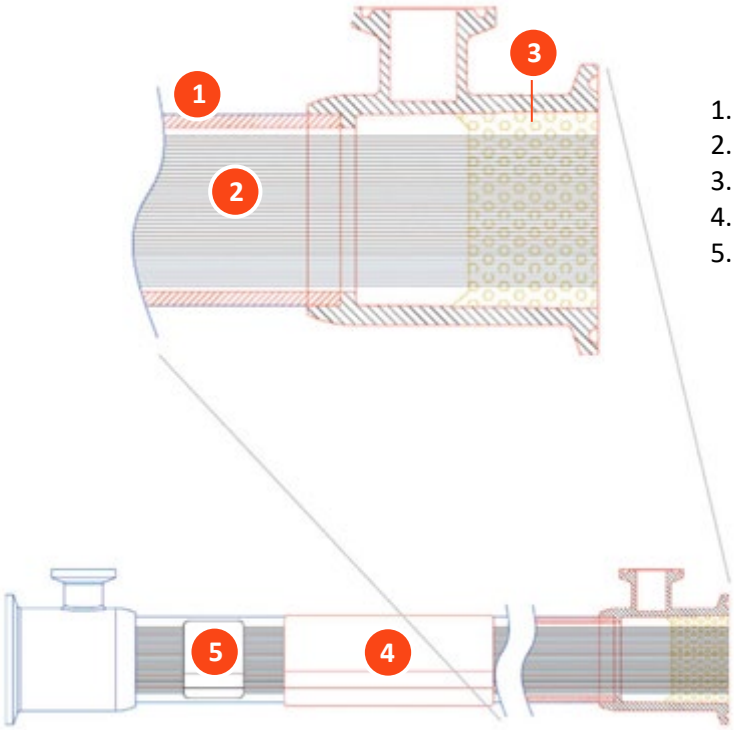
Table 1. Materials of construction in the fluid path of Repligen process filtration products

Filter components	Materials of construction
Spectrum® Hollow Fiber Filter Membrane	Modified polyethersulfone
Support netting	Polypropylene
Housing, End fitting and exterior plastic components	Polysulfone
Potting material	Urethane or epoxy
Seals and gaskets	Platinum-cured silicone

3.1.3 User must validate appropriateness for use

Even with the disclosure of the materials of construction and the results of extractable testing, it is incumbent upon users to validate the appropriateness for use of Repligen Corporation products in specific applications.

Figure 4. Spectrum® Hollow Fiber Filter showing materials of construction of each component

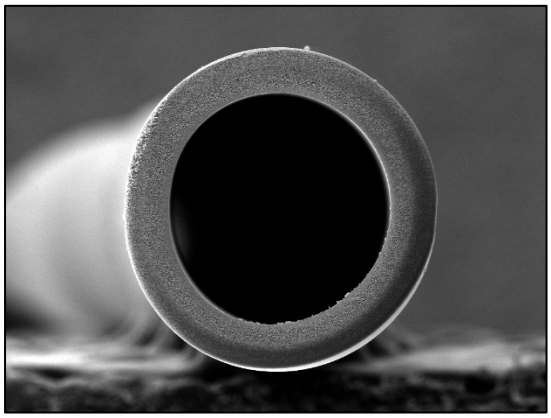


1. Polysulfone housing
2. Spectrum® mPES Hollow Fiber
3. Urethane and epoxy potting
4. Spectrum® Filter Family label
5. Product label

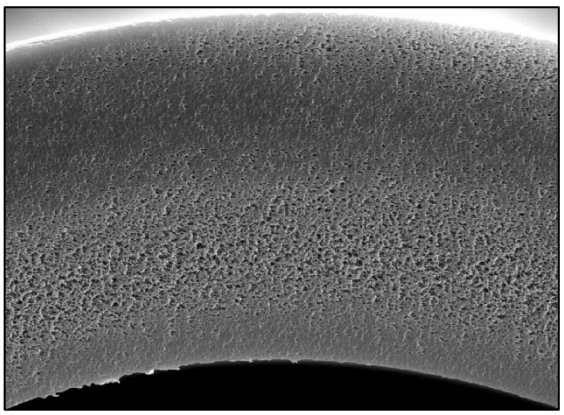
3.1.4 Design of the hollow fibers

The membrane that forms Spectrum® mPES Hollow Fibers is void free and anisotropic in structure (Figure 5). The high-density skin layer of mPES membrane limits fouling, while the more open, outer support structure increases filtration rates.

Figure 5. Spectrum® Hollow Fiber magnified cross sections showing void-free structure



30 kD 0.5 mm ID Spectrum® mPES Hollow Fiber @ 100X magnification

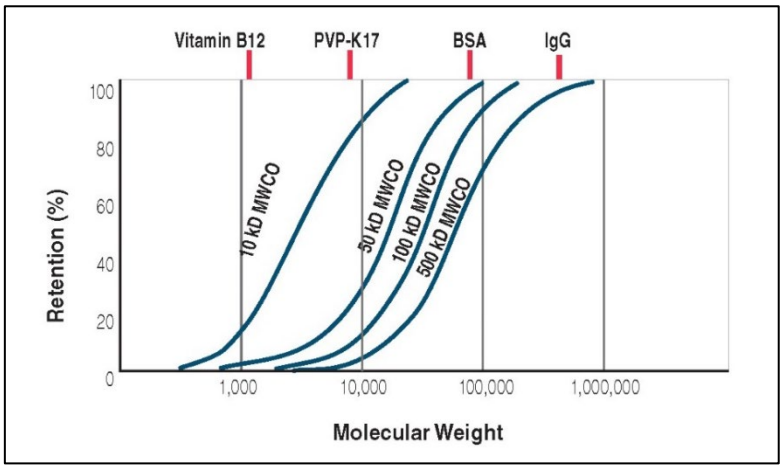


30 kD 0.5 mm ID Spectrum® mPES Hollow Fiber @ 750X magnification

3.1.5 Membrane retention specifications

The general retention characteristics of Spectrum® mPES Hollow Fiber Membrane is illustrated in Figure 6. Specific fiber specifications, including passage and retention marker information, is proprietary information. Repligen can provide this information to customers upon request when needed for process development and validation purposes. Contact the technical support team at Repligen for additional information.

Figure 6. Solute retention of Repligen Ultrafiltration Membranes



3.2 Product performance

Design elements and materials of construction, combined with Repligen manufacturing and quality processes, enable the following claims and features in regard to Spectrum® mPES Hollow Fiber Filter Modules:

- Low bioburden
- 100% integrity tested
- Fluid path meets USP Class VI standards for biocompatibility and animal derived component free
- Manufactured under an ISO 9001 Quality Management System. Manufactured in an ISO Class 7 clean room

From a performance standpoint, and compared to non-mPES filters, Spectrum® mPES Hollow Fiber Filter Modules provide:

a. Higher flux rates for faster processing times.
b. Excellent selectivity for separation applications.
c. Low protein binding for higher product yields.

3.3 Applications

You can use Spectrum® mPES Hollow Fiber Filter Modules in many filtration and separation processes required for the production of drug and biotech products (Figure 7):

- Cell concentration, clarification, and diafiltration
- Lysate clarification
- VLP and virus concentration and diafiltration
- VLP and virus clarification
- Protein purification, concentration, and diafiltration
- Nucleic acid diafiltration and concentration
- Nanoparticle and latex particle diafiltration and fractionation
- In situ conjugation and fractionation
- Bacteria concentration and diafiltration
- Liposome, siRNA concentration and diafiltration
- Inclusion body clarification and concentration
- Bioreactor cell perfusion and media exchange

Figure 7. Spectrum® mPES Hollow Fiber Filter Modules

MicroKros Filters for small R&D volumes

Processing volumes: 1 – 100 ml
Connections: MLL x FLL
Effective lengths: 20, 41.5 and 65 cm
Surface areas: 13 cm^2 – 60 cm^2

MidiKros Filters for small starting batch

Processing volumes: 100 ml – 3 L
Connections: FLL x FLL
Effective lengths: 20, 41.5 and 65 cm
Surface areas: 75 cm^2 – 370 cm^2

MidiKros TC Filters for small starting batch

Processing volumes: 100 ml – 3 L
Connections: ½" TC x FLL
Effective lengths: 20, 41.5 and 65 cm
Surface areas: 75 cm^2 – 370 cm^2

MiniKros Sampler Filters for small batch

Processing volumes: 3 L – 15 L
Connections: ¾" TC x ¾" TC
Effective lengths: 20, 41.5 and 65 cm
Surface areas: 490 cm^2 – 2,600

MiniKros Filters for pilot-scale volumes

Processing volumes: 5 L – 50 L
Connections: 1½" TC x ¾" TC
Effective lengths: 20, 41.5 and 65 cm
Surface areas: 1,550 cm^2 – 8,500

KrosFlo® Filters for production-scale

Processing volumes: 10 – 100 L
Connections: 3" TC x 1 ½" TC
Effective lengths: 20, 41.5 and 65 cm
Surface areas: 7,850 cm^2 – 4.1 m^2

KrosFlo® MAX Filters for production-scale

Processing volumes: 100 L – 1000+ L
Connections: 6" TC x 1 ½" TC
Effective lengths: 41.5, 50, 68 and 108
Surface areas: 4.3 m^2 – 12.8 m^2

3.4 Scalability

Hollow fiber filtration systems from Repligen cover a wide range of processed liquid volumes. Systems start at hand-pumped-syringe disposable sample products with liquid volumes as low as 1 milliliter to pilot and production-scale systems to handle liquid volumes greater than 1,000 liters. The range allows the user full scalability since the data acquired with research and development systems is directly applicable at production volumes.

Table 2. Spectrum® Hollow Fiber Filter scalability

Product	Process volumes
MicroKros Hollow Fiber Filter Module	1 - 100 mL
MidiKros Hollow Fiber Filter Module	100 mL - 3 L
MiniKros Sampler Hollow Fiber Filter Module	3 - 15 L
MiniKros Hollow Fiber Filter Module	5 - 50 L
KrosFlo® Hollow Fiber Filter Module	10 - 100 L
KrosFlo® MAX Hollow Fiber Filter Module	100 - 1000+ L

Considering the expense and time involved in bringing new biopharmaceutical products to market, there is a clear need to quickly scale systems from research volumes through prototype volumes to production volumes. Process stability at all volumes and stages of new product introduction is important as well. An important part of this stability results from the chosen filtration steps.

One advantage of Spectrum® Hollow Fiber Filter Modules is direct scalability as long as the fiber path length is held constant. An efficient and cost effective method for scale-up is to determine a steady state flux rate (Liter/M^2/H or LMH) on a small manageable scale.

By holding the operating parameters constant and scaling up only the membrane surface area and recirculation rate, larger scale volumes can be processed in the same way and using the same steps as the small-scale operations. For example, the charts shown below are typical water flux (LMH) versus trans-membrane pressure (TMP) for the various size modules made with:

- 0.5 mm 100 kD MWCO mPES fibers (Figure 8)
- 1 mm 100 kD MWCO mPES fibers (Figure 9)
- 0.5 mm 10 kD MWCO mPES fibers (Figure 10)
- 1 mm 10 kD MWCO mPES fibers (Figure 11)

Figure 8. Typical LMH versus TMP for modules made with 100 kD 0.5 mm mPES fibers

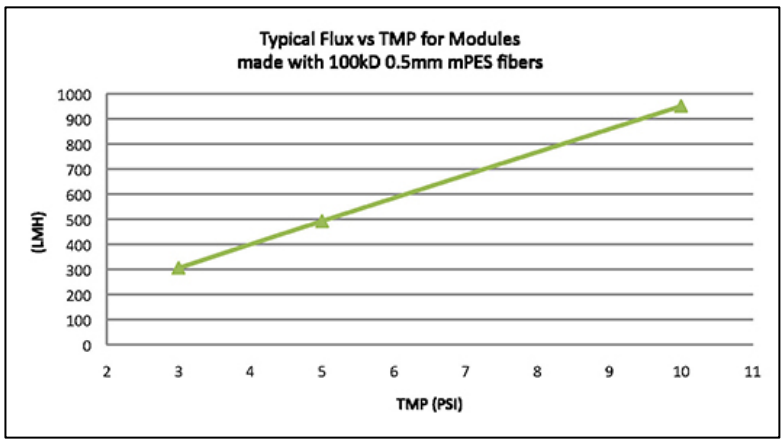


Figure 9. Typical LMH versus TMP for modules made with 100 kD 1 mm mPES fiber

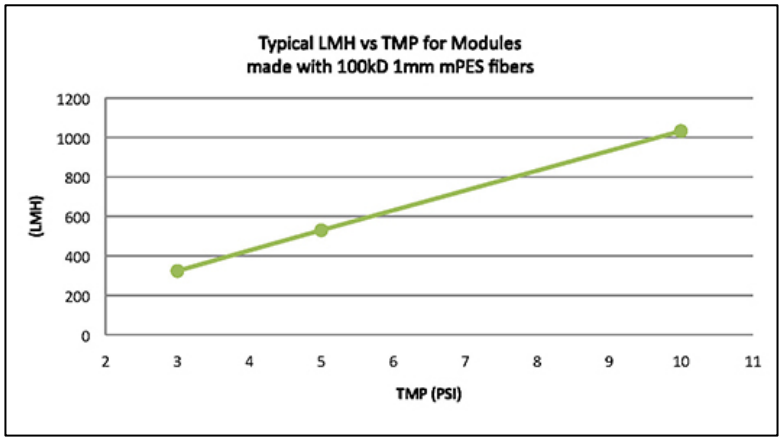


Figure 10. Typical LMH versus TMP for modules made with 10 kD 0.5 mm mPES fibers

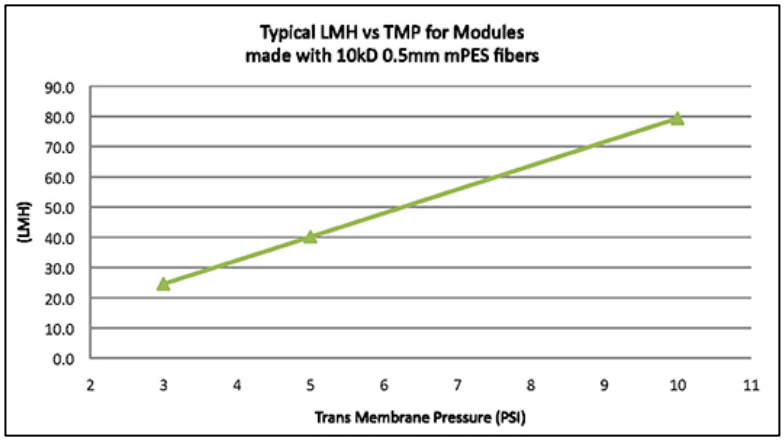
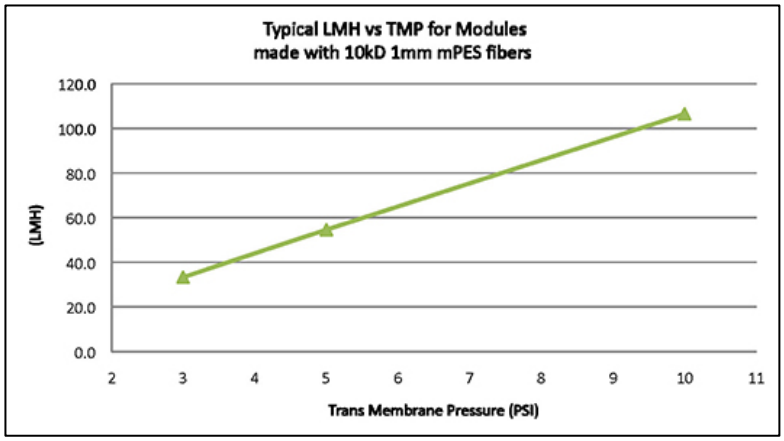


Figure 11. Typical LMH versus TMP for modules made with 10 kD 1 mm mPES fibers



3.5 Normalized water permeability

Normalized Water Permeability (NWP) is the water flux (LMH) divided by TMP. NWP can be determined by taking your actual measured LMH and dividing it by the TMP. The minimum NWP requirements for the various mPES MWCO fibers are listed below.

Table 3. Minimum normalized water permeability requirement for mPES fibers

0.5 mm fiber		1 mm fiber	
Description of Spectrum® mPES Hollow Fiber Membrane	NWP (L/m²H/psi)	Description of Spectrum® mPES Hollow Fiber Membrane	NWP (L/m²H/psi)
3 kD, 0.5 mm	≥ 2.5	3 kD, 1.0 mm	≥ 2.5
5 kD, 0.5 mm	≥ 3.0	5 kD, 1.0 mm	≥ 3.0
10 kD, 0.5 mm	≥ 5.0	10 kD, 1.0 mm	≥ 5.0
30 kD, 0.5 mm	≥ 20	30 kD, 1.0 mm	≥ 20
50 kD, 0.5 mm	≥ 30	50 kD, 1.0 mm	≥ 30
70 kD, 0.5 mm	≥ 50	70 kD, 1.0 mm	≥ 40
100 kD, 0.5 mm	≥ 80	100 kD, 1.0 mm	≥ 60
300 kD, 0.5 mm	≥ 75	300 kD, 1.0 mm	≥ 100
500 kD, 0.5 mm	≥ 100	500 kD, 1.0 mm	≥ 100

3.5.1 Increasing the surface area of a hollow fiber filtration system

There are three ways to increase surface area for hollow fiber filtration:

1. Increase the number of fibers.
2. Increase the length of the fibers.
3. A change in the combination of the number of fibers and the length of fibers for direct scale-up, the number of fibers is increased. This is done by selecting a module from a larger product family.

3.5.2 Test Articles

The following table (Table 4) lists the 28 different modules that were evaluated.

Table 4. Test articles: 28 different evaluation modules

Fiber type	Product family	Effective length (cm)	Module # / Lot #
100 kD 0.5 mm mPES	MicroKros	20	C02-E100-05-N Lot 3259678-06/12-18
100 kD 0.5 mm mPES	MidiKros TC	20	T02-E100-05-N Lot 3256433-01/12-03
100 kD 0.5 mm mPES	MidiKros TC	41.5	T04-E100-05-N Lot 3260655-08/12-01
100 kD 0.5 mm mPES	MidiKros TC	65	T06-E100-05-N Lot 3254005-11/11-03
100 kD 0.5 mm mPES	MiniKros Sampler	20	S02-E100-05-N Lot 3260646-08/12-01
100 kD 0.5 mm mPES	MiniKros	20	N02-E100-05-N Lot 3260647-08/12-01
100 kD 0.5 mm mPES	KrosFlo®	20	K02-E100-05-N Lot 3260648-08/12-01
100 kD 1 mm mPES	MicroKros	20	C02-E100-10-N Lot 3257312-02/12-01
100 kD 1 mm mPES	MidiKros TC	20	T02-E100-10-N Lot 3259659-06/12-01
100 kD 1 mm mPES	MidiKros TC	41.5	T04-E100-10-N Lot 3254588-11/11-02
100 kD 1 mm mPES	MidiKros TC	65	T06-E100-10-N Lot 3254589-11/11-02
100 kD 1 mm mPES	MiniKros Sampler	20	S02-E100-10-N Lot 3254606-11/11-01
100 kD 1 mm mPES	MiniKros	20	N02-E100-10-N Lot 3254609-11/11-02
100 kD 1 mm mPES	KrosFlo®	20	K02-E100-10-N Lot 3260650-08/12-01
10 kD 0.5 mm mPES	MicroKros	20	C02-E010-05-N Lot 3255689-11/11-05
10 kD 0.5 mm mPES	MidiKros	20	T02-E010-05-N Lot 3256429-01/12-11
10 kD 0.5 mm mPES	MidiKros TC	41.5	T04-E010-05-N Lot 3252875-10/12-01
10 kD 0.5 mm mPES	MidiKros TC	65	T06-E010-05-N Lot 3260651-08/12-01
10 kD 0.5 mm mPES	MiniKros Sampler	20	S02-E010-05-N Lot 3260643-08/12-01
10 kD 0.5 mm mPES	MiniKros	20	N02-E010-05-N Lot 3260644-08/12-01
10 kD 0.5 mm mPES	KrosFlo®	20	K02-E010-05-N Lot 3260645-08/12-01
10 kD 1 mm mPES	MicroKros	20	C02-E010-10-N Lot 3262866-10/12-01
10 kD 1 mm mPES	MidiKros TC	20	T02-E010-10-N Lot 3262867-10/12-01
10 kD 1 mm mPES	MidiKros TC	41.5	T04-E010-10-N Lot 3262876-10/12-01
10 kD 1 mm mPES	MidiKros TC	65	T06-E010-10-N Lot 3262878-10/12-01
10 kD 1 mm mPES	MiniKros Sampler	20	S02-E010-10-N Lot 3262868-10/12-01
10 kD 1 mm mPES	MiniKros	20	N02-E010-10-N Lot 3262869-10/12-01
10 kD 1 mm mPES	KrosFlo®	20	K02-E010-10-N Lot 3262870-10/12-01

The purpose of this test is to document the scalability of 5 different 20 cm length mPES TFF module families: C02, T02, S02, N02, and K02.

This test also documents the scalability of 20, 41.5 and 65 cm length of mPES TFF MidiKros modules.

3.5.3 Water flux of 20 cm length modules

The test module was flush with DI water at 3 - 5 psi TMP and collected a permeate volume of 2 ml/cm^2 of the test module surface area. Retentate and permeate test fluids were not re-circulated. Conducted water flux on the module at 3, 5 and 10 TMP and recorded the results.

Integrity tested the module for air diffusion and recorded the result.

3.5.4 Water flux and pressure drop of 20, 41.5 and 65 cm length modules

The test module was flushed with DI water at a TMP of 3 - 5 psi and a permeate volume of 2ml/cm^2 of the test module surface area was collected. Retentate and permeate test fluids were not re-circulated. Both permeate ports of the module were capped. Appropriate tubing was connected, and DI water circulated thru the end ports of the module at 1000, 1500, 2000, 4000, 6000, 8000, 10000, and 15000 inverse seconds shear. No back pressure was applied at the retentate tubing. The corresponding pressures were recorded at each of the running shear rates. Water flux was measured on the module at 3, 5 and 10 psi TMP and the results were recorded. The steps were repeated using 25% glycerin in place of water. The module was integrity tested for air diffusion and the result was recorded.

3.5.5 Test results LMH verses TMP

The following four charts show the average measured water flux (LMH) for each of the modules made with a specific fiber type. For example, Figure 12 shows the average water flux, along with the standard deviation (SD) vs TMP for all seven modules made from the 100 kD 0.5 mm mPES listed above in Table 4. Variations in measured flux between modules can be attributed to:

1. Tolerances in the water flux of the fiber.
2. Tolerances in the fiber's dimensions.
3. Differences in tubing and fitting configurations used for the different module sizes.

Figure 12. Typical LMH versus TMP for modules made with 100 kD 0.5 mm mPES fibers

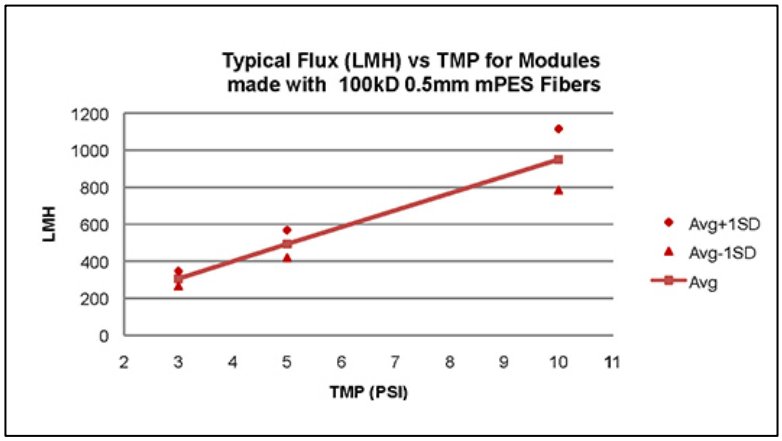


Figure 13. Typical LMH versus TMP for modules made with 100 kD 1 mm mPES fibers

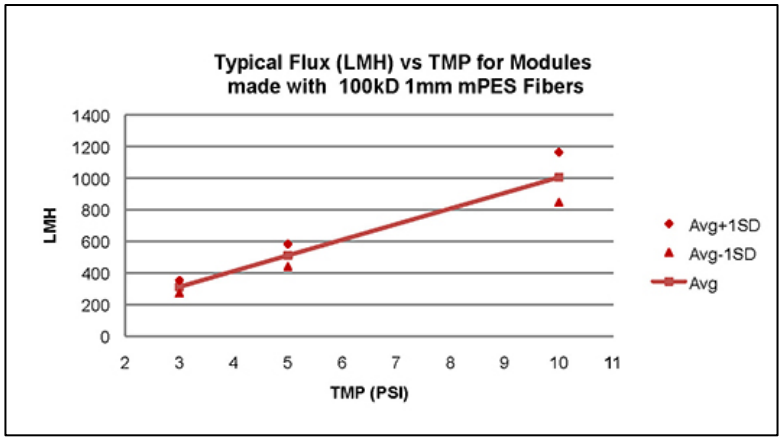


Figure 14. Typical LMH versus TMP for modules made with 10 kD 0.5 mm mPES fibers

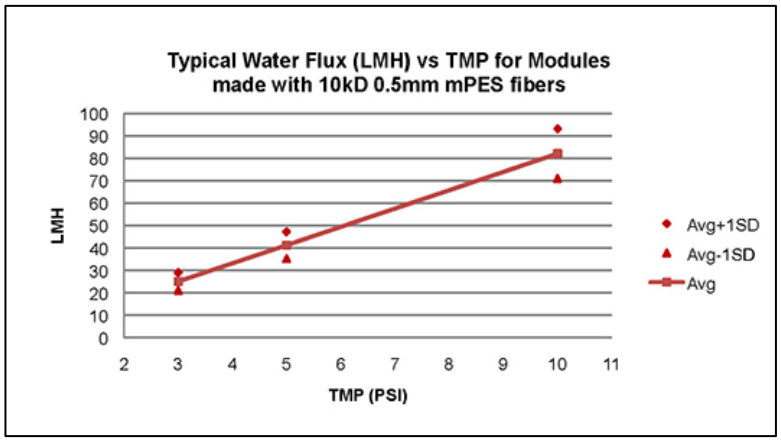
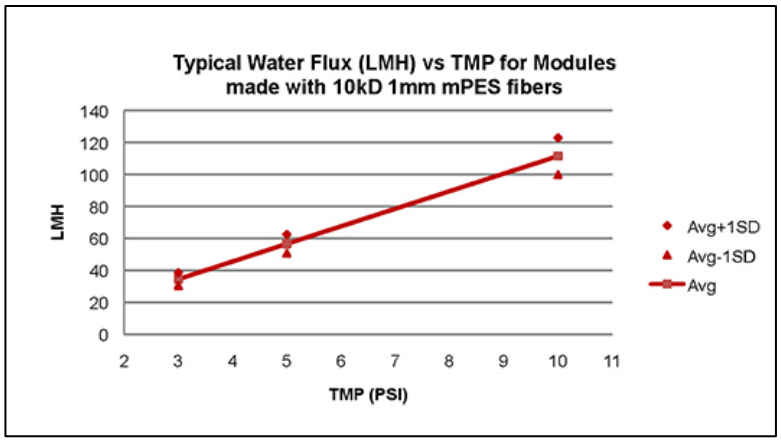


Figure 15. Typical LMH versus TMP for modules made with 10 kD 1 mm mPES fibers



3.5.6 NWP scalability

These four charts show the average normalized water permeability (NWP) for each of the modules made with a specific fiber type. For example, Figure 16 shows the NWP, along with the standard deviation (SD) vs TMP for all seven modules made from the 100 kD 0.5 mm mPES listed above in Table 4. Referring to Figure 16, the average NWP for the 0.5 mm 100 kD modules was around 99. This is about 23% higher than the minimum ≥ 80 listed for this fiber in Table 2. Variations between modules can be attributed to:

1. Tolerances in the water flux of the fiber.
2. Tolerances in the fiber's dimensions.
3. Differences in tubing and fitting configurations used for the different module sizes.

Figure 16. Average NWP versus TMP for modules made with 100 kD 0.5 mm mPES fibers

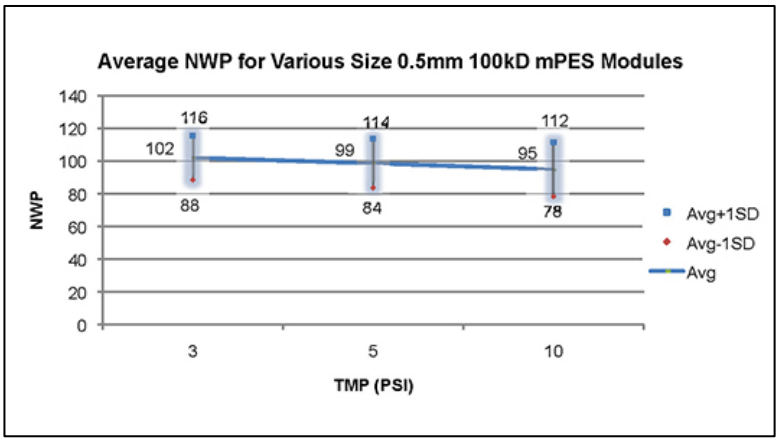


Figure 17. Average NWP versus TMP for modules made with 100 kD 1 mm mPES fiber

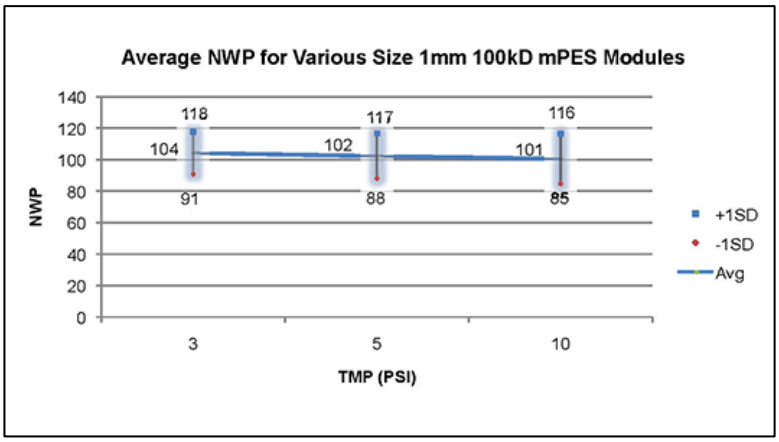


Figure 18. Average NWP versus TMP for modules made with 10 kD 0.5 mm mPES fibers

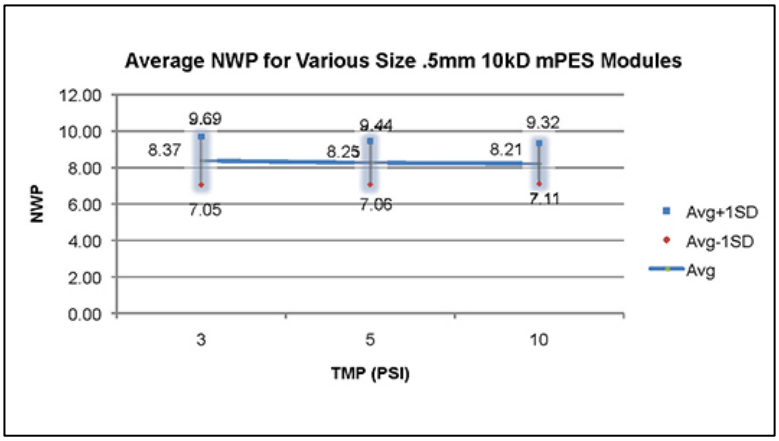
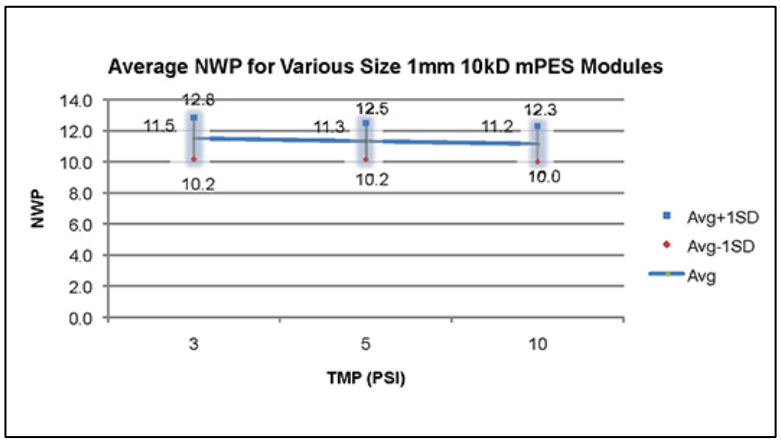


Figure 19. Typical NWP versus TMP for modules made with 10 kD 1 mm mPES fibers



3.5.7 Process lengths and pressure drop

Repligen has three standard active product lengths include 20, 41.5, and 65 cm. If you are scaling up by increasing the fiber length, then you must use the same recirculation rate, but a different flux rate result.

As fiber length increases, the pressure drop also increases for a given recirculation rate. The following four charts show the measured pressure drops for each of 3 active length modules while running water and a 25% glycerin solution. It should be noted that a larger pressure drop will occur for a 0.5 mm ID fiber than a 1 mm ID fiber. For example, Figure 20 shows that for a given shear rate the pressure drop will increase as the length of the module increased. Variations between modules do occur and are mostly attributed to:

1. Tolerances in the fiber's dimensions.
2. Variations in the tubing and fitting configurations used for the different module sizes.

Figure 20. Pressure drop versus shear 1 mm MidiKros TC (water)

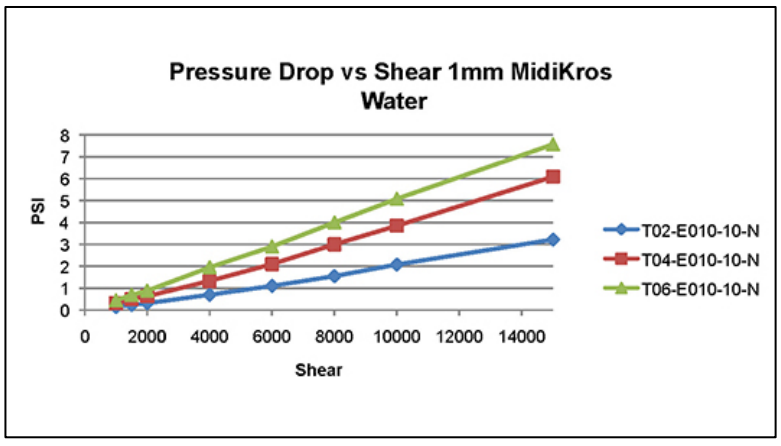


Figure 21. Pressure drop versus shear 1 mm MidiKros TC 25% glycerin solution (15cP)

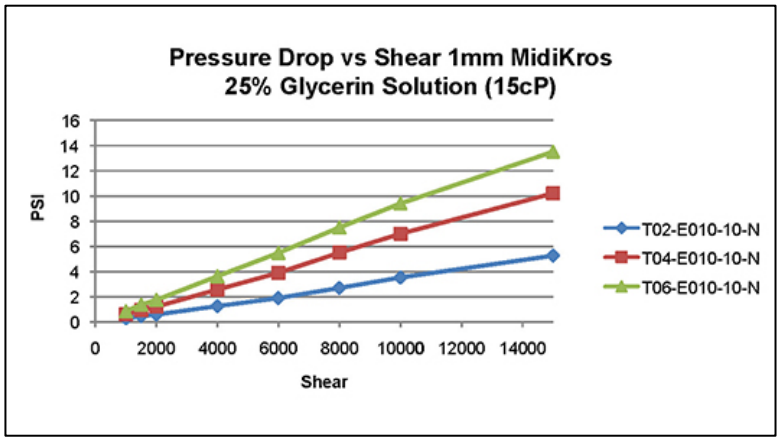


Figure 22. Pressure drop versus shear 0.5 mm MidiKros TC (water)

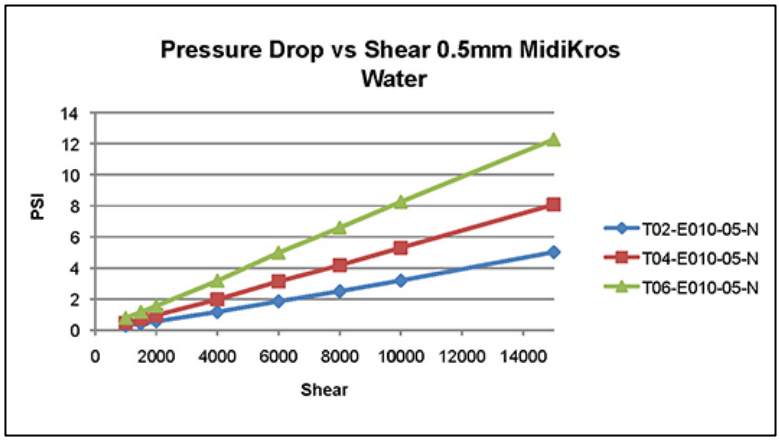
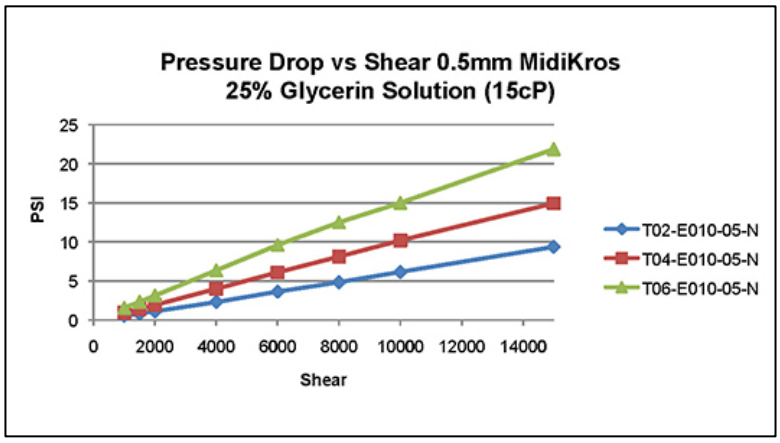


Figure 23. Pressure drop versus shear 0.5 mm MidiKros TC 25% glycerin solution (15cP)



3.5.8 Conclusions

Spectrum® Hollow Fiber TFF Modules from Repligen are scalable. Specifically, Figures 16 - 19 demonstrate scalability by showing that the various size modules have a constant average NWP for the different TMP tested. Performance variations do occur between modules. Module variations can be attributed to:

1. Tolerances in the water flux of the fiber.
2. Tolerances in the fiber's dimensions.
3. Differences in tubing and fitting configurations used for the different module sizes.

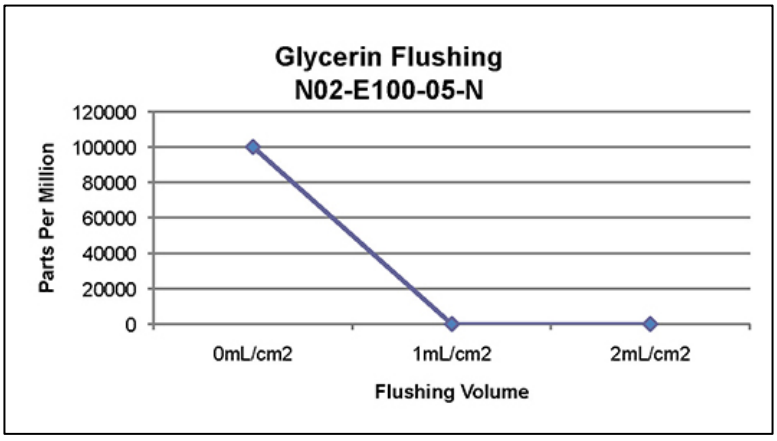
Higher shear rate flow increases pressure drops both across the module and within the tubing and fittings. As the effective length of the fiber length increases, the pressure drop also increases for a given shear rate. For a given shear rate and a given effective length a larger pressure drop occurs for a 0.5 mm ID fiber than for a 1 mm ID fiber. As the viscosity of the test fluid increases – the pressure drop across the module will also increase.

4. Standard procedures for use

4.1 Preparing a new module for use

This regulatory support file will address single-use only. Sanitization prior to use will be included but post use cleaning and storage will not be included.

Figure 24. Glycerin flushing



4.1.1 Flushing the storage solution from the filter module

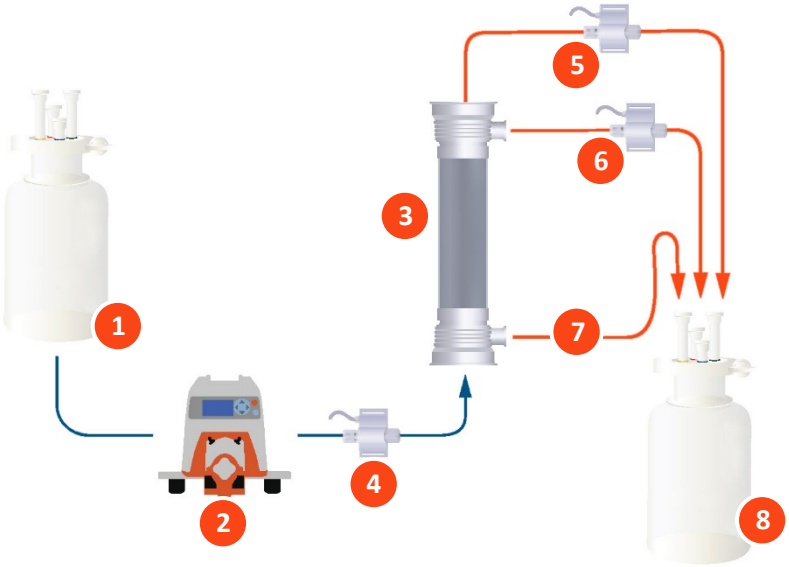
New Spectrum® mPES Hollow Fiber Filter Modules are flushed with a 15 % glycerin solution and dried before bagging. Before using a new filter module, you must flush the storage solution from the filter module and condition it for use in the new process following these steps:

1. Install the filter module in the system (Figure 25).
2. Fully close the retentate valves and fully open the permeate valve.
3. Fill feed reservoir with deionized water, water for injection, or buffer.
4. Ramp the feed pump up to 50% of the processing feed rate to flush.
5. Flushing volume should be 2.0 mL/cm^2 of membrane area.
6. Drain the system and permeate lines completely.
7. Flood the module with buffer.
8. Isolate the buffer in the filter module by closing the retentate and permeate valves.

Note: *Opening the bottom and top permeate valves facilitates complete draining of the module and permeate lines.*

Note: *Flushing 2.0 mL/cm² membrane area across the membrane will reduce glycerin to near undetectable levels.*

Figure 25. Typical system Set-up for flushing storage solution from a new filter module



1. Feed reservoir
2. Pump
3. Filter module
4. Pressure transducer
5. Retentate transducer
6. Permeate transducer 1
7. Permeate 2
8. Waste reservoir

4.1.2 Conditioning the filter module before use

Before you process your product, check the pH or conductivity of the permeate stream to confirm the filter mirrors the operational conditions of the upcoming feed stream. Then flood the feed side of the filter and permeate side of the fiber with buffering solution prior to starting the process.

Note: *The reason for the conditioning of the hollow fiber module is to ensure the membrane pH and salt condition are similar to the starting processing material to minimize fouling and loss of product.*

4.1.3 Filter module integrity testing

All hollow fiber filter modules are integrity tested prior to shipment. However, Repligen strongly recommends an integrity test be performed prior to use. The following pressure hold test is recommended to verify the integrity of a wetted module:

1. Fully wet the module. Then close the permeate side of the wetted module and system.
2. Drain the feed and retentate loop but keep the permeate flooded. Close the retentate and use air or nitrogen gas to pressurize the module and system up to 5 psig, then close the feed.
3. If pressure drops greater than 0.5 psi/min/(m^2 of membrane area), then the system connections may be leaking. Tighten all connections, pressurize to 5 psig and check for pressure drop again. A pressure decay is to be expected. Pressurize back up to 5 psig before continuing.
4. After assuring system integrity, open the permeate and observe pressure decay as excess water or buffer is passed through the fibers.

5. Biocompatibility

5.1 Introduction

Safety testing is a key factor for determining the appropriateness for use of Repligen membrane filter products in medical, pharmaceutical and life science applications. The materials of construction with direct process fluid contact are independently tested to assure that requirements for USP Class VI are met or are certified as such by Repligen suppliers based on suitable equivalent testing.

While no specific testing requirements have been stipulated by the regulatory bodies, USP Class VI is a minimum standard adopted throughout the pharmaceutical filtration industry. Repligen ensures that all fluid path materials of construction for products sold into pharmaceutical, medical device, or life science applications are compliant with testing required for USP of tests required for USP Class VI classification.

When this testing is sponsored by Repligen or one of our business partners, it is conducted by a qualified independent laboratory in accordance with guidelines set forth by the United States Pharmacopoeia (USP) and/or in accordance with equivalent ISO standards or protocols for biological safety. Certifications of suppliers having performed this testing are verified through additional correspondence, as well as data review when appropriate, to assure that the supplier information has equivalent integrity.

5.2 Background for USP testing

All in vivo biological reactivity tests, also known as the Plastics Class Tests, are defined by the United States Pharmacopoeia (USP). Pyrogen testing is also defined by the USP to identify the risk of fever as a direct result of injection of solution, although bacterial endotoxin test protocols are becoming more widely adopted. Since European Pharmacopoeia protocols defined by ISO 10993, Biological Evaluation of Medical Devices differ slightly from USP test protocols, the U.S. Food and Drug Administration (FDA) is working to harmonize these requirements in regard to medical device approvals. A comprehensive set of currently prescribed USP biological reactivity tests may include:

- Cytotoxicity
- Sensitization
- Irritation
- Systemic toxicity
- Chronic toxicity
- Subchronic toxicity
- Intracutaneous toxicity
- Implantation
- Hemocompatibility
- Carcinogenicity

Repligen can provide specific validation testing support in accordance with any of the above listed test protocols for custom applications and OEM products. Generally, representative assemblies from the most popular families of Repligen products have been tested and successfully passed all biocompatibility tests recommended to substantiate suitability for life science applications.

5.2.1 Standard USP Class VI test summary

The United States Pharmacopoeia (USP) Biological Reactivity describes three in vivo tests:

1. Systemic toxicity testing
2. Intracutaneous toxicity testing
3. Implantation test

These tests determine the biological response of animals to elastomeric, plastics and other polymeric material with direct or indirect patient contact, or by injection of the specific extracts prepared from the material under test. The USP classification is based upon the biological responses to a series of tests for which extracts, materials and methods of administration are specified. The toxicity testing procedures are based upon the use of a variety of extracts, at specified temperatures and times. Repligen requires that all fluid path materials meet USP Class VI biosafety requirements.

5.2.1.1 Extractables of pre- and post-Gamma-irradiated TFF

Extractables from P-D1-100E-100-01N hollow fiber modules (surface area of 115 cm^2) were analyzed before and after gamma irradiation. The study indicated that the total volatile organic extractables and total metal extractables of these irradiated modules did not increase over those of the non-irradiated modules when exposed to water or 0.9 % saline for 24 hours. The study is described below.

5.2.1.2 Test method and equipment: modules

Production-equivalent Spectrum® Hollow Fiber TFF Modules manufactured with modified polyethersulfone (mPES) fibers were selected for this study. Two were irradiated (Table 5).

Table 5. TFF modules that were evaluated in the study

Module	Lot #/SN	Sterilization status	Test fluid
P-D1-100E-100-01N	Lot 3242106-10/09-05	Non-Irradiated	Water
P-D1-100E-100-01N	Lot 3242106-10/09-08	Gamma-Irradiated	Water
P-D1-100E-100-01N	Lot 3242106-10/09-06	Non-Irradiated	0.9 % saline
P-D1-100E-100-01N	Lot 3242106-10/09-07	Gamma-Irradiated	0.9 % saline

5.2.2 Equipment and materials

The following list identifies the study equipment and materials:

1. Platinum-cured silicone tubing No. 73 (721-01758-001, Lot No. 9K121), 1 54 inches for each test sample (inlet = 40 inches, outlet = 10 inches, and permeate = 4 inches).
2. The test fluids include reverse osmosis (RO) water and 0.9% saline.
3. Containers used to store samples include 2- L glass beaker (cleaned using standard chemical ware procedures prior to testing) and a 250 ml centrifuge tube (polypropylene, sterile, Corning part No. 430776).
4. Watson Marlow 323E peristaltic pump.

5.2.3 Method description

The test method included having Repligen approved sub-processor, Sterigenics®, gamma-irradiate the production-equivalent TFF modules on December 12, 2009. The dosage was 25 k - 40 kGy.

Prior to each test, a total of 2 mL of fluid per cm^2 of surface area was used to wet and rinse the module. The wetting fluid was not recirculated. Each test TFF module was secured to a test stand and the inlet tubing, outlet tubing, and permeate tubing were placed in a 250 ml centrifuge tube. The peristaltic pump was placed between the centrifuge tube and the module inlet and 150 ml of test fluid was introduced to the system and circulated for 24 hours. At the 24-hour mark, the centrifuge tube with the test fluid was removed from the system, labeled and sent to an independent test lab, Exova, for extractable testing. Exova analyzed the fluid samples for volatile organics extractables by gas chromatography/mass spectrometry and total metal extractables by inductively coupled plasma/mass spectrometry.

5.2.3.1 Extractable test results—Volatile organic

Table 6 presents the total volatile organic extractables removed from the test samples after exposure to the test fluids.

Table 6. Extractable results—Volatile organic extractables

TFF module, test solution, and extractables in PPM (mg/L)		
	3242106-10/09-05 Non-Irradiated	3242106-10/09-08 Gamma-Irradiate
Compound	**Water**	**Water**
Isopropanol	21	16
Acetone mm	1.2	1.3
Methyl formate	0.65	Non detected
Methyl ethyl ketone	0.031	0.006
Tetrahydrofuran	0.001	0.003
Methylene chloride	Non detected	0.005
Trimethylsilanol	0.004	0.002
Total	22.886	17.316

TFF module, test solution, and extractables in PPM (mg/L)		
	3242106-10/09-06 Non-Irradiated	3242106-10/09-07 Gamma-Irradiated
Compound	**0.9 % saline**	**0.9 % saline**
Isopropanol	39	15
Acetone mm	1.8	1.3
Methyl formate	0.93	0.49
Methyl ethyl ketone	0.007	0.002
Tetrahydrofuran	Non detected	Non detected
Methylene chloride	Non detected	Non detected
Trimethylsilanol	0.002	0.002
Total	41.739	16.794

5.2.3.2 Extractable test results—Total metals

Table 7 presents the total volatile organic extractables removed from the test samples after exposure to the test fluids.

Table 7. Extractable results—Total metal extractables

TFF module, test solution, and extractables in PPM (mg/L)			
3242106-10/09-05 Non-irradiated water		3242106-10/09-08 Gamma-irradiated water	
Metal	PPM	Metal	PPM
Boron	0.042	Boron	Not detected[1]
Bromine	Not detected	Bromine	Not detected
Copper	0.003	Copper	Not detected
Magnesium	Not detected	Magnesium	Not detected
Sodium	Not detected	Sodium	Not detected
Strontium	Not detected	Strontium	Not detected
Total	0.045		0

TFF module, test solution, and extractables in PPM (mg/L)			
3242106-10/09-06 Non-Irradiated saline		3242106-10/09-07 Gamma-Irradiated saline	
Metal	PPM	Metal	PPM
Boron	Not detected	Boron	Not detected
Bromine	0.2	Bromine	0.18
Copper	0.003	Copper	Not detected
Magnesium	Not detected	Magnesium	0.048
Sodium	3180	Sodium	3170
Strontium	0.007	Strontium	0.009
Total	3180		3170

5.2.4 Bioburden

The bioburden level of the modules assembled with Repligen mPES fibers must be < 1000 Colony Forming Units (CFU) per modules per the VDmax25 sterilization requirements.

5.2.5 Pyrogenicity

Production processes are monitored to minimize sources of endotoxins. Product line is not claimed to be endotoxin free. Specific claims may be made available for special circumstances.

5.2.6 Conclusions

This information is made available to our customers to assist with their independent determination regarding what, if any, impact the extractables reported may have on the intended purpose of our Spectrum® Hollow Fiber Filter Modules.

5.3 Gamma sterilization validation

5.3.1 Introduction

Repligen implemented and validated a sterilization process for products manufactured at Rancho Dominguez, California. This section provides an overview of the sterilization process, references methods employed to ensure sterility, and summarizes the validation work completed to ensure a high standard of quality for our sterile products.

5.3.2 Method

Repligen develops sterile products in accordance with the VDmax method, ANSI/AAMI/ISO 11137-1 and ANSI/AAMI/ISO 11137-2. This method—developed for health care products—is approved for use by the FDA. The assurance of sterility for any product can only be objectively defined as a function of probability. The sterility assurance level (SAL) is defined as the probability of any given unit being non-sterile after exposure to a validated sterilization process using a routine dose. The VDmax method substantiates the use of 25 kilograys (kGy) as a routine dose. This method uses a verification dose of a SAL of 10^{-1} to attain a SAL of 10^{-6} and may only be applied to products with average bioburden below 1000 CFUs.

The application of this method is not limited by batch size or production frequency. The method employs as its basis the standard distribution of resistances (SDR) and embodies the following three principles:

1. Existence of a direct link between the outcome of the verification 1 dose experiment and the attainment of a SAL of 10^{-6} at a sterilization dose of 25 kGy of gamma-irradiation.
2. Possession of a level of conservativeness at least equal to that of the SDR.
3. For a given bioburden, use a maximum verification dose (VDmax) commensurate with substantiation of 25 kGy.

The VDmax studies were performed by Sterigenics® on Repligen module, bag, and tubing set ProConnex® products. The test samples consisted of 48 finished, routine product samples submitted in standard, final packaging. These units were pulled from three independent lots after completing all steps of production except sterilization. The sample product submitted for validation testing represents the worst-case configuration that can be assembled based on average total bioburden.

5.3.3 Validating the sterilization process, sterile barrier, and packaging

5.3.3.1 Product and process validation

A comprehensive assessment of sterility includes validation elements for both the product and the processes involved in their manufacture and delivery. The results for Repligen sterility validation studies are detailed below.

5.3.3.2 VDmax sterilization process validation

Repligen has validated that the minimum gamma-irradiation sterilization exposure for product assembled and packaged at Repligen, Rancho Dominguez, California, will achieve a Sterility Assurance Level (SAL) of 10^{-6} in accordance with ANSI/AAMI/ISO 11137-2: Sterilization of Health Care Products – Radiation – Establishing the sterilization dose – Method VDmax25 when sterilization processing is provided by Sterigenics®, Corona, California, and sterilization verification testing is

performed by SteriPro® Consulting, Itasca, Illinois, in accordance with the VDmax method described in ANSI/AAMI/ISO 11137-2.

SteriPro® Labs, division of Sterigenics®, commenced validation testing on the ProConnex® Flow Path on September 24, 2008 to substantiate a 25-kGy dose and validate the effectiveness of gamma-radiation for sterilization of the ProConnex® Flow Path. The validation was based on the practices recommended by ANSI/AAMI/ISO 11137-2. A protocol for substantiation of 25 kGy was utilized to verify that a minimum sterilization dose of 25 kGy will provide a Sterility Assurance Level (SAL) of 10^{-6} or no more than one non-sterile unit for each one million units sterilized.

The pre-sterilization bioburden level was determined for all three independent lots in this study. A bioburden recovery factor was determined for the product; the factor was used to adjust each bioburden result. The verification dose was determined utilizing (Table 9) ANSI/AAMI/ISO 11137-2.

This study supports the release of products for which exposure to the minimum dose of 25 kGy is demonstrated by the use of calibrated dosimeters. Statistical verification was successfully completed since not more than one positive sterility test culture was observed after irradiation at the calculated verification dose. The average bioburden was less than 1,000 organisms, statistical verification of the bioburden resistance was accepted, and therefore the sterilization dose of 25 kGy is the 10^{-6} SAL dose for the ProConnex® Flow Path (Table 8).

Table 8. Summary of Sterigenics® final report No. 797080474-F

Sterilizing dose	25 kGy
Sterility assurance level (SAL)	10^{-6}
Total average bioburden	< 300 CFU/device
Verification dose	8.6 kGy

5.3.3.3 Sterile barrier validation

Studies were conducted to validate the viability of Repligen equipment and processes in creating a reliable sterile barrier. These studies validated that Repligen sterile package sealing operation for the ProConnex® product line meets the requirements of ISO 11607-1 and 11607-2 "Packaging for terminally sterilized medical devices" as well as predetermined acceptance criteria for seal strength and visual characteristics as defined in Repligen procedure 300-12462-000, Finished Goods/Final Package Release.

After being exposed to the maximum specified irradiation dose (40 kGy +/- 10%), the burst strength, seal peel strength and dye migration testing was performed on the ProConnex® sterile barrier. All tests met all acceptance criteria for the "ProConnex® Package Seal Integrity Testing" section of the ProConnex® (Top Level) Sterilization Validation Protocol (345-12320-000)

- Burst strength testing was performed in accordance to ASTM F1140-00
- Seal peel strength testing was performed in accordance to ASTM F88-00
- Dye migration testing was performed in accordance to ASTM F1929-98 (2004)

5.3.3.4 Shipping and packaging validation

A study was conducted to validate the ability of the shipping/packaging configurations to provide adequate protection for the shipment of sterile product to the customers without delivering defective product. The study concluded that packaging and product configurations were subjected to typical hazards encountered in the shipping and distribution environment as outlined in the ISTA 3A (2008) test protocol. Packaging and product integrity were maintained for all applicable test conditions.

5.3.3.5 Ongoing sterility process monitoring

To substantiate the continued validity of 25-kGy dose as a 10^{-6} SAL dose, quarterly dose audits (QDA) are performed according to an established schedule, as specified in ANSI/AAMI/ISO 11137-2. QDA's are done on products that represent current worst-case configurations, based on average total bioburden.

5.3.4 References

Many regulatory, guidance, and report documents support the validation of the gamma radiation sterilization process (Table 9).

Table 9. References supporting the validation of Gamma-radiation sterilization

ANSI/AAMI/ISO 11137-1:2006	Sterilization of health care products – Radiation –Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
ANSI/AAMI/ISO 11137-2:2006	Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose
ISO 11607-1:2006	Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems
ISO 11607-2:2006	Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes
ASTM F-1140-00	Standard Test Methods for Internal Pressurization Failure Resistance of Unrestrained Packages for Medical Applications
ASTM F-88-00	Standard Test Method for Seal Strength of Flexible Barrier Materials
ASTM F-1929-98 (2004)	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration
AAMI TIR 17:1997	Radiation sterilization material qualification
345-12320-000	ProConnex® (Top Level) Sterilization Validation Protocol
346-12320-001	ProConnex® (Top Level) Sterilization Validation Test Report
346-12320-000	Packaging Seal Parameter Optimization Report for the ProConnex® Product Line
345-12499-000	ProConnex® Shipping Validation Protocol
346-12499-000	ProConnex® Shipping Validation Report
361-12517-000	ProConnex® VDmax Sterilization Validation Protocol
797080307-P	SteriPro® Consulting Test Protocol VD-Max25 Radiation Validation for Module, Bag
797080474-F	SteriPro® Consulting Final Report VD-Max25 Radiation Validation for Module, Bag
346-12320-000	Packaging Seal Parameter Optimization Report for the ProConnex® Product Line
346-12320-002	SteriPro® Package Integrity Testing for Irradiated Samples Report
300-12462-000	Finished Goods/Final Package Release SOP

6. Chemical compatibility

6.1 Chemical compatibility list

Chemical solutions that are not compatible with the materials of construction of mPES hollow fiber filter modules can damage the filter module or significantly decrease filtration performance. Use the chemical compatibility table as a guide (Table 10). Since variations in temperature, concentrations, durations of exposure, and other factors may affect the performance of the filter module, confirm the compatibility of your process solutions and cleaning fluids through trials.

Table 10. Chemical compatibility list: Spectrum® mPES Hollow Fiber Filter Modules

Chemical	Compatible	Chemical	Compatible
Acetic acid (diluted-5%)	R	1,4 Dioxane	L
Acetic acid (medium concentration-25%)	L	Ethers	NR
Acetic acid (glacial)	NR	Ethyl acetate	NR
Acetone	NR	Ethyl alcohol	R
Acetonitrile	NR	Ethyl alcohol (15%)	R
Alconox (1%)	R	Ethyl alcohol (95%)	L
Ammonium hydroxide (diluted)	R	Ethylene dichloride	NR
Ammonium hydroxide (medium concentration)	R	Ethylene glycol	R
Amyl acetate	NR	Ethylene oxide	R
Amyl alcohol	L	Formaldehyde (2%)	R
Aniline	NR	Formaldehyde (30%)	R
Benzene	NR	Formic acid (25%)	R
Benzyl alcohol	NR	Formic acid (50%)	R
Boric acid	R	Freon®	R
Brine	R	Gasoline	L
Bromoform	NR	Glycerin / Glycerol	R
Butyl acetate	NR	Hydrochloric acid (diluted-5%)	R
Butyl alcohol	R	Hydrochloric acid (concentrated-25%)	R
Butyl cellosolve	NR	Hydrochloric acid (concentratuon-37%)	R
Butyraldehyde	NR	Hydrofluoric acid (25%)	L
Carbon tetrachloride	NR	Hydrogen peroxide (30%)	L
Cellosolve	R	Iodine solutions	NR
Chloroacetic acid	NR	Isobutyl alcohol	R
Chloroform	NR	Isopropanol	R
Chromic acid	NR	Isopropyl acetate	NR
Citric acid (2%)	R	Isopropyl alcohol / Isopropanol	R
Cresol	NR	Isopropyl ether	R
Cyclohexane	L	Jet fuel 640A	R
Cyclohexanone	NR	Kerosene	R
Diacetone alcohol	NR	Lactic acid	R
Dichloromethane	L	Methyl acetate	NR
Dimethyl formamide	NR	Methyl alcohol	R
Dimethylsulfoxide (50%)	L	Methyl alcohol (98%)	L

Table 11. Chemical compatibility list: Spectrum® mPES Hollow Fiber Filter Modules - continued

Chemical	Compatible	Chemical	Compatible
Methyl cellosolve	R	Phosphoric acid (25%)	L
Methyl chloride	NR	Potassium hydroxide (1N)	R
Methyl ethyl ketone	NR	Potassium hydroxide (50%)	R
Methyl formate	NR	Propanol	R
Methyl isobutyl ketone	NR	Pyridine	NR
Methylene chloride	NR	Silicone oil	R
N-methyl-2-pyrrolidone	NR	Sodium hydroxide (0.1N)	R
Mineral spirits	R	Sodium hydroxide (diluted-5%)	R
Monochlorobenzene	NR	Sodium hydroxide (25%)	R
NALCON 7647 (< 1%)	R	Sodium hydroxide (concentration-50%)	R
NALCON 7678 (< 1%)	R	Sodium hydroxide (concentrated)	R
NALCON 7330 (< 1%)	R	Sodium hypochlorite	R
Nitric acid (diluted-5%)	R	Sulfuric acid (diluted-5%)	R
Nitric acid (medium concentration-25%)	R	Sulfuric acid (medium concentration -25%)	R
Nitric acid (6N)	L	Sulfuric acid (6N)	R
Nitric acid (concentration-70%)	NR	Sulfuric acid (concentrated)	L
Nitric acid (concentrated)	L	Tetrahydrofuran	NR
Nitrobenzene	NR	Toluene	NR
Nitropropane	NR	Trichloroacetic acid (25%)	R
Oils, mineral	R	Trichlorobenzene	NR
Pentane	R	Trichloroethane	L
Peracetic acid (0.1N)	R	Trichloroethylene	R
Perchloric acid (25%)	NR	Triethylamine	NR
Perchloroethylene	NR	Turpentine	NR
Petroleum based oils	R	Urea	R
Petroleum ether	R	Urea (6N)	NR
Phenol (0.5%)	R	Water	R
Phenol (10%)	L	Xylene	NR

(R = recommended, L = limited exposure, NR = not recommended, U = unknown)

7. Packaging, storage and labeling

7.1 Packaging

New unsterilized filter modules are flushed with a 15% glycerin solution, dried, double bagged, and placed in a box or shipping tube. New sterilized filter modules are flushed with a 15% glycerin solution, dried, and double bagged. An Irradiation sticker is place on the inner bag. The bagged product is then placed in the box or shipping tube and sterilized. Unsterilized and sterilized filter modules are double-bagged and boxed. The inner bag of sterilized filter modules is considered the sterile barrier.

7.2 Shipping

Repligen has conducted shipping tests on several size modules including its worst case irradiated KrosFlo® MAX Filter Modules and ProConnex® Flow Paths. This testing involves exposing packaged modules to the ISTA 3A general simulation performance test procedure Packaged-Products

for Parcel Delivery System Shipment for 70 kg (150 lb) or Less. After being exposed to ISTA 3A general simulation performance test conditions, by an independent test lab, the package is returned to Repligen for evaluation.

- The outer package must have no unusual external physical damage
- The sterile barrier must remain undamaged
- The module itself must be undamaged and pass the standard integrity test
- Packaged modules are typically placed in larger over pack cartons for extra protection when shipped

7.3 Storage and shelf life

Store new filter modules in the original packaging in a cool, dry, storage area at room temperature, away from direct sunlight. Non-sterilized filter modules have a shelf life of 5 years from the data of manufacture. Irradiated products have a shelf life of 3 years from the data of manufacture.

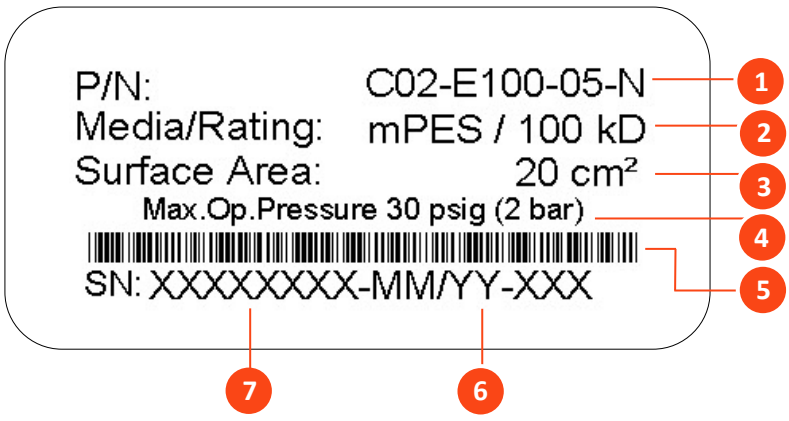
7.4 Labeling and product identification

7.4.1 Specification label

Each double-bagged Spectrum® Hollow Fiber Filter Module is packed in a box along with a certificate of quality and directions for use. A specification label is attached in three locations: on the filter module, on the certificate of quality, and on the exterior of the box. The specification label provides you with important information such as the part number, data of manufacture, and maximum operating pressure (see Figure 26).

Note: *MiniKros and smaller modules are shipped in tubes. Label is only on module and certificate of quality.*

Figure 26. Spectrum® Filter Module product label example



1. Part number
2. Media type and rating
3. Membrane surface in the module
4. Maximum operating pressure
5. Bar code
6. Manufacturing date and module serial number
7. Lot number

7.4.1.1 Traceability and bar codes

Procedures and methods are established to identify the product and status of product throughout Repligen manufacturing process and distribution. Our unique serial number identification allows us to trace back production and material details of any particular TFF filter. A serial number is printed on every product identification label and is both, barcode readable, barcode type “Code 39”, and human readable. A typical Repligen serial number configuration is as follows:

- SN: XXXXXXX-MM/YY-ZZ
- Where: XXXXXXX: Unique lot number
- MM: Manufacturing Month
- YY: Manufacturing Year
- ZZ: Individual Number

7.4.2 Irradiation verification label

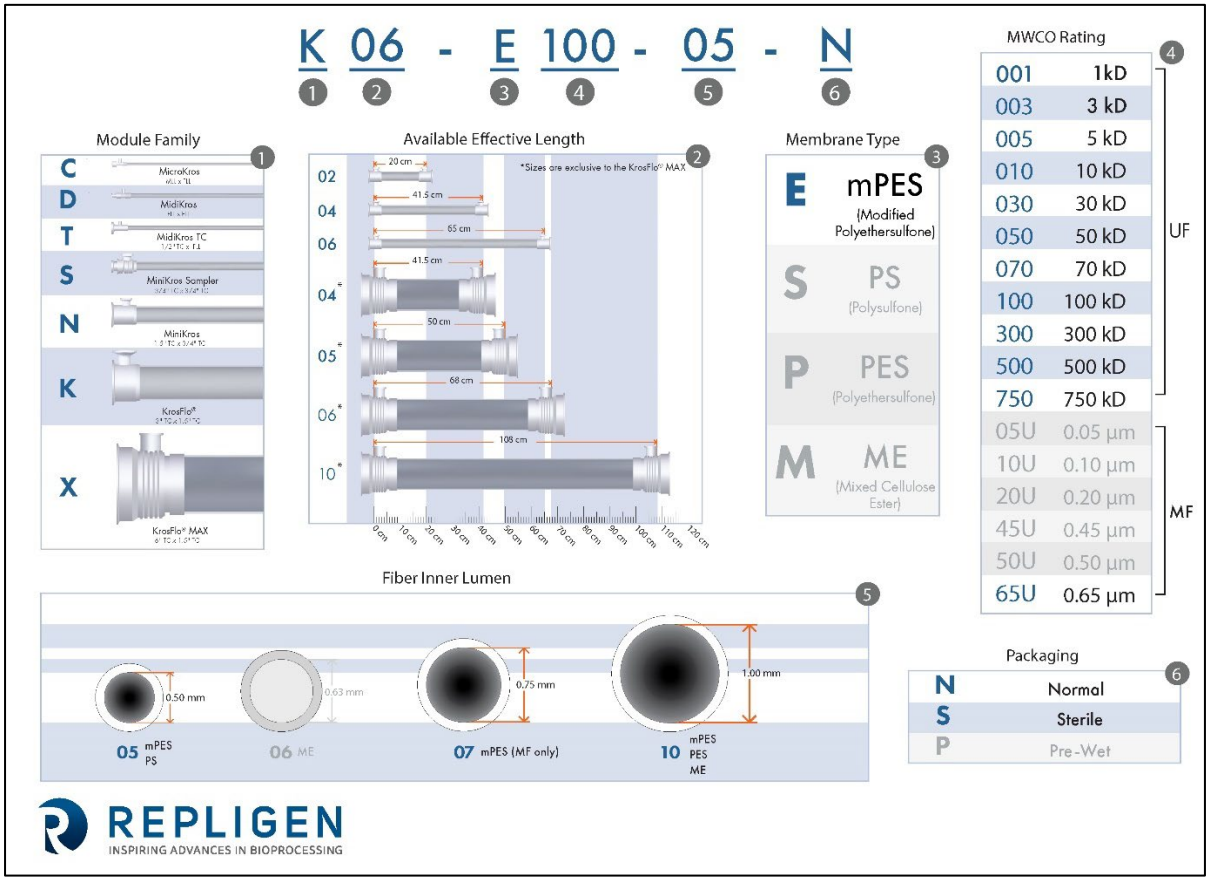
A sterilized Spectrum® Hollow Fiber Filter Module includes a radiation indicator label to verify proper exposure to radiation (Figure 28). The radiation indicator labels meet performance specifications as described in ISO 11140-1 Sterilization of health care products - Chemical indicators - Part 1: General Requirements, for Class 1 Process Indicators. When exposed to radiation, the label changes color from yellow to red.

Figure 27. Example of a radiation indicator label showing color change

7.5 Spectrum® Hollow Fiber Filter Key

The Spectrum® Hollow Fiber Filter includes a label that identifies the filter module type and configuration. From the product key, you can learn about the filter module including type of connections, hollow fiber length, membrane type, MWCO, and more (Figure 28).

Figure 28. Spectrum® Hollow Fiber Filter Key



* Non-mPES items have been greyed out.

8. Index