KrosFlo® TFDF® Lab System and ProConnex® TFDF® Flow Path

Regulatory Support File

REPLIGEN
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Abbreviations

BPSA	Bio-Process Systems Alliance
°C	Degrees Celsius
CE	Conformitée Européenne
CE	European Conformity
cm	centimeter
CMC	Chemistry and manufacturing control
COA	Certificate of Analysis
COQ	Certificate of Quality
E&L	Extractables and leachables
EMEA	European Medicines Agency
EtOH	Ethanol
FAS	Field Application Scientist
g	Gram
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
GMP	Good Manufacturing Practice
Hz	Hertz
in	Inches
ISO	International Organization for Standardization
ISTA	International Safe Transit Association's
kg	Kilogram
kGy	Kilogray
lb	Pound
mL	milliliter
NaCl	Pounds
PE	Polyethylene
PEG	Pressure Sensor
PEG 400	Polyethylene Glycol 400
PET	Polyethylene Terephthalate
PP	Polypropylene
PS	Polysulfone
PSI	Pounds per square inch
PUDV	Pulsed Ultrasound Doppler Velocimeter
RODI	Reverse Osmosis/Deionization
RSF	Regulatory support file
SDS	Sheet (SDS) is needed.
SOP	Standard Operating Procedure
TFDF®	Tangential Flow Depth Filtration
TUV	Technischer Überwachungsverein
ug	microgram
UL	Underwriters Laboratories
UPC	Universal Product Code
USP	United States Pharmacopeia
USA	United States of America

1. Introduction

The KrosFlo® TFDF® Lab System and ProConnex® TFDF® Flow Path Regulatory Support File (RSF) is written as a guide for the following applications:

- Process development of clinical and commercial purification processes
- Validation of manufacturing processes
- Reference for CMC submissions
- Supplier audits
- Alternative to Drug Master File submission

This Regulatory Support File covers all TFDF® Filter sizes.

Repligen commits to providing all relevant technical, manufacturing, and quality information. However, this document contains only non-confidential information. Confidential details may be made available upon request through a formal confidentiality agreement or as part of a supplier audit.

1.1 Repligen Quality Policy

Copies of the Repligen Quality Policy, and ISO Certificate can be found on repligen.com/resources.

1.2 Safety notices

- Follow all local regulations for safe disposal
- For laboratory and manufacturing production only

1.3 Responsible official

The following individual is designated responsible for quality and regulatory affairs for Repligen, and to whom all correspondence or requests for audits should be addressed:

Senior Director of Quality
Telephone: +1-781-250-0111
Email: customerserviceUS@repligen.com

2. Product information

2.1 Product overview

KrosFlo® TFDF® Technology provides a complete solution for the separation of cells from media during cell culture processes in both GMP and non-GMP environments. The KrosFlo® TFDF Lab System is designed for process development runs in a non-GMP environment while the process scale systems are designed to meet GMP requirements within bioprocessing. Hardware, software and a single-use filter combine to achieve the filtration result. Please direct questions regarding specific applications of the technology to your regional sales representative or field application scientist.

This reference document is updated regularly. For the latest version of the document, please visit repligen.com/resources. It is highly recommended that a trained Repligen Engineer execute the installation process of the KrosFlo® TFDF® System. For further support with troubleshooting or process optimization, please contact your local Repligen field application scientist.

2.2 Quality standards

In order to meet the needs of GMP manufacturing, KrosFlo® TFDF® Filters and ProConnex® TFDF® Flow Paths are manufactured in the USA under the following quality standards:

- Repligen maintains an ISO 9001-compliant Quality Management System that is currently certified by TUV Americas and BSI, a copy of the current ISO certifications can be downloaded from repligen.com/resources.
- All materials in the direct fluid contact path meet USP Class VI, and USP <88> requirements for *in vivo* Biological Reactivity.
- All filters and ProConnex® TFDF® Flow Paths are manufactured in a controlled, classified clean room that meets ISO Class 7 Non-Viable Particulate (NVP) standards.
- All fluid contact components are free from materials of animal origin or compliant with EMA 410/01 Rev 3.

2.3 KrosFlo® TFDF® System Features Overview

2.3.1 ProConnex® TFDF® Flow Path part numbers

ProConnex® TFDF® Flow Paths are manufactured as custom products, therefore each unit possesses a unique part number. The ProConnex® part numbering system comprises of (Figure 1):

Figure 1. Modular ProConnex® TFDF® Flow Path part number format

1. Product category
2. Core product
3. Application
4. Drawing UPC base code
5. Finishing step

For example, if a customer orders an irradiated custom ProConnex® TFDF® 150 cm^2 Flow Path a clarification application, the part number would be CTFDFCL98765S. The part number code works as follows:

- The first letter (“X”) is the product category (S for standard part, C for custom part)
- The next 4 digits are the core technology (TFDF®)
- The subsequent two letters are the application (“CL” for clarification)

- The next five digits are the UPC base code. This is the unique identifier for the product and mirrors the middle five digits on the engineering drawing for the flow path
- The last letter references finishing step:
  - "S" is irradiated
  - "N" is not irradiated
  - "T" is irradiated, and integrity tested (AQL 4.0)
  - "U" is irradiated and integrity tested (100%)

2.3.2 Summary of KrosFlo® TFDF® Filter production processes

Note: *Section 3 contains more detailed information on the KrosFlo® TFDF® product production process.*

Filter components: All incoming raw materials and custom components are subject to an incoming inspection procedure. Only the parts in compliance with the criteria set forward in the approved Raw Materials and Component Specifications documents are released for ProConnex® TFDF® Flow Path products.

Manufacturing qualification: ProConnex® TFDF® Flow Path and KrosFlo® TFDF® Filter processes are qualified and documented with appropriate SOPs and batch records as specified in the Repligen ISO 9001 Quality Management System.

Quality control and release: The specifications and the results of the release tests are documented on the Certificate of Quality.

Packaging: ProConnex® TFDF® Flow Paths are secured by foam packaging material and shipped in qualified shipping containers. See Figure 2.

Note: *Section 4 contains more information on packaging and shipping qualification.*

Figure 2. Packaging for KrosFlo® TFDF® 6000 cm² Device

2.3.3 Handling instructions

When moving a packaged ProConnex® TFDF® Flow Path inside a warehouse, a pallet jack or forklift should be used for sizes 1500 cm² or larger. If a pallet jack or forklift is not available, two people should lift the packaged flow path, one on each side of the box. The flow path's outer box should be removed before bringing the flow path into a clean room.

WARNING! The ProConnex® TFDF® Flow Path box weight can be up to 80 lb with dimensions of 32 in x 72 in x 17 in (W x D x H). Two people are recommended to lift the box.

2.3.4 Reference documentation

Quality documentation: Industry standards for document control are followed per Repligen ISO 9001 Quality Management System. The Repligen ISO 9001 ISO certificate can be found on repligen.com/resources.

Technical specifications: External packaging dimensions are provided in this Regulatory Support File.

User guide: A user guide for KrosFlo® TFDF® Lab System is available on the Repligen website. Please visit repligen.com/resources for more information.

Technical documents: A variety of supporting presentations, and videos can be found on repligen.com/technologies/TFDF.

Declaration of Conformity: This directive is not applicable for KrosFlo® TFDF® Filters and ProConnex® TFDF® Flow Paths and therefore no filters or ProConnex® TFDF® Flow Paths will be CE-signed. The KrosFlo® TFDF® Lab Systems are CE-certified.

2.4 Product contact materials of construction

KrosFlo® TFDF® Filters are designed using polymers suitable for downstream processing applications of biologic molecules. All components within the standard offering and the ProConnex® Flow Path component library meet the following criteria. The KrosFlo® TFDF® System was designed, developed and tested as an integrated system towards specifications. Substitution of system components with customer-specified components is not recommended as system performance against Repligen quality standards may be impacted. All parts are manufactured as fit for purpose.

- Suitability for pharmaceutical use with process fluid contact
- USP Class VI compatibility
- Low levels of extractables
- Free from materials of animal origin and/or compliant with EMEA 410/01

Figures 3, 4 and 5 describe the components used in the construction of a ProConnex® TFDF® Flow Path.

Figure 3. ProConnex® TFDF® Flow Path (part # STFDFCL15110S)

1. CPC AseptiQuik® Genderless Aseptic Connector
2. Tubing (retentate)
3. Disposable pressure sensor (retentate)
4. Module end caps
5. Vent port
6. Pinch clamp
7. KrosFlo® TFDF® Module with enclosed tubular filter
8. Disposable pressure sensor (permeate)
9. Disposable pressure sensor (feed)
10. CPC AseptiQuik® genderless aseptic connector
11. Magnetic pump head
12. Ferromagnetic fixation disc

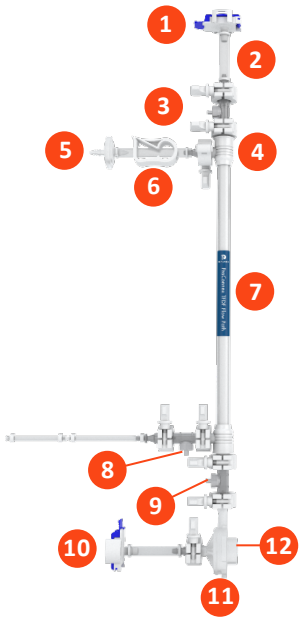

Figure 4. KrosFlo® TFDF® Module and enclosed filter tube components (part # STFDFCL15110S)

1. Module end cap
2. Module housing
3. KrosFlo® TFDF® tubular depth filter

Figure 5. KrosFlo® TFDF® Module cross-section image with 40 tubular filter

1. Module internal potting material
2. KrosFlo® TFDF® tubular depth filter
3. Module end cap

Table 1. Product contact materials

Component	Material	USP	Extractable	Animal origin
KrosFlo® TFDF® tubular filter	Poly Propylene (PP)/ Polyethylene Terephthalate (PET)	Class VI USP <88>	Available, Sec. 5.8	Animal free
Module housing and end caps	Polysulfone (PS)	Class VI USP <88>	Available upon request (report # 346-12788-001)	Animal free
Module potting material	Polyurethane	Class VI USP <88>	Available upon request (report # 346-12979-006)	Animal free
Magnetic pump head	Polypropylene (PP)	Class VI	Please refer to supplier package	
Disposable pressure transducers	Polysulfone (PS)	Class VI	Please refer to supplier package	
Plastic fittings (reducers and connectors)	Polypropylene (PP) and PVDF	Class VI	Please refer to supplier package	
Tubing	C-flex®/PharMed®, platinum-cured silicon and PharmaPure	Class VI	Please refer to tubing supplier package	
Vent filters	Polypropylene with PVDF membrane	Class VI	Please refer to vent filter supplier package	

Non-product contact materials summary:

- Clamps
- Zip ties

2.5 Warranty

Repligen is committed to provide complete customer satisfaction and implements the following warranty policy for KrosFlo® TFDF® Filters and ProConnex® TFDF® Flow Paths:

- If the ProConnex® TFDF® Flow Paths arrive at the customer site in damaged condition, Repligen will accept the damage risk and issue a replacement at no charge.
- If the filter or flow path fails passing specifications as agreed to on the ProConnex® TFDF® Flow Path Specification Sheet, Repligen will conduct troubleshooting efforts and, if unsuccessful, will ask for the product to be returned for further evaluation. If the root cause of the failed test is determined to be a compromised filter or flow path design, Repligen will provide a replacement at no charge.
- If an end user does not operate the filtration product as described in the KrosFlo® TFDF® user specifications and/or CoA, the above warranty will be considered void.

2.6 Safety Data Sheet (SDS)

ProConnex® TFDF® Flow Paths are made from plastic components only and therefore no Safety Data Sheet (SDS) is needed.

3. Manufacturing information

3.1 Introduction

All KrosFlo® TFDF® Filters and ProConnex® Flow Paths are manufactured at 18617 South Broadwick Street, Rancho Dominguez, CA 90220, USA. Quality Assurance (QA) and Quality Control (QC) operations are also based in the same location. Neither the facility nor products manufactured require registration or market approval. Therefore, filter facility and products manufactured herein are not subject to regulatory review or audit by organizations such as the US Food and Drug Administration or European Medicines Agency.

3.2 Manufacturing quality assurance standards and policy

Repligen recognizes the need for high quality standards and has therefore established an ISO 9001 Quality Management System. Refer to Section 1 of the Repligen Quality Policy.

3.3 Manufacturing facilities

The KrosFlo® TFDF® Filter and ProConnex® TFDF® Flow Paths consist of multiple ISO Class 7 rooms. The cleanroom environment is controlled and monitored as follows:

- Air quality is maintained by 100% HEPA filtered air.
- Filter manufacturing and ProConnex® Flow Path room air quality is tested to ISO Class 7 standards for non-viable particulates.
- Room pressure differentials are maintained and monitored according to SOPs.
- All rooms are on a routine cleaning and disinfection schedule.
- Access is restricted to authorized personnel only.
- Appropriate gowning is required for entry into controlled areas.

3.4 Manufacturing controls and SOPs

Training: Manufacturing is performed by qualified and trained operators. Training documentation is maintained by Quality Assurance.

Process documentation: Repligen manufacturing processes are governed by an ISO 9001-compliant Quality Management System. All manufacturing work instructions are contained in controlled documents, which are issued in advance of each manufacturing batch. Batches and process intermediates are 100% traceable through an internal lot numbering system. All manufacturing data are recorded by operators at the time of manufacturing. Batch records are archived for three years on site, and then stored off site for a minimum of 10 years.

Raw materials and components: All raw materials are controlled, and each raw material has a pre-approved specification. Receipt of material is verified and released by QA prior to use in manufacturing.

Supplier management: Repligen identifies critical suppliers of raw materials and components based on the impact to the quality of the product. Critical suppliers are subject to a qualification process and are monitored and are routinely audited according to a pre-determined schedule. The supplier audit schedule is established based on a critical supplier audit cycle, supplier performance, past audit results and business requirements.

Change management: Manufacturing process changes are governed by change management procedures that include provisions for customer notification of major changes.

Product storage control: Product is stored at ambient temperature.

Preventive maintenance and calibration: Equipment and monitoring devices are controlled through the Repligen Equipment Control process. Each piece of equipment is uniquely identified and has a preventive maintenance and/or calibration schedule, as necessary.

High purity water: Purified water is supplied to all manufacturing areas from a Reverse Osmosis/Deionization (RODI) system. The RODI system is fully automated and provides high quality water in a continuously circulating loop. Water quality is monitored and is routinely sampled and tested by Repligen Quality Control for endotoxin, conductivity and bioburden.

Business continuity policy: The Repligen Corporation Business Continuity Management System (BCMS) is designed to maintain the continuity of critical business activities in the case of an emergency and/or an event that severely impacts business operations and ultimately the ability to supply product. Such events may include operational incidents, un-forecasted product demand, man-made or environmental incidents or threats, and natural disasters. Proper maintenance and application of BCMS processes will allow for the control and restoration of business practices in an acceptable amount of time to maintain product reliability and mitigate the possibility of a product shortage. For KrosFlo® TFDF® Filter and ProConnex® TFDF® Flow Paths, recovery of production is assumed to be 24 weeks within the United States.

3.5 KrosFlo® TFDF® Filter and ProConnex® TFDF® Flow Path manufacturing

3.5.1 Packing environment and environmental controls

All KrosFlo® TFDF® Filters and ProConnex® Flow Paths are packed in ISO Class 7 classified clean rooms.

3.5.2 Filter module integrity testing, ProConnex® Flow Path and primary packing

KrosFlo® TFDF® Filters and ProConnex® TFDF® Flow Paths are assembled from qualified and controlled components. Inspected and released component parts are taken from inventory and are brought into the ISO 7 classified cleanroom. The processes for manufacturing KrosFlo® TFDF® Filters and ProConnex® TFDF® Flow Paths have been qualified and validated.

The following points summarize the major steps which occur during manufacture of the KrosFlo® TFDF® Filter and ProConnex® TFDF® Flow Path:

1. Filter tube is manufactured to specification, inspected, assembled into the module and potted with urethane.
2. Filter is integrity tested and flushed with alcohol and inspected.
3. ProConnex® TFDF® Flow Paths is assembled according to engineering drawing specifications.
4. The product in primary and secondary packaging and boxed and shipped to the irradiation facility.
5. Product certification is created.
6. Product is ready for shipment.

3.6 ProConnex® TFDF® Flow Path Certificate of Quality (CoQ)

Each ProConnex® TFDF® Flow Path unit is delivered with a Certificate of Quality (CoQ) with the content noted in Table 3 and Figure 6.

NOTE: *Please consult the Repligen website for the most up to-date information on ProConnex® TFDF® Certificate of Analysis details, including templates.*

Table 2. ProConnex® TFDF® Certificate of Quality components

Certificate of Quality component	Gamma-irradiated and non-irradiated filters
Date of manufacture	✓
Lot number	✓
Filter module integrity testing	✓
Fiber membrane lot testing	✓
Material lot traceability	✓
Filter flow paths manufacturing (ISO 7 cleanroom)	✓
ISO 9001 Compliance Statement	✓
Product Contact Materials Compliance Statement (Animal-free, EMA 410/01, USP Class VI)	✓
Irradiation status	✓
Intended usage/Shelf life (2 years from manufacturing date)	✓
Country of origin	✓

Figure 6. ProConnex® TFDF® Flow Path Certificate of Quality (3 - 6000 cm^2)

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Repligen Corporation
18617 S. Broadwick Street
Rancho Dominguez, CA 90220-6435
Phone: 310-885-4600
Fax: 310-885-4666

Certificate of Quality

Affix Label Here

ProConnex Flow path

This is to certify that this product as indicated by the affixed label complies with the following descriptions and specifications:

Product Description – ProConnex® TFDF™ Flow path

The month/year of manufacture is indicated after the first dash of the labeled lot number.

The filter was manufactured in an ISO Class 7 (GMP 10,000) clean room.

All materials of construction are 100% lot traceable.

All materials in product fluid path meet USP Class VI requirements and in accordance with EMA/410/01 guidelines (TSE/BSE free).

The fiber membrane lot was tested to verify product performance.

Each filter module has been integrity tested.

Part numbers ending in I, S, T or U have been exposed to 25-40kGy of gamma radiation after final packaging. This is not applicable to part numbers ending in N, V or W.

Lots for part numbers ending in T and V have been integrity test at AQL level 4.0. Part numbers ending in U and W have been 100% integrity tested.

Intended for single use within two (2) years from the date of manufacture.

Origin of Manufacture: U.S.A.

Product is manufactured in compliance with ISO 9001.

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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3.7 ProConnex® TFDF® Flow Path labeling

NOTE: *Please consult the Repligen website for the most up to-date information on ProConnex® TFDF® Certificate of Analysis details, including templates.*

Each individual ProConnex® TFDF® Flow Path is labeled with the following information. Label content will vary based on type of filter.

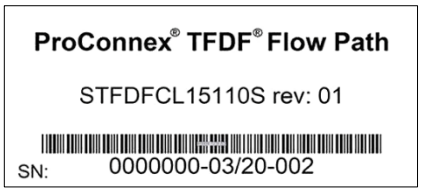
Example:

- Part number: STFDFCL14874S
- Media: TFDF®
- Surface area: 6000 cm^2
- UPC code: 990-14874-000
- Lot number: 0000000-03/20-002
- Date of manufacture: 0000000-03/20-002 (March 2020)

Figure 7. Example ProConnex® TFDF® 6000 cm^2 label

The label in Figure 7 is placed on the outer pouch. Lot number and part number information along with the barcode is also placed on the final shipping box.

Figure 8. Example KrosFlo® TFDF® 3 cm^2 Filter label on ProConnex® TFDF® Flow Path



4. Shipping qualification

4.1 Summary

To certify the packaging and product integrity performance remains intact during and after shipping, International Safe Transit Association (ISTA) tests were conducted on a variety of ProConnex® TFDF® Flow Path sizes. A third-party certified laboratory performed the shipping tests, and Repligen tested performance pre and post shipping. Results from the studies show the packaging withstands the stresses of commercial shipping, and that the product integrity is maintained.

4.2 Shipping introduction

4.2.1 Objective

The objective of the shipping studies is to demonstrate the ProConnex® TFDF® Flow Path packaging arrives intact after worst case shipping simulations.

ProConnex® TFDF® Flow Paths employ different packaging based on the size of the filter module. To cover the range of different packaging methods and materials, the following filter sizes were evaluated:

- ProConnex® TFDF® Flow Path, 150 cm^2 filter area (Part # STFDFCL15112S)
- ProConnex® TFDF® Flow Path, 1500 cm^2 filter area (Internal part # STFDFCL15114S for validation purposes)
- ProConnex® TFDF® Flow Path, 6000 cm^2 filter area (Internal part # STFDFCL15116S for validation purposes)

Figure 9. ProConnex® TFDF® Flow Path shipping container

4.2.2 Acceptance criteria

The shipping tests documented in this regulatory support file have acceptance criteria as detailed below.

- Per ISTA guidelines, procedures 3A call for a simple pass/fail assessment based on a visual test of packaging materials. This assessment is made by the certified ISTA test facility and documented in a summary report.

4.3 Method: ISTA 3A tests

ISTA Procedure 3A is a general simulation test for individual packaged products shipped through a parcel delivery system. The test is appropriate for four different types of packages commonly distributed as individual packages, either by air or ground. The types include standard, small, flat, and elongated packages.

The test is used to:

- Evaluate the integrity of the product post-shipment
- Evaluate the integrity of the outer box post shipment

During the test, the package and product are considered together and not separately.

4.3.1 Tests and conditions

All studies were performed by Performance Testing Laboratories, Inc. (PTL) in Santa Ana, CA, a certified ISTA test facility, per ISTA guidelines. The specific test conditions are described further in Table 4. All ProConnex® TFDF® Flow Paths were manufactured by Repligen, packaged into their respective shipping containers, picked up by PTL, shipped to their certified testing facility, and tested according to the applicable standards. After the tests were complete, PTL returned the shipping containers to Repligen for post-testing analysis.

Table 3. ISTA 3A testing conditions (ProConnex® TFDF® Flow Paths 150 - 6000 cm^2)

Test name	Test details
Atmospheric conditioning	19.8 - 28 °C, Relative humidity 28% - 66% for > 12 hours
Controlled temperature and humidity conditioning	20 - 27 °C, Relative humidity 28% - 65%
Compression testing	ProConnex® TFDF® Flow Paths 6000 cm^2: 70 - 300 lb. ProConnex® TFDF® Flow Paths 1500 cm^2: 35 - 300 lb. ProConnex® TFDF® Flow Paths 150 cm^2: 45 - 300 lb.
Random vibration testing (Over the road trailer spectrum)	30 - 60 minutes of random vibration Frequency (Hz) — PSD Level, g^2/Hz 1.0 — 0.0007 5 — 0.02 75.0 — 0.003 200.0 — 0.000004
Drop testing	Box on flat surface and on edges dropped 12" (6000cm^2) and 18" (150 cm^2 and 1500 cm^2) to ground (3A) Box dropped 24 (6000 cm^2) and 36" (for 150 cm^2 and 1500 cm^2) inches to the ground for highest surface area facing floor (3A)
Random vibration testing (Pick-up and delivery vehicle (PUDV) spectrum	30 minutes of random vibration Frequency (Hz) — PSD Level, g^2/Hz 1.0 — 0.001 7.0 — 0.0003 100.0 — 0.002 200.0 — 0.00005

Figure 10. KrosFlo® TFDF® vibration test setup

4.4 Visual inspection

Per ISTA Procedures 3A, the certified test facility performed a visual pass/fail inspection of the packaging materials.

4.5 Results: ISTA 3A shipping validation tests

4.5.1 Results: visual inspection

ISTA test facility: After the worst-case shipping simulation tests were completed, Performance Testing Laboratory Inc (PTL, Santa Ana, CA) visually inspected the packaging for signs of damage. Results are documented in test reports issued by PTL to Repligen. For all tests, the custom designed KrosFlo® TFDF® packaging passed the visual inspection without any significant signs of damage.

Repligen: Upon receipt from PTL all shipping containers and columns were inspected and found to be undamaged and intact.

Table 4. ProConnex® TFDF® Flow Path visual inspection post ISTA testing

ProConnex® TFDF® Flow Path components	6000 cm^2	1500 cm^2	150 cm^2 (1)	150 cm^2 (2)	150 cm^2 (3)
Outer box must stay intact	PASS	PASS	PASS	PASS	PASS
Tapes on outer box should stay intact (minor tear and loosening of tack acceptable)	PASS	PASS	PASS	PASS	PASS
No major tear on outer box	PASS	PASS	PASS	PASS	PASS
No major punctures or holes on outer box (puncture or hole should be < 1.0 inches)	PASS	PASS	PASS	PASS	PASS
No major punctures or holes on Inner box (puncture or hole should be < 0.5 inches)	PASS	PASS	PASS	PASS	PASS
No kinks in tubing	PASS	PASS	PASS	PASS	PASS
No visual damage to clamps, cable ties, filter, pressure sensors, or fittings	PASS	PASS	PASS	PASS	PASS
No punctures or holes in bags (vacuum sealed bags must be integral)	PASS	PASS	PASS	PASS	PASS
Result	PASS	PASS	PASS	PASS	PASS

4.5.2 Results: ProConnex® TFDF® Flow Path integrity post shipping simulation

The data summarized in Table 6 shows the filter flow path of all ProConnex® TFDF® Flow Paths under evaluation remains integral following the applicable shipping simulation. ProConnex® TFDF® Flow Paths successfully met the acceptance criteria.

Table 5. ProConnex® TFDF® Flow Path 6000 cm^2 integrity post ISTA testing

ProConnex® TFDF® Flow Path components	6000 cm^2 (module section)	6000 cm^2 (tubing section)
Flow path must hold 30 psi of air pressure with a drop of less than 0.1 psi for 2 min.	PASS	PASS
Pressurize the flow paths with air until a leak is observed. Report leak pressure. Leak Pressure must be > 30psi.	34 PSI PASS	> 40 PSI PASS
Results	PASS	PASS

Table 6. ProConnex® TFDF® Flow Path 1500 cm² and 150 cm² integrity post ISTA testing

ProConnex® TFDF® Flow Path components	1500 cm²	150 cm² (1)	150 cm² (2)	150 cm² (3)
Flow path must hold 30 psi of air pressure with a drop of less than 0.1 psi for 2 min.	PASS	PASS	PASS	PASS
Pressurize the flow paths with air until a leak is observed. Report leak pressure. Leak Pressure must be > 30psi.	36 PSI PASS	> 40 PSI PASS	> 40 PSI PASS	> 40 PSI PASS
Results	PASS	PASS	PASS	PASS

4.6 Conclusion

In summary, the following was observed post worst-case shipping simulation:

- No significant damage to the shipping containers
- No detectable impact on the integrity of the ProConnex® TFDF® Flow Paths
- No detectable damage to the ProConnex® TFDF® Flow Paths

Therefore, ProConnex® TFDF® Flow Paths designed and tested by Repligen for clarification performance, and the shipping containers designed and tested in conjunction with PTL, demonstrate suitable robustness for surviving the harsh environments of commercial shipping.

5. Extractables and Leachables

5.1 Introduction and background

Plastic materials have been used in the manufacturing of therapeutics for many decades. Over the last 15 years, focused product development by many vendors and biotechnology companies has resulted in a plethora of single-use technologies. During this time, the industry has witnessed the development and adoption of critical disposable and single-use technologies like mixers, bioreactors, filters, and connectors. As a result, standards and best practices for evaluating component safety have been set for the selection and qualification of plastics.

In general, plastics used in biopharmaceutical manufacturing have low defined extractables and have been determined to be non-toxic at equivalent therapeutic doses. Many base standards used for guidance have been set by regulatory publications including USP, CFR 21, and EMEA. These basic standards have been elaborated on by industry organizations like the Bio-Process Systems Alliance (BPSA) and Parenteral Drug Association (PDA) as well as product manufacturers through the publication of best practices of testing and assessment of data. In addition, end-user therapeutic manufacturers have become more demanding in their analytical requirements, assessment of data, determination of risk, and minimum threshold for meeting internal standards.

Repligen is aware of the demands of the industry and will therefore supply relevant and applicable information about the plastics used in the product contact components of KrosFlo® TFDF® Filters. In accordance with industry standards, Repligen® uses the definitions for extractables and leachables as stated in the 2007 BPSA document, "*Recommendations for Extractables and Leachables Testing: Part 1.*"

Extractables: Chemical compounds that migrate from any product-contact material when exposed to an appropriate solvent under exaggerated conditions of time and temperature.

Leachables: Chemical compounds, typically a subset of extractables that migrate into a drug formulation from any product contact material as a result of direct contact under normal process conditions.

There is a general consensus that it is the responsibility of the product technology vendor to provide an extractable data package. In recent years, there have been efforts to standardize the testing procedures for extractables, and wherever possible it is the intent of Repligen to comply with these standardization efforts. In addition, in compliance with CFR 21, Part 211.65, KrosFlo® TFDF® Filters are designed such that all product contact materials are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond established requirements.

Therefore, using the BPSA guidance as a backdrop, Repligen has designed an extractables program to produce a robust data package by conducting extractables testing using two solvents as well as exaggerated time and temperature conditions. Solvents were chosen for their common usage in clarification applications. Leachables, however, are considered to be process-specific and the responsibility of the end user to define within specific process parameters.

5.2 KrosFlo® TFDF® Filter extractables strategy

Based on the prior experience, Repligen has applied the following approach to developing a meaningful extractables and leachables package for KrosFlo® TFDF® Filters:

1. All plastics used will be certified to meet two criteria:
    a. USP <88> Biological Reactivity Tests, *In Vivo* (USP Class VI).
    b. Animal Free or compliant with EMEA 410/01.
2. Extractables from the KrosFlo® TFDF® Filter platform were selected according to an approved, written experimental rationale for exaggerated time and temperature conditions and tested against an approved protocol.
3. Repligen will not conduct, nor present data for leachables in this Regulatory Support File for any process-specific solution beyond what is determined in the extractables testing. Repligen will, on request, support client-based leachable testing by providing component test materials.

5.3 USP Class VI: USP<88> biological reactivity tests, *in vivo*

Six plastic classes are defined in Table 7. This classification is based on responses to a series of *in vivo* tests for which extracts, materials, and routes of administration are specified. These tests are directly related to the intended end-use of the plastic articles.

Table 7. Summary of USP <88> plastics classes

Plastic classes						Tests to be conducted		
I	II	III	IV	V	VI	Extract	Species	Procedure
P	P	P	P	P	P	USP 0.9% NaCl	Mouse	Systemic-intravenous
P	P	P	P	P	P		Rabbit	Intracutaneous irritation
	P	P	P	P	P	1:20 EtOH/NaCl	Mouse	Systemic-intravenous
	P	P	P	P	P		Rabbit	Intracutaneous irritation
		P		P	P	PEG 400	Mouse	Systemic-intravenous
				P	P		Rabbit	Intracutaneous irritation
		P	P	P	P	Cottonseed oil	Mouse	Systemic-intravenous
			P	P	P		Rabbit	Intracutaneous irritation
			P		P	Muscle implant	Rabbit	Intramuscular (7 day, no histopathology)

5.4 Acute systemic toxicity test

Purpose: *In-vivo* systemic tests evaluate the impairment or activation of a system rather than the impairment of individual cells or organs. In "acute" systemic toxicity tests, the test material (extract) is tested for systemic toxic effects as a result of a single, acute exposure. This test is designed to evaluate systemic responses to the extracts of materials following injection into mice.

5.4.1 Irritation test: intracutaneous irritation test

Purpose: The irritation tests are *in vivo* screening tests to evaluate the potential of test materials or their extracts to cause irritation on the exposed part of the body. This test is designed to evaluate local responses to the extracts of materials following intracutaneous injection into rabbits.

5.4.2 Implantation test: intramuscular

Purpose: Implant studies evaluate the local pathological effects on living tissue at both the gross and microscopic level of a test article surgically implanted into an appropriate implant site. The implantation test is designed for the evaluation of plastic materials and other polymeric materials in direct contact with living tissue.

5.5 Animal-free and EMA 410/01

NOTE: *This is for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.*

Scientific principles for minimizing risk (EMA 410/01): Use of materials from 'non-TSE-relevant animal species' or non-animal origin is preferred. If materials from 'TSE-relevant animal species' have to be used, consideration should be given to all the necessary measures to minimize the risk of transmission of TSE.

5.6 Extractable test protocol and results

5.6.1 Background

Repligen has performed extractables testing on the product contact components of the KrosFlo® TFDF® Filter element. This data has been consolidated into a format that will be suitable for use in the KrosFlo® TFDF® product literature.

5.6.2 Extractables and Leachables

Materials: The materials used to fabricate single-use processing equipment for biopharmaceutical manufacturing are often polymers such as plastic or elastomers (rubber), as opposed to the traditional metal or glass. Polymers offer favorable versatility, since they are lightweight, flexible and more durable than their traditional counterparts. Plastic and rubber are also disposable, avoiding cleaning and validation process steps. As with all drug-material contact points, the possibility for chemicals to migrate from the material to the drug exists. All materials can produce leachables.

Leachables represent chemicals that migrate from single-use processing equipment into the various components of the drug product during manufacturing. Extractables represent chemicals, both organic and inorganic, that extract from single-use processing equipment using common laboratory solvents in controlled experiments. Extractables represent the worst-case scenario and are used as a tool to predict the types of leachables that can be encountered during pharmaceutical production. Extractables are the “potentials” and leachables are the “actuals.”

Using well-characterized materials to fabricate the manufacturing equipment effectively minimizes and controls leachables. The KrosFlo® TFDF® Filter product contact materials are primarily constructed from a combination of polypropylene (PP) and Polyethylene Terephthalate (PET). PP homopolymer is much less prone to leachables than other types of polyolefins due to its mechanical and physical properties (i.e. melting point, glass transition temperature, molecular weight distribution, and percent crystallinity.) Critical polymer characteristics have been measured and benchmarked for each PP product contact component, enabling their use as a quality control measure for incoming raw materials with similar properties. This can help to ensure consistent, batch-to-batch leachable profiles for the KrosFlo® TFDF® product contact components. Platinum-cured silicone components are durable materials frequently used in medical applications. Materials of construction in ProConnex® TFDF® Flow Paths meet all USP Class VI requirements. Table 8 further itemizes product contact materials.

Table 8. Polymer list and regulatory information

Component	Material	USP	Extractable	Animal origin
KrosFlo® TFDF® tubular filter	Polypropylene (PP)/ Polyethylene Terephthalate (PET)	Class VI USP <88>	Available, Sec. 5.8	Animal Free
Module housing and end caps	Polysulfone (PS)	Class VI USP <88>	Available upon request (report # 346-12788-001)	Animal Free
Module potting material	Polyurethane	Class VI USP <88>	Available upon request (report # 346-12979-006)	Animal Free
Disposable pump head	Polypropylene (PP)	Class VI	Please refer to supplier package	
Disposable pressure transducers	Polysulfone (PS)	Class VI	Please refer to supplier package	
Plastic fittings	Polypropylene (PP) and PVDF	Class VI	Please refer to supplier package	
Tubing	C-flex®/PharMed®, platinum-cured silicon and PharmaPure	Class VI	Please refer to tubing supplier package	
Vent filters	Polypropylene with PVDF membrane	Class VI	Please refer to vent filter supplier package	

Testing: Multiple industry groups have published "Best Practices" for conducting this testing.

- The polymers utilized in medical and pharmaceutical applications should be compliant with the appropriate USP guidelines. Compliance with USP Class VI testing requirements is also recommended. These guidelines describe extractables and leachables (E&L) testing programs that should be implemented for bioprocessing materials that directly contact drug formulation.
- Several presentations and publications were prepared by the Product Quality Research Institute (PQRI) for the evaluation and safety assessment of extractables and leachables in packaging for high risk drug dosage entities. These recommendations apply to the primary and secondary packaging associated with these pharmaceutical products.
- The BioProcess Systems Alliance (BPSA) and BioPhorum Operation Group (BPOG) published technical guidelines for evaluating the risk associated with extractables and leachables specifically for single-use processing equipment.

Repligen takes responsibility as the product technology vendor to provide a technical extractable package. Conversely, leachables, are considered to be process specific and are held as the responsibility of the end user to define. With that in mind, Repligen has designed an extractables program to produce a data package by conducting extractables testing using two solvents under exaggerated conditions. Tables 9, 10, 11 and 12 contain the data generated from this comprehensive series of extractables testing.

The materials of contact in the KrosFlo® TFDF® Filter tube is referred to as "Filter Media" (Polyethylene terephthalate (PET)/Polypropylene (PP)).

Repligen prepared samples of each component while a third-party testing facility repurposed samples into 1 g/10 ml for volatile analysis by Headspace GC-MS and 2 g/10 ml for all other test methods.

Water and alcohols extractables test:

- **Extraction solvents:** USP water, isopropyl alcohol
- **Extraction conditions:** Elevated temperature: 50° C with continuous agitation for 72 hours
- **Analysis:** The extracts were analyzed for volatiles by Headspace GC/MS, semi-volatiles by GC/MS, non-volatiles by LC/PDA/MS, and inorganics by ICP-MS

Results: Results for the extracts are summarized in the tables below. Note the following:

- NA: indicates measurement was below the method limit of detection
- All other values are reported in µg/g (ppm)

5.7 KrosFlo® TFDF® Filter material

Table 9. Volatiles

Volatiles by headspace GC/MS	
Extractable	**µg/g (ppm)**
Isopropanol	17

Table 10. Semi-volatiles

Semi-volatiles by GC-MS		
Extractable	**Water (µg/g)**	**Isopropyl alcohol (µg/g)**
None Observed	NA	NA

Table 11. Non-volatiles

Non-volatiles by time of flight LC/MS		
Extractable	**Water (µg/g)**	**Isopropyl alcohol (µg/g)**
Terephthalic Acid	50	NA
Ethylene Glycol Monoterephthalate	43	12
Ethylene Glycol Diterephthalate ($C_{18}H_{14}O_8$) and $C_{20}H_{18}O_9$	13	130
Unknown ($C_{30}H_{26}O_{13}$)	NA	26

The non-volatile organics test indicates low molecular weight oligomers of polyethylene terephthalate (PET) in extracts. PET represents one component of the material of construction of the KrosFlo® TFDF® Filter tube.

Table 12. Inorganics

	Inorganics by ICP-MS	
Extractable	**Water (µg/g)**	**Isopropyl alcohol (µg/g)**
Antimony	1.05	0.19
Phosphorous	0.42	0.10
Sodium	2.60	N/A
Calcium	0.60	N/A
Magnesium	0.16	N/A
Potassium	0.25	N/A

The values presented in the table above are averages of two runs.

5.8 Summary

The KrosFlo® TFDF® Filter tube product contact materials meet USP Class VI requirements for plastics and regulated food contact applications. Product contact components extractables testing was conducted in filter tubes using conditions of 50 °C for 72 hours in two solvents: USP water and 20% isopropanol. The extracts were analyzed for volatiles, semi-volatiles, non-volatiles, and metals. The identified extractables were correlated back to their source of origin in the KrosFlo® TFDF® Filter component so that they can be controlled during manufacturing.

5.9 Supporting references

1. Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, Product Quality Research Institute, Arlington VA, September 8, 2006.
2. D. Jenke, PQRI PODP Workshop, Feb 22-23, 2011.
3. PQRI Review Article, *PDA J Pharm Sci and Tech,* 2013, 67:430-447.
4. Bio-Process Systems Alliance: www.bpsalliance.org. Formed in 2005 as an industry-led corporate member trade association dedicated to encouraging and accelerating the adoption of single-use manufacturing technologies used in the production of biopharmaceuticals and vaccines.
5. Parenteral Drug Association: www.pda.org. The leading global provider of science, technology and regulatory information and education for the pharmaceutical and biopharmaceutical community. Founded in 1946 as a nonprofit organization, PDA is committed to developing scientifically sound, practical technical information and resources to advance science and regulation through the expertise of its more than 9,500 members worldwide.
6. Recommendations for Extractables and Leachables Testing - Part 1: Introduction, Regulatory Issues and Risk Assessment Bioprocess Systems Alliance, *Bioprocess International*, 5(11):36-49, December 2007.
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8. USP General Chapters <88> Biological Reactivity tests, *In Vivo.*
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10. Estimation of Toxic Hazard – A Decision Tree Approach, G.M. Cramer and R.A. Ford, *Fd Cosmet.Toxicol.*, 16: 255-276, Pergamon Press, 1978.
11. Threshold of Toxicological Concern Concept in Risk Assessment, R Kroes, J Kleiner and A Renwick, *Toxicological Sciences*, 86(2): 226-230, 2005.
12. Parenteral Drug Association: Assessment of E/L from Bags, Tubings and Filters.

6. Appendix

6.1 ProConnex® TFDF® Flow Path material certificates (available upon request)

Refer to Section 2 for a summary of the product contact materials. The following documents are available upon request. Please email our Customer Service department at customerserviceUS@repligen.com for more information.

- **KrosFlo® TFDF® 3 - 6000 cm² Filter media:** Certificate of compliance for USP biological reactivity tests (USP Class VI), USP Class VI Documentation, Screening for presence of metals, Animal origin documentation, Extractable documentation detecting presence of non-volatile, semi-volatile and volatile organics
- **KrosFlo® TFDF® 6000 cm² Filter:** Functionality testing and pressure drop profiles
- **KrosFlo® TFDF® 3 cm² Filter:** Filter performance and filtrate quality comparison for irradiated versus non-Irradiated filter
- **KrosFlo® TFDF® 3 cm² Filter:** Filter integrity after exposure to 0.5 M Sodium Hydroxide (NaOH)
- **KrosFlo® TFDF® ISTA 3A shipping validation report:** ProConnex® TFDF® Flow Paths maintained their integrity and passed visual inspection test post shipment

6.2 ProConnex® TFDF® Flow Path examples

Figure 11. KrosFlo® TFDF® 3 Filter only, 3 cm² filter area example

Figure 12. ProConnex® TFDF® Flow Path, 3 cm² filter area example

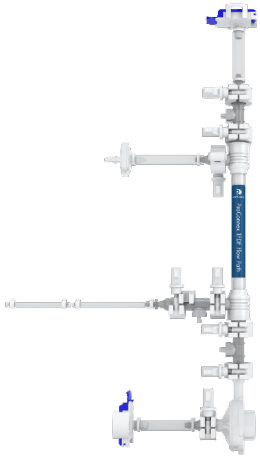

Figure 13. ProConnex® TFDF® Flow Path, 150 cm² filter area example

Figure 14. ProConnex® TFDF® Flow Path, 1500 cm² filter area example

Figure 15. ProConnex® TFDF® Flow Path, 6000 cm² filter area example

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