TangenX®
Filter Plate Insert

Regulatory Support File

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Abbreviations

µm	micron
AAMI	Association for the Advancement of Medical Instrumentation
BSE	bovine spongiform encephalopathy
C	Celsius
cm	centimeter
cm2	centimeter squared
CMC	Chemistry, Manufacturing & Controls
CO2	carbon dioxide
DI	deionized
EPDM	Ethylene Propylene Diene Monomer
EU	endotoxin units
FLAA	Fluorescence-Linked Aptamer Assay
FPI	filter plate insert
GDP	Good Documentation Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
H	height
hr	hour
ICP	Inductively Coupled Plasma
ICP/MS	Inductively Coupled Plasma/Mass Spectrometry
in	inch
IQ	Installation Qualification
ISO	International Organization for Standardization
kg	kilogram
L	length
L	liter
lb	pound
LHV	low holdup volume
LPM	liter per minute
M	molar
m2	meter squared (square meter)
MEM	mammalian cell culture media
mg	milligram
mL	milliliter
mm	millimeter
NaOH	sodium hydroxide
NOC	no observable colonies
OEM	Original equipment manufacturer
OQ	Operation Qualification
PP	polypropylene
psi	pounds per square inch
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
RODI	reverse osmosis deionized water
RSF	Regulatory Support File
SOP	Standard Operating Procedure
TFF	tangential flow filtration
TOC	total organic carbon
TSE	transmissible spongiform encephalopathy
USP	United States Pharmacopeia
W	width

1. Introduction

The Regulatory Support File (RSF) for TangenX® Filter Plate Inserts (FPI) is intended to be used as:

- A guide for appropriate application use in process development, clinical, and commercial purification processes.
- A guide to validation in manufacturing processes.
- A support reference for CMC submissions for regulatory license approval.
- A guide for supplier audits.
- An alternative to a Drug Master File submission.

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

2. Quality Documentation

2.1 Quality Policy

2.1.1 Repligen Corporation – A Higher Standard

Repligen Corporation has over 50 years of experience providing products that meet the quality required in bioprocessing applications. 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.

ISO statement: Product is manufactured in compliance with Repligen ISO 9001 certified Quality Management System. Our ISO certification certificate can be found on the Repligen website.

To meet the needs of GMP manufacturing, TangenX FPI is manufactured in the USA under the following quality standards:

1. TangenX FPI is manufactured in a facility whose Quality Management System is approved by an accredited registering body to the ISO 9001 2015 Quality System Standard.
2. Repligen Corporation certifies that the resin utilized to manufacture each filter plate insert kit meets the following:
    - Current requirements for USP Class VI biological test for plastics.
    - Certifications that the components used in the production filter plate inserts are TSE/BSE free.
    - Certifications that the components used in the production filter plate inserts are free of melamine.
3. All component materials used in the filter plate inserts have been independently tested for USP safety and were shown to be safe according to:
    - L929 MEM Elution per USP <87>.
    - Class VI per USP <88>.
    - Hemolysis - Indirect with Rabbit Blood ISO 10993-4.

2.1.3 Animal Free and BSE/TSE Free statement

Repligen manufactures TangenX Filter Plate Inserts in the United States of America using materials sourced from qualified suppliers. No material of animal origin is used in the raw materials or manufacturing process for this product, and therefore TangenX FPI are free of transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE).

A copy of the Repligen quality policy can be found at https://www.repligen.com/resources/quality.

2.2 Safety Notices

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

2.3 Responsible Official

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

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3. Product Description

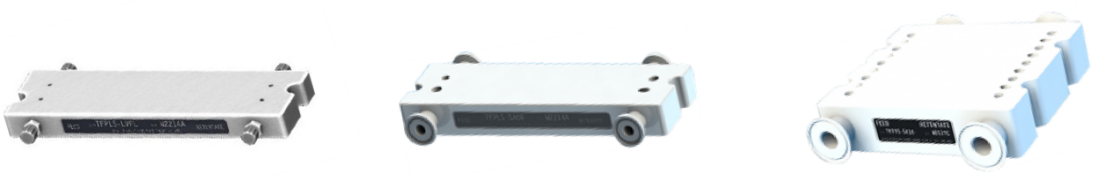
3.1 Product Design

TangenX Filter Plate Inserts are single-use flow distribution manifolds used in conjunction with tangential flow filtration (TFF) flat sheet cassettes for ultrafiltration and diafiltration processes. TangenX FPI kits consist of a polypropylene manifold and isolation plate which directs flow into and out of a TFF Cassette while isolating the fluid path from the stainless-steel cassette holder. Used with TangenX SIUS Cassettes and ProConnex® Single-use Flow Paths, all product contact materials are single-use.

Three sizes of TangenX FPI (Figure 1) are available for pilot and process applications servicing effective membrane surface areas from 0.01 to 20 m^2 when used in conjunction with TangenX SIUS single-use cassettes. This wide selection of TangenX FPIs is designed for processing volumes from 10 milliliters to 10,000 liters of process fluid. TangenX FPIs are engineered to deliver optimal performance as well as exceptional batch-to-batch reproducibility. Each FPI undergoes QA lot release testing to verify it meets release specifications.

Figure 1. Filter Plate Inserts

TangenX SIUS LV FPI **TangenX SIUS PD FPI** **TangenX SIUS FPI**



Designed for use in a wide range of biopharmaceutical applications, particularly those that are protein based, filter plate inserts manufactured by Repligen are compatible with all TangenX branded TFF Cassettes. Filter plate inserts provide a disposable flow path when used in conjunction with SIUS Single-use Cassettes and stainless steel holders. Once the cassette and FPI are clamped in the holder, the FPI can be connected to tubing or a TFF system using luer lock connections for the low holdup volume FPI or sanitary tri-clamp fittings for the larger FPI. TangenX FPIs are constructed using FDA approved polypropylene that has been validated for use in biopharmaceutical applications.

3.2 Materials of Construction

TangenX FPI are constructed of USP Class VI approved polypropylene.

Table 1. Materials of Construction

Component	Material
Filter Plate Insert	Polypropylene (PP) — White
Isolation Plate	Polypropylene (PP) — Natural
Luer lock Fittings (LVFL Only)	Polypropylene (PP) — Natural

Table 2. FPI Specifications

Parameter		TFPLS-LVFL	TFPLS-SA08	TFP75-SE16	TFP99-SP20
Dimensions (L x W x H)		8.5 x 3.0 x 0.75 in 21.6 x 7.6 x 1.9 cm	8.5 x 3.8 x 1.0 in 21.6 x 9.7 x 2.5 cm	8.75 x 9.75 x 2.0 in 22.2 x 24.8 x 5.1 cm	8.75 x 9.75 x 2.36 in 22.2 x 24.8 x 6.0 cm
Hold-up volume	Feed/Retentate Permeate	0.6 mL 0.6 mL	10 mL 8 mL	252 mL 118 mL	312 mL 121 mL
Typical Working Volume		10 – 500 mL	0.2 – 50 L	2L – 4000 L	10L – 10,000 L
Temperature Range		4 – 50°C			
Max Pressure		100 psi			
Max Flow Rate		0.5 LPM	9 LPM	49 LPM	140 LPM
Connectors	Feed/Retentate Permeate	Luer Lock Luer lock	½" tri-clamp ½" tri-clamp	1" tri-clamp 1" tri-clamp	1.5" tri-clamp 1" tri-clamp
Weight (FPI Only)		0.47 lb 0.21 kg	0.72 lb 0.33 kg	4.23 lb 1.92 kg	4.49 lb 2.04 kg

3.3 Product Contents

TangenX FPI Contents:

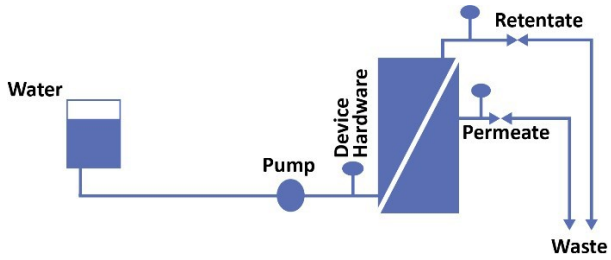
- One (1) TangenX Filter Plate Insert (FPI)
- One (1) Isolation Plate
- Certificate of Quality
- Information Guide

4. Operational Considerations

4.1 Unpacking the FPI

TangenX FPI should be unpacked from the box and moved to a clean surface. Do not lift FPI using fittings or drop the FPI while handling. Doing so can crack or chip the fittings. The TangenX FPI is double-bagged under a partial vacuum. Depending on environmental conditions, the amount of air in the bags will vary.

Figure 2. Example FPI Flush Flow Path



4.2 Equilibration of TangenX FPI

FPI should be equilibrated with an appropriate buffer (e.g., phosphate buffered saline) to ensure the neutralization of the 0.2 M sodium hydroxide storage agent in the membrane filter. Verify that the pH of the effluent from the cassette is neutralized to minimize any possible interaction with your application. For most applications, further sanitization is not required.

4.3 Disposal of Used TangenX FPI

The fluid path of the TangenX FPI should be contained to minimize potential hazards of the process fluid. Disposal will be dependent on the feed stream used and the user's facility requirements.

4.4 Storage of TangenX FPI

Unused FPI should remain sealed in their original packaging prior to use to maintain their cleanliness.

4.5 FPI Batch Numbers

FPI batch numbers are printed on each product label. The batch number is the eight (8) digit manufacturing process order number assigned by the SAP system. A batch is defined as a group of consecutively built cassettes manufactured on the same day and generated from the same SAP process order. Batch traceability is maintained on the batch record and in the quality system.

4.6 FPI Catalog Numbers

FPI catalog numbers are printed on each product label. The catalog number and description for each FPI type is summarized in Table 3.

Table 3. Catalog Part Numbers

Catalog Number	Description
TFPLS-LVFL	SIUS-LHV Filter Plate Insert x Female Luer
TFPLS-SA08	SIUS-LS Filter Plate Insert x 1/2" TC
TFP75-SE16	SIUS-75 Filter Plate Insert x 1" TC
TFP99-SP20	SIUS-150 Filter Plate Insert x 1-1/2" TC

5. TangenX FPI Shelf Life

5.1 Shelf Life Study

The following section describes the method used to evaluate the shelf life of the TangenX Filter Plate Insert (FPI) manufactured by Repligen. The TangenX FPI is manufactured, sanitized, packaged, and stored for a period of time prior to shipment. Once shipped, the FPI may then remain unopened for another period of time before it is put into use. The maximum projected duration for the filter plate insert shelf life has been determined to be up to three years.

TangenX FPI are manufactured using SOP conforming to the Repligen standard manufacturing process. The following steps were taken as part of the study:

1. FPI were prepared using best manufacturing practices.
2. FPI were sampled and studied following this procedure.

Procedure TX1001-POQ-151 was used to evaluate shelf life stability, including determination of appropriate time points for sampling and evaluation. Each FPI was evaluated in accordance with the Repligen standard QC release procedure and acceptance criteria (Table 4).

Table 4. TangenX FPI Shelf Life Study Acceptance Criteria

Acceptance per TX1001-POQ-151	Limit
Visual Inspection	No Cracked, broken, or leaking parts
Endotoxin Level	<0.25 EU/mL
Total Organic Carbon (TOC)	<0.013 mg/cm^2

5.1.1 Shelf Life Study Results

Several filter plate inserts were manufactured and evaluated in triplicate. Each filter plate insert was prepared using current SOP and reflect the standard filter plate insert manufacturing process. The following steps were taken as part of the study:

- Filter plate inserts were prepared using SOP-0529
- Each FPI was released following the QC release procedure SOP-0535
- The FPI were sampled and studied following the procedure TX1001-POQ-151

This summary provides final results from filter plate inserts manufactured at Repligen for shelf life storage stability. This summary will also be used to review results of the sampling and testing throughout the study. One Filter Plate Insert type (TFPLS-SA08) was chosen as it accurately represents the construction of the entire product line. Each FPI tested will represent the entire FPI line manufactured by TangenX. The storage study consists of one condition at ambient temperature and was designed to simulate exposure at a normal or median temperature. This study was concluded within (3) three years and considered a standard storage study at ambient temperature.

Each filter plate insert type at a given time point was evaluated in triplicate. In the event one FPI failed during the study, a failure analysis would have been conducted through the deviation procedure. If all three failed during any one time point, the endpoint of the study would have been reached and the study concluded. The filter plate insert acceptance criteria and each filter plate insert part that met the approved acceptance criteria and is summarized in the tables below.

Table 5. FPI Shelf Life Study Results

Test	Time-initial	1 Year	2 Years	3 Years
Release test (TX1001-SPE-348)	Pass	Pass	Pass	Pass
Endotoxin (EU/mL)	<0.005	<0.005	<0.005	<0.005
Total Organic Carbon (TOC; mg/cm^2)	0.009	0.007	0.010	0.009

5.1.2 Conclusions

The study report (TX1001-POQ-151-R) summarized the results of the shelf life storage study of the filter plate over three years. Several filter plate inserts were manufactured and evaluated in triplicate. Each filter plate insert was prepared using standard SOP and reflect the standard filter plate insert manufacturing process at the time of the study.

In addition to the release testing, the filter plate inserts were tested for endotoxin levels and total organic carbon (TOC). The published specification for the maximum allowable endotoxin level for the FPIs is 0.25 EU/ml and was shown to be below the limit after three years. The value for the level of TOC initially extracted from the FPIs is 0.009 mg/cm^2 and was shown to be comparable after three years.

The results show the tangential flow filtration filter plate inserts meet or exceed all release specifications at ambient conditions after three years. The filter plate insert storage study successfully reached its three year conclusion.

6. Chemical Compatibility

Table 6. FPI Chemical Compatibility

Acids		Bases		Organic Solvents	
Acetic acid 10%	✓	Acid salts	✓	Acetone	✓
Acetic acid 100%	✓	Aqua ammonia	✓	Aniline	✓
Acetic acid 50%	✓	Basic salts	✓	Benzol	X
Acetic acid 75%	✓	Calcium hydroxide	✓	Butyl alcohol	✓
Benzoic acid	✓	Caustic soda	✓	Carbon disulfide	X
Boric acid	✓	Neutral salts	✓	Carbon tetrachloride	X
Butyric acid	✓	Nitroferricyanide	✓	Chlorobenzene	X
Chlorohydric acid 10%	✓	Potassium bicarbonate	✓	Chloroform	X
Chlorohydric acid 37%	✓	Potassium hydroxide	✓	Ethyl acetate	✓
Chromic acid	✓	Potassium permanganate	✓	Ethyl alcohol	✓
Citric acid	✓	Sodium cyanide	✓	Ethyl dichloride	X
Hydrobromic acid 25%	✓	Sodium hypochlorite	✓	Ethyl ether	X
Hydrocyanic acid	✓			Formalin 37%	✓
Hydrofluoric acid	✓			Heptanes	X
Maleic acid	✓			Methyl alcohol	✓
Nitric acid 5%	✓			Methyl ethyl ketone	X
Nitric acid 65%	X			Methylene (di)chloride	X
Oleic acid	✓			Nitrobenzene	X
Oxalic acid	✓			Petrol	X
Perchloric acid	✓			Phenol	✓
Phosphoric acid 25%	✓			Toluene	X
Phosphoric acid 85%	✓			Trichlorethylene	X
Phthalic acid	✓				
Sulphuric acid 10%	✓				
Sulphuric acid 78%	✓	✓: Compatible, no significant changes observed			
Sulphuric acid 93%	X	X: Not compatible, significant change noted			
Tannic acid	✓	Reference: PP polypropylene - chemical resistance (as of January 18, 2024) https://www.engineeringtoolbox.com/polypropylene-pp-chemical-resistance-d_435.html			
Tartaric acid	✓				

7. Safety Information

7.1 USP Class VI

The purpose of UPS Class VI testing is to verify the biological safety of each component(s) used in the TangenX FPI product line. Samples for both USP and extractables testing required preparation prior to analysis. Each sample was fabricated, sanitized with 0.2 M NaOH and rinsed with purified water prior to testing as part of the standard manufacturing process. Each sample was individually packaged in the certified clean-room manufacturing space and released per standard SOP. Approved procedures were followed during preparation of samples and for USP safety testing. The procedures were used to provide a record of the samples to be prepared, as well as the method of preparation. Any experimental deviations and their corrections were recorded, as were the effect, if any, on the experiment.

All components used in the filter plate inserts manufactured by Repligen have been independently tested for USP safety and were shown to be safe according to:

- Class VI per USP <88>
- L929 MEM Elution per USP <87>
- Hemolysis - Indirect with Rabbit Blood

The study proposal for the USP testing conducted with Toxikon (now Labcorp) is found in Toxikon GLP laboratory reports 14-04427-G1, 14-04427-G2, and 14-04427-G3. The study results generated by Toxikon are found in the complete USP report that can be provided by Repligen. A summary of the test results is shown below (Table 7).

Table 7. USP Class VI Test Results

Test ID	Test Description	GLP Report Number	Result
USP Class VI	USP 37, NF 32, 2014 <88> Biological Reactivity Tests, In Vivo	14-04427-G1	Pass
MEM Elution	USP 37, NF 32, 2014 <87> Biological Reactivity Tests, In Vitro	14-04427-G2	Pass
Hemolysis	ASTM F 756-13, Standard Practice for Assessment of Hemolytic Properties of Materials, 2013	14-04427-G3	Pass

7.2 TangenX FPI Leachables Study

A controlled leachables study was performed on the TangenX FPI, simulating routine component exposure. Several batches of TangenX FPI were manufactured and evaluated for leachables in purified water. Each FPI was prepared using current SOP and reflected the standard manufacturing process at Repligen. The following steps were taken as part of the study:

- Extract the samples in purified water with a 1:1 ratio (mL:cm^2) extraction ratio
- Analyze extract samples for total organic carbon (TOC)
- Analyze sample extracts for metals using ICP

Test samples were removed from their packaging and extracted in purified water for 24 hours at 40°C. The test articles were agitated using a rocking table for the duration of the extraction. Once the sample time point was reached, the extraction fluid was drained from the FPI and analyzed for leachables. The following is a summary of the testing performed.

Total Organic Carbon (TOC) was conducted based upon the following references:

- USP-NF Issue 2 2023 <643> Total Organic Carbon.
- ISO/IEC 17025, 2017, General Requirements for the Competence of Testing and Calibration Laboratories.

The test and control samples were analyzed for total organic carbon by converting TOC to carbon dioxide (CO_2) by acidification and chemical wet oxidation with sodium persulfate. The CO_2 liberated from the test samples was measured using an infrared detector. The test article (DI Water Extract – 24hr at 40°C) and the control article (DI Water Sample – Control), both in glass vials, were analyzed for TOC and the results were reported (Table 8).

Induction Coupled Plasma (ICP) was conducted based on the following references:

- EPA Method 3010A – Acid Digestion of Aqueous Samples and Extracts for Total Metals for Analysis by FLAA or ICP Spectroscopy, July 1992.
- ASTM D1971-16(2021)e1: Digestion of Water Samples for Determination of Metals by Flame Atomic Absorption, Graphite Furnace Atomic Absorption, Plasma Emission Spectroscopy or Plasma Mass Spectroscopy.
- SW 846 Method 6010B, 1996, United States Environmental Protection Agency. Inductively Coupled Plasma – Atomic Emission Spectrometry (ICP).
- USP-NF 2023. <730> Plasma Spectrochemistry.
- ISO/IEC 17025, 2017, General Requirements for the Competence of Testing and Calibration Laboratories.

A 10 mL aliquot each of the test and control were acid digested on a hot block to reduce interference by organic matter and to convert metals associated with particulate to a form that could be measured by ICP/MS. The digestate was analyzed for metals by ICP/MS (Figure 3).

Table 8. TOC Results Summary

Sample Description	Extraction Solvent	Results – 24 Hours at 40°C	
		ug/mL	µg/cm²
TangenX FPI	WFI	0.5	0.5

Figure 3. ICP Results Summary

DI Water Extract – 24 hrs at 40C			
Element	Results (µg/L)		Reporting Limit (µg/L)
	Sample	Control	
Aluminum	ND	ND	20.0
Antimony	ND	ND	1.00
Arsenic	ND	ND	1.00
Barium	ND	ND	1.00
Beryllium	ND	ND	5.00
Boron	ND	ND	30.0
Cadmium	ND	ND	1.00
Calcium	ND	ND	40.0
Chromium	ND	ND	1.00
Cobalt	ND	ND	1.00
Copper	ND	ND	1.00
Iridium	ND	ND	1.00
Iron	ND	ND	20.0
Lead	ND	ND	1.00
Magnesium	ND	ND	20.0
Manganese	ND	ND	1.00
Molybdenum	ND	ND	1.00
Nickel	ND	ND	1.00
Palladium	ND	ND	1.00
Platinum	ND	ND	1.00
Potassium	ND	ND	30.0
Rhodium	ND	ND	1.00
Ruthenium	ND	ND	1.00
Selenium	ND	ND	5.00
Silicon	ND	ND	20.0
Silver	ND	ND	5.00
Sodium	48.9	63.4	20.0
Strontium	ND	ND	1.00
Thallium	ND	ND	1.00
Titanium	ND	ND	1.00
Tungsten	ND	ND	1.00
Vanadium	ND	ND	1.00
Zinc	ND	ND	10.0

ND = Not Detected at Detection Limit

7.3 Endotoxin Test

TangenX FPI produced by Repligen are sanitized in 0.2 M sodium hydroxide, rinsed with purified water, dried, and then packaged prior to shipment. The careful preparation of these FPI allows them to be used in a biopharmaceutical process with minimal preparation. The following study was conducted to verify that TangenX FPI do not contain an amount of endotoxin that could potentially contaminate a process stream. This study quantifies the amount of endotoxin extracted from each FPI in purified water and evaluated for endotoxin count by an approved contract lab.

Figure 4. Endotoxin Report

Report Date 3/5/2015
Final Non-GLP Report 14-04428-N3

Test Article	Filter Plate Insert
Lot/Batch #	W4336A, W4336B, W4336C
Study	Amoebocyte Lysate Chromogenic Testing – USP
Comments	None

REFERENCES: The study was conducted based upon the following references: USP 37, NF 32, 2014. <85> Bacterial Endotoxins Test.

ISO/IEC 17025, 2005, General Requirements for the Competence of Testing and Calibration Laboratories.

GENERAL PROCEDURE: Each test article (3 units) was individually immersed in 200 mL of SWFI and the extraction fluid remained at room temperature for 60 ± 2 minutes. Each test article extract was individually assayed in duplicate at the neat concentration. A standard curve of endotoxin was prepared with concentrations of 0.005, 0.05, 0.5, and 5 EU/mL in duplicate. A positive product control (PPC) was prepared containing 0.09 mL of the test article and 0.01 mL of the 5 EU/mL endotoxin standard to give a final concentration of 0.5 EU/mL. Bacterial Endotoxin Water (endotoxin–free) served as the negative control. The microtiter plate was pre-incubated in the plate reader at 37 ± 1 °C for ≥ 10 minutes. After incubation, Lysate (0.1 mL) was added to each well and the absorbance of each well at 405 nm was read every 150 seconds for a total of 40 data points or until the concentration reaches 0.2 absorbance units. The Kinetic QCL reader uses the initial reading of each well as its own blank. The absolute value of the correlation coefficient (r) must be ≥ 0.980 in order for the test to be valid. The study and its design employed methodology to minimize uncertainty of measurement and control of bias for data collection and analysis.

RESULTS:

Sample	Dilution	RAW EU/mL	EU/Device	Valid PPC (Yes/No)
W4336A	Neat	< 0.005	< 1	Yes
W4336B	Neat	< 0.005	< 1	Yes
W4336C	Neat	< 0.005	< 1	Yes

CONCLUSION: The test articles each contained < 0.005 EU/mL and < 1 EU/Device. The absolute value of the correlation coefficient for the linear regression was calculated to be 0.999.

Three lots of FPIs were manufactured and evaluated for endotoxin. Each FPI was prepared using approved SOP and reflected the standard manufacturing process at Repligen.

The FPI was immersed in purified water, held in a sterile media bottle for 60 minutes with a minimum volume of purified water, then tested for endotoxin. The samples were analyzed, and the results reported (Table 9). The results of the endotoxin count study show that the level of endotoxin was below the detection limit and below acceptable limits when compared to industry standards of <0.25EU/mL.

Table 9. Endotoxin Study Results

Sample ID	Total Wetted Area	Collection Volume	Endotoxin	Endotoxin
W4336A	480 cm^2	200 mL	<0.005 EU/mL	<1 EU/cm^2
W4336B	480 cm^2	200 mL	<0.005 EU/mL	<1 EU/cm^2
W4336C	480 cm^2	200 mL	<0.005 EU/mL	<1 EU/cm^2

7.4 Bioburden

The purpose of this summary is to report the procedure and the testing results of bioburden testing conducted on the TangenX Filter Plate Insert. The following study was conducted to quantify the bioburden count from an extraction of TangenX Filter Plate Inserts used with the tangential flow filtration cassettes. The experiment was performed in triplicate. Three FPI were extracted in 3 L of RODI water in a 4 liter glass vessel with a Teflon™-lined cap. A control vessel was also prepared without an FPI utilizing the same volumes as the samples. All the vessels were agitated once every hour for 4 hours prior to collecting 500 mL extract samples. The samples were evaluated for bioburden count by a contract lab.

The TangenX SIUS PD Filter Plate Insert (TFPLS-SA08) was chosen as it accurately represents the construction of the entire product line. Devices were manufactured and evaluated in triplicate. Each device was prepared using current SOP and reflected the standard FPI manufacturing process at Repligen. The following steps were taken as part of the study:

- FPI were prepared using approved procedures
- FPI were extracted for 4 hours and the liquid analyzed

Figure 5. Aerobic, Anaerobic, Yeast and Mold (AAMI) Bioburden Test

REFERENCES: The study was conducted based upon the following references: ANSI/AAMI/ISO 11137-1, 2006/(R2015) A1: 2013 & A2: 2019 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 11737 - 1: 2018 Sterilization of health care products - Microbiological methods - Part 1: Determination of the population of microorganisms on products.

ISO/IEC 17025, 2017, General Requirements for the Competence of Testing and Calibration Laboratories.

GENERAL PROCEDURE: One (1) liquid sample was provided by the Sponsor for bioburden testing. Following membrane filtration (6 x 50 mL) and rinse with 10 mL of Phosphate Buffered Saline (PBS), each filter was aseptically placed, in duplicate, onto Trypticase Soy Agar (TSA) plates and incubated aerobically and anaerobically at 30-35 °C for 4 days, and in duplicate, onto Sabouraud Dextrose Agar (SDA) plates and incubated aerobically at 20-25 °C for 7 days. Samples of PBS (from the same lot used), served as the negative control, and were similarly filtered, plated, and incubated. Colony Forming Units (CFU) were determined for each filter. The study and its design employed methodology to minimize uncertainty of measurement and control of bias for data collection and analysis.

Acceptance criterion for bioburden testing was <10 CFU/100 mL.

The samples were analyzed, and the results reported (Table 10). The soak samples from each set of FPI (sampled in triplicate) were analyzed for bioburden (AAMI) following the approved study method. Each of the FPI soak samples exhibited no observable colonies (NOC) of bacteria and therefore met the acceptance criteria for bioburden count. The raw data from each FPI may be found in the TangenX Filter Plate Insert Bioburden and Particulates Testing Report (M-TANGENX-230904).

Table 10. Bioburden Study Results

Sample ID	Bioburden	Pass/Fail
FPI081123-TEST1	NOC	Pass
FPI081123-TEST2	NOC	Pass
FPI081123-TEST3	NOC	Pass
FPI081123-CTRL	NOC	Pass

7.5 Particulate Testing

The purpose of this summary is to report the procedure and the testing results of particulate testing conducted on the TangenX Filter Plate Inserts. The following study was conducted to quantify the particulate count of TangenX Filter Plate Inserts used with the tangential flow filtration cassettes. The experiment was performed in triplicate and 500 mL samples were evaluated for particulate matter by a contract lab.

Several FPI (TFPLS-SA08) were manufactured and evaluated in triplicate; each FPI was prepared using current SOP and reflected the standard manufacturing process. The following steps were taken as part of the study:

- FPI were prepared using approved procedures
- FPI were extracted for 4 hours and the liquid analyzed

The particulate count analysis was conducted under USP NF 2023. <788> Particulate Matter in Injections. The results of the particulate count study show the test articles met the test requirements as defined in the USP guidelines. The sample complies with the test if the average number of particles present in the units tested does not exceed 25 per milliliter 10 – 25 µm and 3 per milliliter ≥25 µm.

The results of the particulate study are summarized in Table 11. The control data was for the container alone. The control sample consisted of a 500 mL of water from the same volume used for the extraction. The FPIs were then evaluated in triplicate.. The raw data from each FPI may be found in TangenX Filter Plate Insert Bioburden and Particulates Testing Report (M-TANGENX-230904).

Table 11. Particulate Study Results

Sample Number	Particles 10 – 25 Micron	Particles >25 Micron	Pass/Fail
FPI081123-TEST1	9.0000/mL	0.5500/mL	Pass
FPI081123-TEST2	5.9500/mL	0.7000/mL	Pass
FPI081123-TEST3	9.0500/mL	0.8000/mL	Pass
FPI081123-CTRL	6.8500/mL	0.0000/mL	Pass

The data show the control contributes to a portion of the particles found in the test samples but did not contribute to a failure. In conclusion, the particulate count study showed the test articles meet the test requirements as defined in the USP guidelines <788> for particulate matter in injections and that the FPI manufacturing process minimizes the particulate count prior to shipment of the cassette products.

7.6 BSE Free Materials

Raw materials used in the manufacture of Repligen filter plate inserts have been accepted for use in accordance with standard operating procedures and meet all incoming release criteria. Repligen certifies that the components used in the production of the FPI are not formulated with derivatives of tissue or cells of animal origin based on statements provided by approved suppliers. This certification ensures that the components used in the production of filter plate inserts are TSE/BSE free as stated in the Quality Assurance Certificate QS-2996.

7.7 Melamine Free Materials

Raw materials used in the manufacture of Repligen filter plate inserts have been accepted for use in accordance with standard operating procedures and meet all incoming release criteria. Repligen certifies that the components used in the production of the FPI are melamine free based on statements provided by approved suppliers. This certifies that all materials provided to Repligen Corporation are free of melamine contamination as identified in the FDA Guidance for Industry – Pharmaceutical Components at Risk for Melamine Contamination (August 2009). As such, this material can be declared free of melamine as stated in the Quality Assurance Certificate QS-2996.

8. Qualification

An IQ and OQ were performed for each piece of critical equipment utilized in the production of the membrane and FPI assembly. Initial qualifications are performed when a new process is used or a piece of equipment is introduced that is unique in application. Repeat or supplementary qualification activities are performed when a significant change in process, equipment, or system are introduced.

8.1 Installation Qualification (IQ)

IQ is verification that the item qualified was installed correctly. The following criteria was considered in each IQ:

- Equipment design features (i.e. materials of construction, cleanability, etc.)
- Installation conditions (wiring, utilities, functionality, etc.)
- Calibration, preventative maintenance, cleaning schedules
- Safety features
- Supplier documentation, prints, drawings, and manuals
- Software documentation
- Spare parts list and inventory
- Environmental conditions (such as clean room requirements, temperature, humidity)

8.2 Operation Qualification (OQ)

Parameters were challenged to assure that outputs met all defined requirements under all anticipated conditions of operations. To establish process control limits, critical parameters and or product characteristics were challenged. These control limits were established and documented to determine the robustness of the process through the spectrum of potential ranges. The following criteria were considered in each OQ:

- Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
- Documented procedures and work instructions
- Software parameters
- Raw material specifications
- Process operating procedures
- Material handling requirements
- Potential failure modes, action levels and worst-case conditions (failure mode and effects analysis, fault tree analysis)

Qualifications were performed with a risk based approach, addressing potential risks associated with the processes, system, analytical method, and/or equipment that were addressed with appropriate risk level and mitigation. Any risk identified as major or critical was challenged during qualification and/or validation activities.

8.3 Responsibilities

System Owner: Ensures that the validation parameters, requirements, and the acceptance criteria are properly determined.

Operator/Executor: Ensures protocol is performed per the approved document and executes the qualification/validation in accordance with the protocol and good documentation practices (GDP).

Technical Lead: Generates draft protocols which are circulated to subject matter experts within the organization for review and approval. Reviews and approves the final validation report to confirm that the process, system, analytical method, and/or equipment are suitable for intended use.

Quality Assurance: Reviews and approves the validation protocol and approves the final report to confirm that the protocol was properly executed and that any deviations/discrepancies have been addressed and documented.

9. Manufacturing Process Validation

The objective of the process validation is the collection and evaluation of data from the process design stage throughout commercial production to establish scientific evidence that a process is capable of consistently delivering quality product. This involves a series of activities taking place over the manufacturing process. Validation of the filter plate manufacturing process was conducted following the Repligen validation program specified in the validation master plan (VMP-PRO-104-TX1001).

The process validation consisted of an evaluation of a defined, documented procedure to consistently deliver an expected result. Considerations included:

- Equipment and systems put into place established in IQ
- Actual product and process parameters and procedures established in OQ
- Assurance of process capability and control as established in OQ
- Process repeatability, long term process stability
- Acceptability of the product

Final reports summarize the results of an executed qualification and/or validation protocol and document the supported conclusion based on the data obtained. The report summarizes all data collection and analysis as specified in the protocol. It also summarizes all non-conformances, deviations, observations, and data acquired during the execution of the approved protocol for the validation and/or qualification.

9.1 TangenX FPI Process Validation

This section of the document describes the process validation report for the TangenX FPI manufacturing operation at the Repligen Marlborough facility. The validation included approved procedures for incoming inspection, part washing, FPI assembly, bagging, and packaging with their corresponding forms. The FPI assembly process has met the acceptance criteria and is currently a validated process.

This summary defines the validation within the Repligen Marlborough facility for the TangenX FPI manufacturing process. Three (3) batches, each in triplicate for a of a total nine (9) FPI were produced during the process validation. The matrix includes three sets of TFPLS-SA08 filter plate inserts representing the full TangenX FPI product line. The FPI vary between part numbers, but the FPI assembly process is the same for each configuration. This process validation was carried out per VPL-PRO-104-TX1001, the Validation of the Filter Plate Insert Assembly Process protocol.

The development team is responsible for writing the report and ensuring that the report meets the requirements stated the Repligen process validation protocols. Engineering is responsible for ensuring that the validation is performed in compliance with the protocol and with any designated SOP. Drafting, reviewing, and approving validation protocols and/or reports and all associated data is also the responsibility of the development group. Manufacturing supports validation activities, generating and providing supporting data and ensures access to necessary raw materials, utilities, and resources for execution. Quality is responsible for reviewing and approving validation protocols and/or reports and all associated data. Quality is also responsible for maintaining records of executed and completed validation protocols and/or reports and all supporting documentation.

Prerequisites include evidence that all raw materials used in the validation were approved and released by Quality Assurance. All specifications must be written and approved. All the equipment used during the process validation must be qualified. The critical equipment must be calibrated, and the calibration recorded in corresponding logbooks. Protocols and process parameters to be controlled/calibrated can be referenced in approved IQ/OQ test protocols.

The individual procedures were combined and executed as three validation groups where three (3) consecutive batches of cassettes were manufactured. Each of the cassettes used in the FPI were individually tested according to the approved FPI QC Test Procedure and released.

Following the validation, Quality Assurance conducted a review of the batch data, verifying the adherence to set specifications. Quality Assurance was responsible for the final review of the executed validation procedures and test results. The test results for each FPI are in Table 12.

Table 12. FPI Process Validation: Data Summary

Catalog #	Batch ID	Quantity Tested	Quantity Produced	Test Yield	Target Yield	Result
SFPLS-SA08	W5114A	3	3	100%	>75%	Pass
XP300S05L	W5114B	3	3	100%	>75%	Pass
XP050S15L	W5114C	3	3	100%	>75%	Pass

All FPIs passed testing per criteria and final inspection defined in the final QC release test procedure. All validation documentation was successfully completed with a process yield of 100%, per the validation protocol VPL-PRO-104-TX1001. The TangenX FPI assembly process was considered validated and released for production usage with the completion of the process validation.

10. Certificate of Quality

Figure 6 shows an example of the standard Quality Assurance Certificate provided with each TangenX FPI manufactured by Repligen. A specific product part number, batch number, and description will be included on the label attached in the upper left corner of the certificate.

Figure 6. QA Certificate of Quality for TangenX FPI

REPLIGEN
INSPIRING ADVANCES IN BIOPROCESSING

Repligen Corporation
111 Locke Drive
Marlborough, MA 01752

Quality Assurance Certificate

This is to certify that the TangenX® SIUS® Filter Plate Insert Kit as indicated by the affixed label complies with the following descriptions and specifications:

REPLIGEN Marlborough, Massachusetts USA
www.repligen.com/tangenx

TangenX® SIUS® Filter Plate Insert Kit

USE BY: **06-OCT-2027**
PLATE MATERIAL: **POLYPROPYLENE**
FEED/RETENTATE: **1" TRI-CLAMP**
FILTRATE: **1" TRI-CLAMP**
RETENTATE FLOW: **49 LPM (MAX RECOMMENDED)**

BATCH # **99999999**
CATALOG # **TFP75-SE16**

Product Quality – TangenX® SIUS® Filter Plate Insert Kit

This product has been manufactured in a fully validated and documented manufacturing process under an ISO 9001:2015 quality management system.

Repligen Corporation also certifies that all raw materials used to manufacture this product have been received and approved for use according to approved standard operating procedures.

Additionally, it certifies the finished product has been manufactured and tested in accordance with standard operating procedures, meeting all specified release criteria. Furthermore, this filter plate insert has been inspected and further ensures each unit meets quality standards set by Repligen.

The results of the release testing were found to meet or exceed the minimum requirements set by our Quality Assurance Department. Therefore, Repligen Corporation certifies that this product will perform according to published specifications providing it is used according to the manufacturer's recommendations.

USP Safety Information

Repligen Corporation certifies that the resin utilized to manufacture each filter plate insert kit meets the following specifications according to the resin manufacturer:

1. Current requirements for USP Class VI biological test for plastics.
2. EMA/410/01 Rev.3
   Note: Trace amounts of animal derived material originating from tallow exist, but the processing conditions meet the requirements described in section 6.4 of the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).
3. Certifications that the components used in the production filter plate inserts are free of melamine.

All components materials used in the filter plate inserts have been independently tested for USP safety and were shown to be safe according to:

1. L929 MEM Elution per USP <87>.
2. Class VI per USP <88>.
3. Hemolysis - Indirect with Rabbit Blood ISO 10993-4.

Multiple lots of filter plate inserts were extracted in one (1) liter of phosphate buffered saline and tested for:

1. Endotoxin testing following references USP 37, NF 32, 2014 <85> bacterial endotoxin test, guidance on validation of the Limulus amebocyte lysate (LAL) test as an end product. These levels were < 0.005 EU/ml as determined by the LAL test method.
2. Total Organic Carbon following references USP 37, NF 32, 2014 <643> Total Organic Carbon. The mean value was found to be 0.013 mg/cm² as determined by the TOC test method.

Signature Required:
Reviewed and approved for accuracy and completeness.
Paul Wallace, Director of Quality
Signature and Title

SAMPLE

Document Number: QS-2996 Revision: 2 Effective Date: 10/8/2024 Legacy Document #: QADOC013
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11. List of TangenX Cassette and FPI studies

1. VMP-TX1001: Validation Master Plan
2. VMP-104-TX1001: FPI Process Validation Master Plan
3. VPL-104-TX1001: FPI Process Validation Plan
4. TX1001-POQ-149: OQ for Washer
5. RA-5042A: FPI Risk Analysis
6. TX1001-POQ-151: FPI Shelf Life Study Procedure
7. TANGENX-230904: TangenX FPI Bioburden and Particulates Testing Report

12. References

1. Class VI Test per USP <88> Includes: Systemic Injection, Intracutaneous Injection, and 7-Day Muscle Implant.
2. Bioburden: ANSI/AAMI/ISO 11137-1 2006 /R2010 & A1:2013 Sterilization of healthcare products; Part 1 Determination of a population of microorganisms on products
3. USP 42, NF 37, 2019 <85> Bacterial Endotoxin Test, USP current revision, <161> Medical FPIs Bacterial Endotoxin and Pyrogen Tests.
4. EMA Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).
5. Particulate count analysis was conducted under USP NF 2023. <788> Particulate Matter in Injections.

13. Index

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