XCell® ATF 6 and 10 Single-Use Devices

Regulatory Support File

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Customer Support
customerserviceUS@repligen.com
+1-800 622-2259 (Option 1)

Repligen Corporation
41 Seyon Street Building 1, Suite 100
Waltham, Massachusetts 02453
USA
www.repligen.com

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Abbreviations

A2B	XCell ATF Device to Bioreactor connection
A2C	XCell ATF Device to Controller connection
ABS	Acrylonitrile Butadiene Styrene
AIT	Assembly Integrity Test
ATF	Alternating Tangential Flow
BPOG	BioPhorum Operations Group
CFU	Colony Forming Units
COQ	Certificate of Quality
COP	Certificate of Processing
DAC	Disposable Aseptic Connector
DDVR	Displacement to dead volume ratio
DIT	Diaphragm Integrity Test
EU	Endotoxin units
FAS	Field Applications Scientist
FDA	Food and Drug Administration
FSE	Field Service Engineer
GMP	Good manufacturing practice
HFF	Hollow Fiber Filter
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
L	Liter
LPM	Liters per minute
LS	Large Scale Controller
PD	Process development
PES	Polyethersulfone
PMMA	Polymethyl methacrylate
PPE	Personal protective equipment
PS	Polysulfone
PVDF	Polyvinylidene Fluoride
QC	Quality control
QMS	Quality Management System
SS	Stainless steel
SSB	Stainless steel bioreactor
SU	Single-use
SUB	Single-use bioreactor
USP	United States Pharmacopeia
WFI	Water for Injection

Definitions

ATF rate	Rate at which cell culture is exchanged between the bioreactor and XCell ATF Device. *ATF Rate (L/min) = Pump displacement volume (L) ÷ Cycle time (min)*
Filtration rate	Rate at which cell culture fluid flows across the hollow fiber membrane. The surface area of the hollow fiber membrane largely determines the value.

1. Introduction

The XCell® ATF 6 and 10 Single-Use Devices 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 a Drug Master File submission

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. This reference document is updated regularly. For the latest version of the document, please visit repligen.com/resources.

This Regulatory Support File presents product information for XCell ATF 6 and 10 Single-Use Devices from Repligen Corporation. This information should be used to guide validation activities, process development, and scaling up the process.

The XCell ATF 6 and 10 Single-Use Devices come with user instructions as well as product quality and performance data. This product quality and performance data, combined with the information in this document and data collected from process development studies, provide much of the information needed to validate an upstream process effectively and efficiently.

1.1 Where to get help

For more information about alternating tangential flow (ATF) and filter module validation, contact the technical support team at Repligen. The technical support team includes scientists and engineers who can:

- Answer your technical questions.
- Assist in the selection and design of ATF systems.
- Provide user training programs.

Specifically, Repligen provides the following support:

- Process optimization and evaluation support
- Integrity testing
- Validation protocol development
- Troubleshooting
- Preventive maintenance to ensure the continued efficiency of the ATF 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.

1.2 Quality policy and standards

A copy of the Repligen Quality Policy can be found on repligen.com/resources.

To meet the needs of GMP manufacturing, these products are manufactured in the USA under the following quality standards:

- Repligen maintains an ISO 9001:2015 compliant Quality Management System that is currently certified by 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/or ISO 10993 Biosafety for *in vivo* biological reactivity.
- All filters and 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.

2. Product design and performance

2.1 Product overview

XCell ATF technology provides a complete solution for cell retention within a bioreactor during cell culture processes. XCell ATF technology optimizes cell retention due to its effectiveness, proven reliability, and scalability in commercial processes. The devices are designed to enable linear scaling from XCell ATF 1 to 10 to support multiple scales of cell culture development and cGMP manufacturing for scale-up to 5000 L. XCell ATF technology combines hardware, software, a filtration device, and an innovative pumping method to achieve the filtration result.

Large-scale bioreactors are often used in pilot installations to validate a wide range of cell-culture processes developed at bench-scale process development and for commercial biomanufacturing operations. These processes include cell line characterization, media optimization, development of fed-batch intensification, and long-term perfusion applications, as well as other intensified processes. XCell ATF devices are designed to enable reliable scaled-up, high-density/high-viability cell culture applications with linear flux and shear parameters. They are operated using the XCell Lab or legacy XCell C24 for ATF 1 (Lab only), 2, and 4 and XCell LS or legacy XCell C410 Controllers for ATF 4, 6 and 10. The controllers and their integrated accessories constitute a robust platform for clinical and commercial manufacturing of biomolecules such as monoclonal antibodies, recombinant proteins, plasmid DNA cultivated meat, and cell therapies.

Figure 1: XCell ATF Devices are an integrated solution that scales from PD to commercial scale

	XCell ATF 1	XCell ATF 2	XCell ATF 4	XCell ATF 6	XCell ATF 10
Typical bioreactor size (L)	0.5-2	2-10	10-50	50-200	200-1000+
Format	SU	SU, SS	SS	SU, SS	SU, SS
Chemistry	PES	PES, PS	PES, PS	PES, PS	PES, PS
Typical pore size SU	0.2 µm	0.2 µm	N/A	0.2 µm	0.2 µm
Typical pore size SS	N/A	0.2µm, 0.5µm, 50kDa, 30 kDa	0.2µm, 0.5µm, 50kDa, 30 kDa	0.2µm, 0.5µm, 50kDa, 30 kDa	0.2µm, 0.5µm, 50kDa
Effective surface area (m^2)	0.022	0.13	0.77	2.5	11
Filter height (cm)	60	60	30	60	60
Displacement volume (L)	0.017	0.1	0.4	1.3	6.0
ATF flow range (LPM)	0.008-0.140	0.3-1.5	3-8	10-17.2	20-80
XCell C24 Controller (legacy)		Supports XCell ATF 2 and 4			
XCell Lab Controller	Supports XCell ATF 1, 2, and 4				
XCell C410 Controller (legacy)			Supports XCell ATF 4, 6, and 10		
XCell LS Controller			Supports XCell ATF 4, 6, and 10		

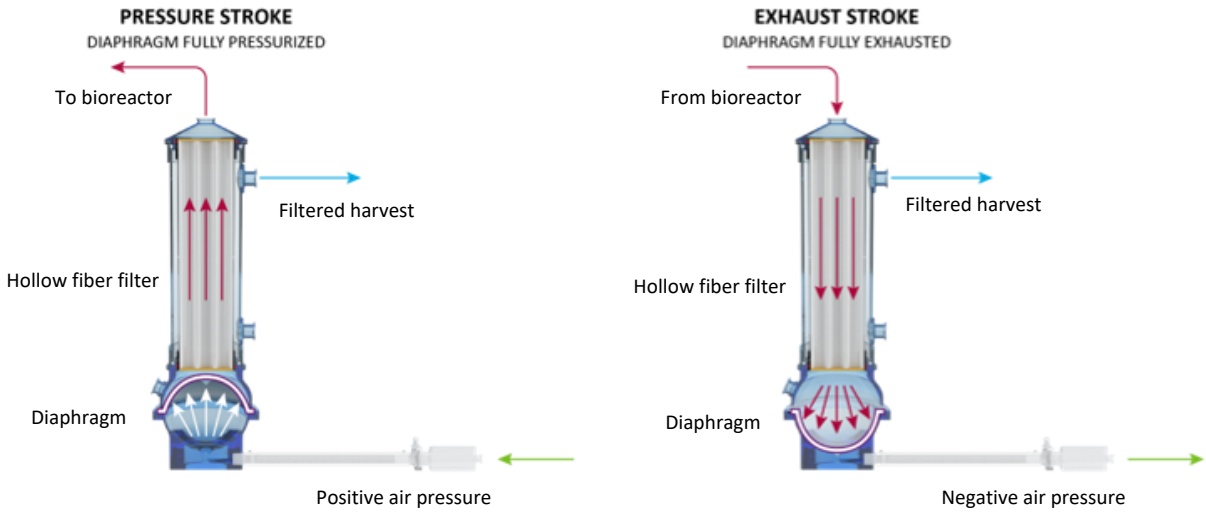
2.2 XCell ATF Devices pump cycle

XCell ATF technology extends filter lifetime by utilizing the innovative principle of alternating tangential flow. XCell ATF devices utilize a diaphragm pump to provide alternating tangential flow through a hollow fiber filter, back and forth between the device and the bioreactor. ATF is a pulsating, reversible flow of liquid between a process vessel and diaphragm pump. In contrast to traditional tangential flow filtrations (TFF) methods, alternating flow creates a beneficial backflush to dislodge film and facilitate filter self-cleaning. The diaphragm movement is constant and uninterrupted, creating a low shear flow for the cell suspension.

The process consists of two cycles (**Figure 2, Figure 3**) the pressure cycle (P-cycle) and the exhaust cycle (E-cycle). The P-cycle occurs when air is fed into the ATF pump, moving the diaphragm up towards the pump liquid-side (PL) hemisphere and driving the liquid from the diaphragm pump through the hollow fiber filter and into the process vessel.

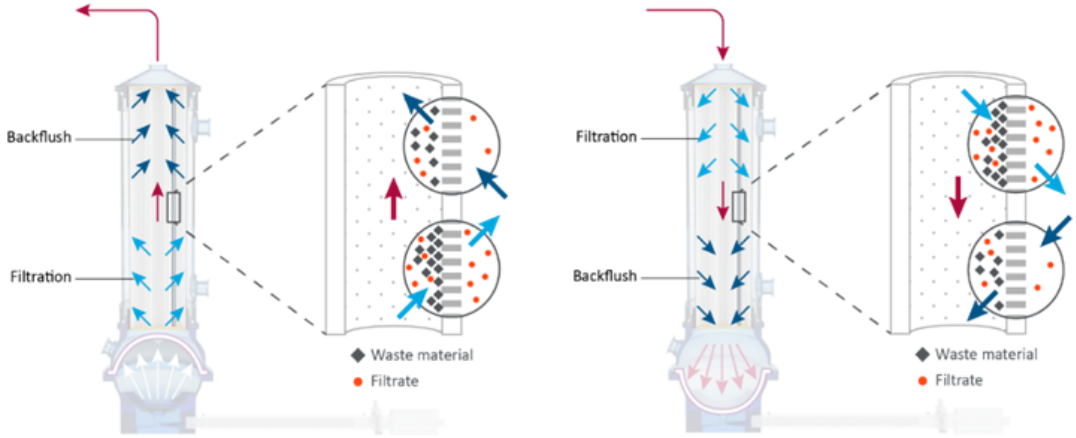
The E-cycle occurs when a vacuum is introduced, thus pulling the diaphragm down towards the pump air-side (PA) hemisphere, and liquid is pulled from the process vessel through the HFF (Hollow Fiber Filters), and back into the diaphragm pump. The diaphragm must travel between the two extremes to complete one cycle. The flow through the hollow fiber filter generates tangential flow in each direction in an alternating fashion. This minimizes biofilm build-up, keeping the filter clean, and enabling a longer perfusion process. The device flow rate is controlled by a dedicated XCell Controller, which relies on pressurized air and vacuum utilities to drive the diaphragm. A range of flow rates is possible and can be optimized to the requirements of a particular cell line and the intended intensified cell culture process.

Figure 2: Alternating tangential flow is driven by air and vacuum applied to the diaphragm pump



Note: *XCell ATF Devices require a vacuum (negative pressure) to move the diaphragm to its lowest position. Positive pressure from the bioreactor is insufficient to completely deflate the diaphragm, necessitating the use of vacuum to ensure proper XCell ATF Device operation.*

Figure 3: Alternating flow in a zoomed single membrane fiber



XCell ATF Device sizes range from the bench scale XCell ATF 1 Device designed for cell culture development work at 500 ml to 2 L working volumes to the large scale XCell ATF 10 Device meant for GMP manufacturing at 200 L to 5,000 L and beyond. Most devices are available in both stainless-steel as well as single-use formats and can be connected to almost any type of bioreactor. The XCell ATF Single-use Device is supplied pre-sterilized and only requires wetting with sterile cell culture media or WFI prior to use. There is no need to sanitize prior to use. The devices are designed to be single-use and are therefore not designed to be cleaned, sanitized, or stored for repeat use. Hollow fiber membranes used within XCell ATF 6 and 10 Single-use Devices are made of polyethersulfone (PES) or polysulfone (PS) with a 0.2 µm pore size and 1 mm inner diameter (ID). The shared properties (Materials of construction, pore size, ID) ensure linear scalability across all device sizes.

Although the use of this device may represent an initial step into this scale of processing, it is assumed that similar processing with the smaller scale XCell ATF 1, 2 or 4 systems has been performed. Therefore, there is a presumption that the individuals following this guide are already skilled in the areas of aseptic technique, process scale fluid handling, interfacing the XCell ATF device with the bioreactor and the use of Repligen's XCell ATF controllers. Additional information on the use of XCell ATF systems can be found in the corresponding controller User Guides at repligen.com/resources.

This guide is not intended to provide optimization guidance for the cell culture process. For further support in optimizing or troubleshooting, please contact your local Repligen Field Applications Scientist (FAS).

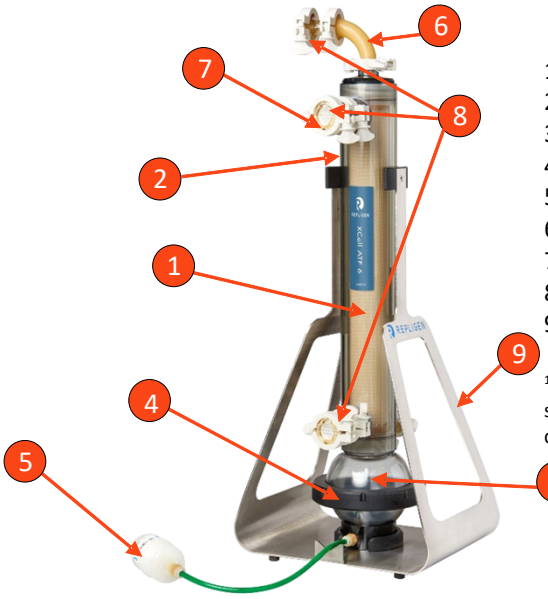
Table 1. General precautions

Phrase	Symbol	Description
IMPORTANT:		The XCell ATF 6 and 10 Devices are designed to be single-use. Any attempt to misuse, reuse, or disassemble it will likely result in a loss of sterility and integrity causing leakage, culture contamination, poor performance and/or damage to the XCell ATF 6 and 10 Devices.
IMPORTANT:		Sterility: The connection between XCell ATF 6 and 10 Device and bioreactor is made utilizing Cytiva ReadyMate™ DACs and CPC AseptiQuik® sterile connectors. It is important to use sterile techniques when connecting and securing the aseptic connector assembly. For wetting and installation, multiple sterile flow path configurations may need to be established. Isolate and clamp tubes along the flow path to maintain sterility.
IMPORTANT:		Ensure the built-in clamps are correctly positioned to establish the requisite flow paths. For best performance, inspect the tubing carefully each time the clamps are removed to ensure the tubing is not crimped. If necessary, gently roll the tubing to re-establish proper flow.
IMPORTANT:		The total length of the A2B tubing from the top of the XCell ATF Single-use Device to the bioreactor port must not exceed 40” for both XCell ATF 6 and 10 Single-use Devices.
WARNING:		Power: Use only the Repligen provided power supply. • Use only high-voltage cord specific for your region provided by Repligen • Do not use a damaged power supply • Do not use a damaged power cord.
WARNING:		Tubing: Tubing breakage between the XCell ATF 6 and 10 Devices and bioreactor may result in fluid spraying from the pump. Use appropriate measures to protect the operator and equipment.
WARNING:		Wear standard laboratory personal protective equipment (PPE), including lab coat, protective eye wear and gloves.

2.3 XCell ATF 6 Single-use Device product design and description

The XCell ATF 6 Device components include a diaphragm pump, filter housing, inlet elbow, and a hollow fiber filter cartridge fitted within the filter.

Figure 4: XCell ATF 6 Single-use Device Components



1. Hollow fiber filter
2. Housing
3. Diaphragm pump
4. Pump closure ring
5. Hydrophobic vent filter
6. Inlet elbow
7. Sanitary clamps
8. Aseptic connectors[1]
9. Stainless steel stand

[1]Device shown has ReadyMate™ DAC; not shown is device with AseptiQuik® connectors.

2.3.1 Diaphragm pump

The diaphragm pump consists of a spherical chamber at the base of the device. A silicone diaphragm separates the air-side hemisphere and the liquid side hemisphere of the pump. The silicone diaphragm moves up and down as either pressurized air or vacuum is applied to the air side of the pump. As the diaphragm pump cycles through exhaust and intake, cell culture suspension moves from the bioreactor to the device and back to the bioreactor. This alternating tangential flow draws cell suspension in a continuous back and forth motion through the lumen of the hollow fiber filters. Alternating flow creates a backflush, enabling filter self-cleaning that minimizes fouling.

2.3.2 Filter module

The filter module contains a hollow fiber filter within a housing. The hollow fiber filter, sitting above the liquid side hemisphere of the diaphragm pump separates media from cells. The filter housing contains five ports: two permeate ports (top and bottom), condition/drain port, and ports to connect the XCell ATF Device to the XCell Controller (A2C) and to connect the XCell ATF Device to the bioreactor (A2B).

Note: *The top permeate port directs permeate to the harvest vessel, while the bottom port may be clamped off.*

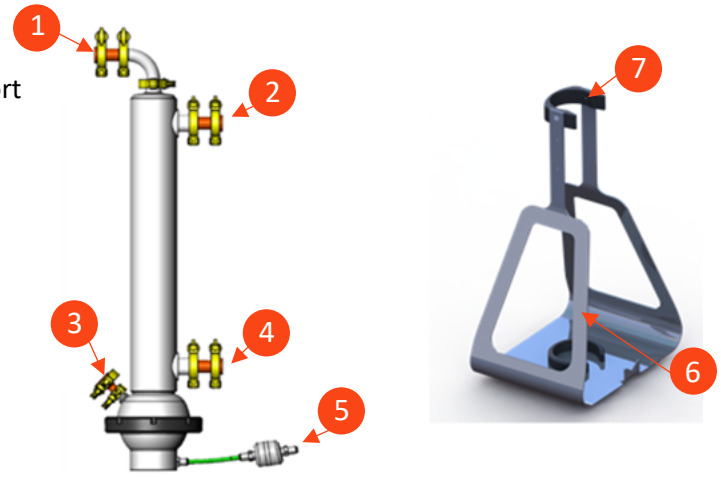
2.3.3 Device ports

The device contains five ports/connection points:

- Top retentate (A2B) port
- Condition/drain port
- Top permeate port
- Bottom permeate port
- XCell ATF Device to XCell Controller (A2C) port

Figure 5: XCell ATF 6 Single-use Device ports and stainless-steel stand

1. Top retentate, A2B port
2. Top permeate
3. Condition/drain port
4. Bottom permeate
5. A2C port
6. Stand bottom ring
7. Stand top ring



All ports, except the A2C port, are supplied dead-ended with disposable aseptic connectors. The A2C port, dead-ended with a vent filter and located at the lowest point on the pump base, is connected to the XCell LS or 410 Controller, allowing pressurized air and vacuum to be delivered to actuate the diaphragm according to the parameters established by the XCell LS or 410 Controller. The remaining four ports carry liquid between the XCell ATF Device and bioreactor or the XCell ATF Device and the permeate vessel. Two ports are connected to the feed side of the cartridge and the other two ports are connected to the permeate cavity. The top retentate port is used to make a connection between the XCell ATF 6 Device and a bioreactor using the A2B1 and A2B2 tubing sets, respectively. Typically, the top permeate port is used for harvesting purposes and the lower permeate port remains closed off throughout the process, but it can be aseptically connected to a pressure transducer to monitor the permeate pressure during the process.

2.3.4 Stainless-steel stand

To ensure stability during set-up and use, it is recommended that the device be placed in the stainless-steel, reusable stand (see **Figure 5**). The stand features a ring to hold the bottom of the device securely and a snap ring to hold the filter housing near the top of the device. The device snaps into the stand with a single click. After use, the device can be easily removed from the stand. The stand is provided with a notch to orient and secure the A2C line. This feature also helps orient the entire device for efficient connectivity and easy access to all the ports. The stainless-steel stand needs to be ordered separately for the XCell ATF 6 Device.

2.3.5 XCell ATF 6 Single-use Device tubing set kits

Fluid management for XCell ATF Devices includes tubing set kits and accessories that connect the device to the bioreactor and the XCell Controller. The tubing set kits ensure that the ratio of displacement volume to hold-up volume is greater than or equal to one at the minimum and maximum flow rate. (Displacement to dead volume ratio (DDVR) >/ = 1).

A2B tubing set kits are available in multiple configurations based on the type of bioreactor in use and the desired connectors. In addition to the tubing set kits, accessories are required.

Tubing set kits include pinch clamps for isolating flow paths and sanitary clamps for securing aseptic connectors. All tubing components are constructed of platinum-cured silicone and are configured with vent filters and aseptic connectors. All tubing set kits are sterilized by gamma irradiation and packed in double plastic bags to maintain sterility.

Notes:

- *Unlinked aseptic connectors are not water resistant. To maintain system sterility, extra care must be taken during set-up to not introduce liquid onto the connector.*
- *Although superficially similar, the tubing sets for the different devices are not interchangeable. Check the labeling on your tubing set to make sure it is appropriate for your device.*
- *The tubing set kits, permeate pressure sensor kits, and flow sensor are ordered separately.*

Table 2: XCell ATF 6 Single-use Device tubing specifications

Item	Component	Sterile connector type	Tubing spec (ID, OD, length, in inches)		
			ID	OD	Length
Tubing set kit	A2B	ReadyMate™ or AseptiQuik®	3/4	1.125	24
	Top permeate		3/4	1.125	12
	Bottom permeate		3/4	1.125	6
	Vent tee		3/4	1.125	10
	Sample port/Drain port		1/2	3/4	6
	End cap	N/A	-	1.5	-
Permeate pressure sensor kit	Pressure sensor	ReadyMate™ or AseptiQuik®	3/4	N/A	4

Table 3: XCell ATF 6 Connection kit details

Part	Description	Purpose
Sanitary tri-clamps	1.5” clamps	Clamp connectors
ATF to Bioreactor Connection	A2B1 Tee with vent filter	Connect to bioreactor, pre-use wetting, integrity testing
ATF to Bioreactor Connection	A2B2 weldable line	Connect to bioreactor
Permeate Connection	Top permeate (optional pressure sensor kit)	Connection to top permeate port, pressure monitoring (if included), wetting, integrity testing
Bottom permeate extension	5” tubing with end cap	Clamp off bottom permeate
Drain connection	Drain tee	Connect to drain port, wetting, draining

2.3.6 Connecting XCell ATF 6 Single-use Device to a Bioreactor

Two types of connections between the device and the bioreactor are available. Hard connections are used where steam-in-place (SIP) is an option, such as with stainless steel bioreactors (SSB). Soft connections are used with single-use bioreactors (SUB) and consist of single-use connectors such as AseptiQuik® and Readymate™ DAC.

Fluid management for XCell ATF 6 Devices includes retentate (A2B) tubing set kits and accessories that connect the device with the bioreactor, ensuring proper exchange of cell culture material. Intended for use in pilot scale, clinical, and commercial bioprocessing environments, tubing set kits work with XCell Controllers. Permeate tubing (not provided) connects the device to the harvest vessel and should be sterilized by autoclave or attached with a tubing welder or disposable sterile coupling. The permeate tubing should be compatible with the filtrate/harvest pump.

Note: *Bioreactor adapters, used to connect tubing set kit to the bioreactor, are not provided.*

Several components are required to connect the XCell ATF 6 device to a bioreactor. XCell ATF 6

autoclavable tubing sets are available in two configurations depending on the preferred connectors. All tubing sets have a pressure rating of 25 psi. Additional accessories are required. In addition, use of a SSB requires a bivalve assembly and connector. For detailed instructions on how to connect to a SSB or SUB please refer to the Set-up Guide repligen.com/resources.

Table 4: Part numbers for XCell ATF 6 Single-use Devices

Part #	Description	Included components
SUATF6-G02PS	XCell ATF 6 Device Single-use, 0.2 µm PS	0.2 µm filter, Cytiva ReadyMate™ Sanitary Connections
SUATF6-S02PES	XCell ATF 6 Device Single-use, 0.2 µm PES	0.2 µm filter, Cytiva ReadyMate™ Sanitary Connections
SUATF6-R02P-A	XCell ATF 6 Device Single-use, 0.2 µm PES	0.2 µm filter, CPC AseptiQuik aseptic connections
SUATF6-PES-AQL	XCell ATF 6 Device Single-use, 0.2 µm PES	0.2 µm filter, CPC AseptiQuik aseptic connections

Table 5: Tubing options for SSB and SUB Connections for XCell ATF 6 Single-use Devices

Tubing set part number	Controller	Tubing connection	Included components
SUATF6-TSK-RM	LS	Cytiva ReadyMate™	A2B, vent tee, top and bottom permeate, drain
SUATF6-TSK-AQG		AseptiQuik® (G)	
SUATF6-TSK-AQG-AQL		AseptiQuik® (G & L)	
SUATF6-TSK-AQGL-M1		AseptiQuik® (G & L)	
SUATF6-TSK-AQ	C410	AseptiQuik®	
SUATF6-TubeSetKit		Cytiva ReadyMate™	

Table 6: Additional Accessories for XCell ATF 6 Single-use Devices

Description	Part number	Controller	Aseptic connector	Single- or Multi-use	Pressure rating (psi)	ID (inches)
Permeate Pressure Sensor	SUATF610-PSK-V2	LS	ReadyMate™	SU	25	3/4
	SUATF610-PSK-AQ-V2	LS	AseptiQuik®			
	SUATF610-PSK-AQG-	LS	AseptiQuik®			
XCell ATF 6 Single-use Device Stand	SUATF6-STD	LS or C410	N/A	MU	N/A	N/A
Bivalve assembly*	ATF6-VLV-KIT	LS	N/A	MU	45	3/4
Connector*	SUATF6-RM-TO-	LS	ReadyMate™	SU	25	3/4
	SUATF6-AQG-TO-	LS	AseptiQuik®			
Vent Filter (A2C line)	F46-AIR-LSC	LS	N/A			
	F:AIR1	C410	N/A			

* Needed for stainless-steel bioreactor connection.

Table 7: Tube Set Kit and Accessory Compatibility for XCell ATF 6 Single-use Devices

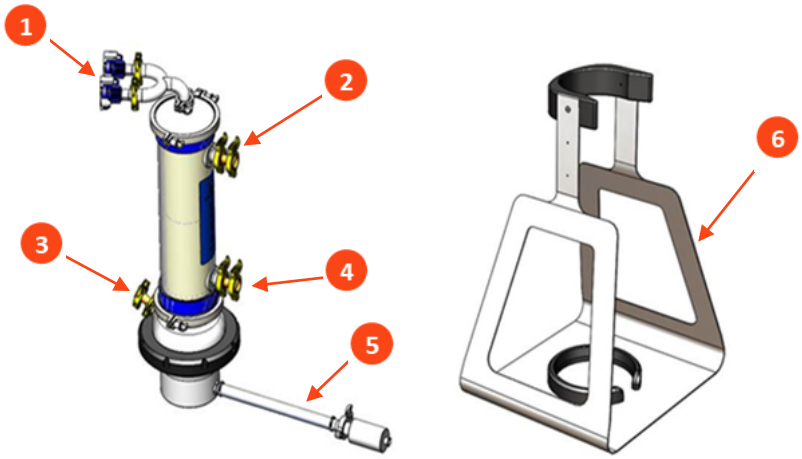
Device	Tube Set Kits	Pressure Sensor Kit	Flow Sensor
suATF6-S02PES suATF6-G02PS	suATF6-Tubesetkit	suATF610-PSK-V2	FS-6C
	suATF6-TSK-AQ		
	suATF6-TSK-AQX-SIL		FS-6
	suATF6-TSK-RM		
	suATF6-AQG-TO-0.75TC		N/A
	suATF6-RM-TO-0.75TC		
suATF6-PES-AQL	suATF6-TSK-LNX		FS-6
	suATF6-TSK-AQG-AQL		
	suATF6-TSK-AQG		
suATF6-R02P-A	suATF6-TSK-AQGL-M1	suATF610-PSK-AQG-V2	

2.3.7 Prerequisites for XCell ATF 6 Device operation

The following equipment is required to operate the XCell ATF 6 Device:

- Controls hardware: An XCell LS or C410 Controller connected to the required air pressure and vacuum pressure sources.
- Permeate (harvest) flow equipment
  - A variable-speed, peristaltic pump able to support flow rates in the range of 50 - 400 mL/min depending on the bioreactor working volume and perfusion rate.
  - A minimum length of 1/4 inch ID tubing, fitted with a single aseptic connector to mate with the XCell ATF 6 Device. It is recommended that the permeate line be sterilized via gamma irradiation or autoclaving.
- Pre-use, off-line filter wetting equipment
  - Fifty liters (50 L) of 0.2 µm filtered WFI or cell culture media dispensed into a single-use bio container (bag) that is fitted with an appropriate length of tubing, a clamp, and a single, terminal, aseptic connector.
  - A sterile 50 L empty single-use bio container (bag) with an appropriate length of tubing, a clamp, and a single, terminal aseptic connector.
  - A variable speed peristaltic pump with a flow capacity of 1 - 4 LPM, and able to accommodate the tubing IDs configured on the media/WFI bag.

Figure 6: XCell ATF 10 Device ports and stainless-steel stand



1. Top retentate
2. Top permeate
3. Condition/drain port
4. Bottom permeate
5. Stainless steel stand

2.4 XCell ATF 10 Device product design and description

The XCell ATF 10 Device includes a diaphragm pump, filter housing, inlet elbow and a hollow fiber filter cartridge fitted within the filter housing. The unit contains five ports/connection points: top

retentate port (A2B), condition/drain port, top permeate port, bottom permeate port and XCell ATF 10 Device to XCell LS or 410 Controller port (A2C). The XCell ATF 10 Device is available with ReadyMate™ DAC on the permeate ports and AseptiQuik® G or L aseptic connectors on the retentate/u-bend ports. (**Figure 7**).

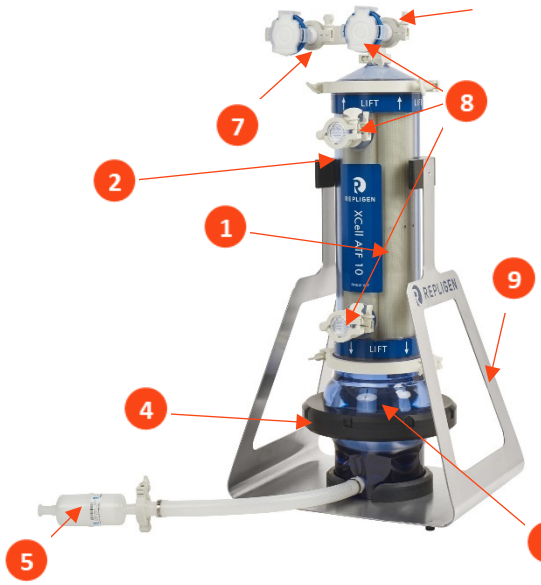
2.4.1 Device ports

The device contains five ports/connection points (**Figure 6**):

- Top retentate (A2B) port (AseptiQuik® G or L)
- Condition/drain port
- Top permeate port (ReadyMate™)
- Bottom permeate port (ReadyMate™)
- XCell ATF Device to XCell LS Controller (A2C) port

The A2C port, dead-ended with a vent filter and located at the lowest point on the pump base, connects to the XCell LS Controller, allowing pressurized air and vacuum to be delivered to actuate the diaphragm according to the user-defined parameters in the XCell LS Controller software. The remaining four ports carry liquid between the XCell ATF Device and bioreactor or the XCell ATF Device and permeate vessel. Two ports are connected to the feed, or retentate, side of the cartridge and two ports are connected to the permeate side. The top retentate port is used to make a connection between the XCell ATF 10 Single-use Device and a bioreactor using the A2B tubing sets. The bottom port on the feed side is the condition/drain port. The top permeate port is typically used for harvesting, and the lower permeate port remains closed off throughout the process but can be aseptically connected to a pressure transducer to monitor the permeate pressure.

Figure 7: XCell ATF 10 Single-Use Device components



1. Hollow fiber filter
2. Housing
3. Diaphragm pump
4. Pump closure ring
5. Hydrophobic vent filter
6. Inlet elbow
7. Sanitary clamps
8. Aseptic connectors[1]
9. Stainless steel stand

[1]Top and bottom permeate have ReadyMate™ DAC; Retentate u-bend has AseptiQuik connectors.

2.4.2 The diaphragm pump

The diaphragm pump consists of a spherical chamber at the base of the device. A silicone diaphragm separates the air-side hemisphere and the liquid side hemisphere of the pump. The silicone diaphragm moves up and down as either pressurized air or vacuum is applied to the air side of the pump. As the diaphragm pump cycles through exhaust and intake, cell culture suspension moves from the bioreactor to the device and back to the bioreactor. This alternating tangential flow draws cell suspension in a continuous back-and-forth motion through the lumen of the hollow fiber filters. Alternating flow creates a backflush, enabling filter self-cleaning that minimizes fouling.

2.4.3 The filter module

The filter module contains a hollow fiber filter within a housing. The hollow fiber filter, sitting above the liquid side hemisphere of the diaphragm pump, separates media from cells. The filter housing contains five ports: two permeate ports (top and bottom), condition/drain port, and ports to connect the XCell ATF Device to the XCell LS Controller (A2C) and to connect the XCell ATF Device to the bioreactor (A2B).

Note: *The top permeate port is used to pull permeate, while the bottom port may be clamped off.*

2.4.4 The stainless-steel stand

To ensure stability during set-up and use, it is recommended that the device be placed in a stainless-steel, reusable stand. The stand features a ring to hold the bottom of the device securely and a snap ring to hold the filter housing near the top of the device. The device snaps into the stand with a single click. After use, the device can be easily removed from the stand. The stand is provided with a notch to orient and secure the A2C line. This feature also helps orient the entire device for efficient connectivity and easy access to all the ports. The stainless-steel stand needs to be ordered separately from the XCell ATF 10 Device.

2.5 XCell ATF 10 Single-use Device tubing set kits

Fluid management for XCell ATF Devices includes tubing set kits and accessories that connect the device to the bioreactor and the Controller. The tubing set kits ensure that the ratio of displacement volume to hold-up volume is greater than or equal to one at the minimum and maximum flow rate (DDVR >/ = 1).

A2B tubing set kits are available in multiple configurations based on the type of bioreactor in use and the desired connectors (Table 10). In addition to the tubing set kits, accessories may be required (Table 11). Each tubing set kit includes pinch clamps for isolating flow paths and sanitary clamps for securing aseptic connectors. All tubing components are constructed of platinum-cured silicone and are configured with vent filters and aseptic connectors. All tubing set kits are sterilized by gamma irradiation and packed in double plastic bags to maintain sterility.

Notes:

- *Unlinked aseptic connectors are not water resistant. To maintain system sterility, extra care must be taken during set-up to not introduce liquid onto the connector.*
- *Although superficially similar, the tubing sets for the different devices are not interchangeable. Check the labeling on your tubing set to make sure it is appropriate for your device.*
- *The tubing set kits, permeate pressure sensor kits, and flow sensor are ordered separately.*

Table 8: XCell ATF 10 Single-use Device tubing specifications

Item	Component	Sterile connector type	Tubing spec (inches)		
			ID	OD	Length
Tubing set kit	A2B	AseptiQuik® G or L	1	1.375	25
	Top permeate	Cytiva ReadyMate™	3/4	1.125	12
	Bottom permeate		3/4	1.125	6
	Vent tee		1	1.375	28
	Sample port/ Drain port		1/2	3/4	6
	End cap	N/A	-	1.5	-
Permeate pressure sensor kit	Permeate	Cytiva ReadyMate™	3/4	N/A	4

Table 9: XCell ATF 10 Connection kit details

Part	Description	Purpose
Sanitary tri-clamps	1.5” clamps	Clamp connectors
ATF to Bioreactor Connection	Tee with vent filter	Connect to bioreactor, pre-use wetting, integrity testing
ATF to Bioreactor Connection	A2B	Connect to bioreactor
Permeate Connection	Top permeate (optional pressure sensor kit)	Connection to top permeate port, pressure monitoring (if included), wetting, integrity testing
Bottom permeate extension	5” tubing with end cap	Clamp off bottom permeate
Drain connection	Drain tee	Connect to drain port, wetting, draining

Table 10: Part numbers for XCell ATF 10 Single-use Devices

Part #	Description	Included components
SUATF10-G02PS	XCell ATF 10 Device Single-use, 0.2 µm PS	0.2 µm filter, Cytiva ReadyMate™ Sanitary Connections
SUATF10-S02PES	XCell ATF 10 Device Single-use, 0.2 µm PES	0.2 µm filter, Cytiva ReadyMate™ Sanitary Connections

Table 11: Tubing options for SSB and SUB Connections for XCell ATF 10 Single-use Devices

Tubing set part number	Controller	Tubing connection	Included components
SUATF10-TSK-AQG	LS	AseptiQuik® L and Readymate™ (permeate ports)	A2B, vent tee, top and bottom permeate, drain
SUATF10-TSK-AQG-AQL		AseptiQuik® G and Readymate™ (permeate ports)	
SUATF10-TubeSetKit	C410	Cytiva ReadyMate™	

Table 12: Additional Accessories for XCell ATF 10 Single-use Devices

Description	Part number	Controller	Aseptic connector	Single- or Multi-use	Pressure rating (psi)	ID (inches)
Permeate Pressure Sensor	SUATF610-PSK-V2	LS	ReadyMate™	SU	25	3/4
	SUATF610-PSK-AQ-V2	LS	AseptiQuik®	SU	25	3/4
XCell ATF 10 Single-use Device Stand	SUATF10-STD	LS or C410	N/A	MU	N/A	N/A
Bivalve assembly*	ATF10-VLV-KIT	LS	N/A	MU	45	1.5
	SUATF610-PSK	C410				
Connector*	SUATF10-AQL-TO-1.0TC	LS	ReadyMate™	SU	25	1
	SUATF10-AQG-TO-1.0TC	LS	AseptiQuik®			
Vent Filter (A2C line)	F10-AIR-LSC	LS	N/A			
	F:AIR-810	C410	N/A			

* Needed for stainless-steel bioreactor connection.

2.6 Connecting XCell ATF 10 Single-use Device to a bioreactor

Two types of connections between the device and bioreactor are available. Hard connections are used where steam-in-place (SIP) is an option, such as with stainless steel bioreactors (SSB). Soft connections are used with single-use bioreactors (SUB) and consist of AseptiQuik® single-use connectors.

Fluid management for XCell ATF 10 Devices include retentate (A2B) tubing set kits and accessories that connect the device with the bioreactor, ensuring proper exchange of cell culture material. Intended for use in pilot scale, clinical, and commercial bioprocessing environments, tubing set kits work with XCell LS Controllers and legacy C410 controllers. Permeate tubing (not provided) connects the device to the harvest vessel and should be sterilized by autoclave or attached with a tubing welder or disposable sterile coupling. The permeate tubing should be compatible with the filtrate/harvest pump.

Note: *Bioreactor adapters, used to connect tubing set kit to the bioreactor, are not provided.*

2.6.1 Prerequisites for XCell ATF 10 Device operation

The following equipment is required to operate the XCell ATF 10 Device:

- Control hardware: An XCell LS or C410 Controller connected to the required air pressure and vacuum pressure sources.
- Permeate (harvest) flow equipment
    - A variable speed peristaltic pump able to support flow rates in the range of 0.4 - 2.5 L/min depending on the bioreactor working volume and perfusion rate.
    - A minimum length of 1/4 - 3/8 inch ID tubing, fitted with a single ReadyMate™ aseptic connector to mate with the XCell ATF 10 Device. It is recommended that the permeate line be sterilized via gamma irradiation or autoclaving.
- Pre-use, off-line filter wetting equipment
    - Two hundred and twenty liters (220 L) of 0.2 µm-filtered WFI or cell culture media dispensed into a single-use bio container (bag) that is fitted with an appropriate length of tubing, a clamp, and a single, terminal Cytiva ReadyMate™ aseptic connector.

- A sterile 220 L empty single-use bio container (bag) with an appropriate length of tubing, a clamp, and a single, terminal Cytiva ReadyMate™ aseptic connector.
- Variable speed peristaltic pumps with flow capacity of 2-15 LPM, and able to accommodate the tubing IDs configured on the 220 L bag of WFI or media.

2.7 XCell 6 and 10 Device wetting

The XCell ATF 6 and 10 Single-use Devices are supplied dry and have not been pre-wetted or flushed. Wetting of the hollow fiber filter in the device is required to ensure robust filter performance. Sterile water or cell culture media (recommended) is required to properly wet the filter. One of two methods, off-line wetting, or on-line wetting can be used to wet the hollow fiber filters. Each method is detailed below.

Off-line wetting allows for the filter in the device to be wetted while not connected to a bioreactor and without the use of the XCell LS or 410 Controllers and the resulting pump action. The off-line wetting configuration and process also allows for pre-use filter integrity testing while maintaining sterility.

The on-line wetting procedure is executed with the device connected to a bioreactor that contains sterile cell culture media (must be done prior to inoculation,). This method utilizes the XCell LS or 410 Controller to generate the pump action to wet the filter. Additional XCell ATF Devices that will be connected to a running bioreactor must undergo off-line wetting.

The off-line wetting procedure is recommended for the following reasons:

- Proper wetting – Filling the unit from the condition/drain port wets the membrane inside-out, which drives more uniform wetting of the filter and minimizes the formation of air bubbles inside the filter.
- Filter integrity – This method allows the user to test filter integrity while disconnected from the bioreactor and to maintain sterility. Integrity testing a filter prior to use reduces process risk.
- Sterility check – Upon completion of the wetting process with cell culture media, the media can be incubated overnight to evaluate the sterility of the device before making a connection to the bioreactor.
- Replacing the device – In the event that there is need to replace the device during a run, using the offline technique does not require the XCell LS or 410 Controller or a bioreactor, which may be in use.

An overview video of the XCell ATF Single-use Device off-line wetting process and additional user manuals, can be found on repligen.com/resources.

Note: *Online wetting also allows testing filter integrity and sterility check. However, the benefit is diminished as the device is sterilely connected to a bioreactor prior to testing.*

2.8 Chemical compatibility

The device should not be exposed to high pH solutions, such as sodium hydroxide, for extended time. Sodium hydroxide or potassium hydroxide could be used for 30 minutes with concentrations of 0.5-1.0 N to decontaminate, if needed. Repligen advises not to expose the device to even dilute caustic solutions prior to use or for storage.

3. Manufacturing information

3.1 Introduction

All XCell ATF Single-Use devices and tubing sets are manufactured at the Repligen manufacturing facilities or manufactured by a third party as noted below. Neither the facility nor the products manufactured require registration or market approval; therefore, the Repligen ATF 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.

Table 13: Manufacturing and Inspection Sites

Product	Manufacturing Site	Inspection & Release Site
XCell ATF Single-use Device	Repligen Corporation 111 Locke Drive Marlborough, MA 01752 USA	Repligen Corporation Inspection Services, 384 South Street Shrewsbury, MA 01545 USA
Tubing sets	Advanced Scientifics Inc. (ASI), a part of Thermo Fisher Scientific Inc., 163 Research Lane Millersburg, PA 17061 USA	Repligen Corporation Inspection Services, 384 South Street Shrewsbury, MA 01545 USA
	Repligen Corporation 99 South St Hopkinton, MA 01748 USA	Repligen Corporation 99 South St Hopkinton, MA 01748 USA

3.2 Manufacturing Quality Assurance Standards & Policy

Repligen recognizes the need for high quality standards and has therefore established an ISO 9001:2015 Quality Management System. Refer to Section 1 for Repligen's Quality Policy.

3.3 Manufacturing facility for Single-Use Devices

The facility consists of ISO Class 7 rooms and a central ISO 8 prep area. Two airlock entry ways are maintained, one for people and one for materials and equipment. In general, product contact parts enter the suite through a validated parts washer and are cleaned with CIP 100 Alkaline Detergent followed by a rinse with reverse osmosis deionized (RODI) water. The suite is segregated from all other product manufacturing at Repligen and is a restricted-access area.

The clean-room environment is controlled and monitored as follows:

- Air quality is maintained by 100% HEPA filtered air
- Environmental monitoring is performed to check for viable contamination
- Preparation room air quality is tested to ISO Class 8 standards for non-viable particulates
- Air quality is tested to ISO Class 7 standards for non-viable particulates
- Room pressure differentials are maintained and monitored according to standard operating procedures (SOPs)
- All rooms are on a routine cleaning and disinfection schedule
- Access is restricted to authorized personnel only
- Gowning is required for entry into controlled areas including a secondary gowning procedure for entry into the ISO Class 7 rooms

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 9001:2015-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 retained for 10 years per the Repligen Documentation Retention Policy.

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

Supplier management: Repligen manages suppliers of raw materials and components based on the impact on the quality of the product. Suppliers are subject to a qualification process and are monitored and are routinely audited according to a pre-determined schedule based upon supplier classification requirements. The supplier audit schedule is established based on a 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 XCell ATF devices and tube sets, recovery of production is assumed to be 16 weeks within the United States. It is recommended that the customer keeps a minimum of 3 months of inventory on hand.

The devices and tube set kits are manufactured in certified ISO Class 7 clean rooms. XCell ATF 6 and 10 Single-use Devices 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 have been qualified and validated.

3.5 Materials of construction

Table 14: Materials of Construction for product contact parts for XCell ATF 6 Single-use Device

Device component	Materials of Construction
Filter housing and pump	Polycarbonate
Adhesive	Acrylated Urethane
Elbow	Polyvinylidene Fluoride (PVDF)
Aseptic Connectors	Polycarbonate with silicone seal
Hollow fiber cartridge	PES Membrane - Polyethersulfone, Polysulfone, Polyurethane, and Polypropylene PS Membrane - Polysulfone, Epoxy, and Polypropylene
Gaskets and diaphragm	Silicone

Table 15: Materials of construction for product contact parts of the ATF 6 Tube Set Kits

Tubing Set Kit components	Materials of construction
Tubing	Silicone/TPE
Hosebarb Fittings	Polypropylene
Aseptic Connectors	Polycarbonate with platinum cured silicone seal
Gaskets	Silicone
Air Filter	PVDF and Polypropylene

Table 16: Materials of construction for product contact parts for the XCell ATF 10 Single-use Device

Device component	Materials of construction
Filter housing and pump	Polycarbonate
Adhesive	Acrylated Urethane
Elbow	Polyvinylidene Fluoride (PVDF)
Aseptic Connectors	Polycarbonate with silicone seal
Hollow fiber cartridge	PES Membrane - Polyethersulfone, Epoxy, Polysulfone, and Polypropylene PS Membrane - Polysulfone, Epoxy, and Polypropylene
Gaskets and diaphragm	Silicone

Table 17. Materials of construction for product contact parts for the XCell ATF 10 Tube Set Kits

Tubing Set Kit components	Materials of construction
Tubing	P/N suATF10-TSK-CRZ: Silicone/TPE P/N suATF10-TubeSetKit: Silicone
Hosebarb Fittings	Polypropylene
Aseptic Connectors	Polycarbonate and Silicone
Gaskets	Silicone
Air Filter	PVDF and Polypropylene

Table 18. Materials of construction for non-product contact parts for the XCell ATF 6 and ATF 10 Single-use Devices

Device component	Materials of construction
Tubing and sanitary clamps	Platinum cured silicone tubing, Glass-Filled Nylon clamps
Pump closure ring	Acrylonitrile Butadiene Styrene (ABS)
Stand	ABS, SS

3.6 Lot & Serial Number System

Each device is assigned a lot number generated by SAP and sequential serial number that is tied to a production order. This provides full traceability to production records and materials used.

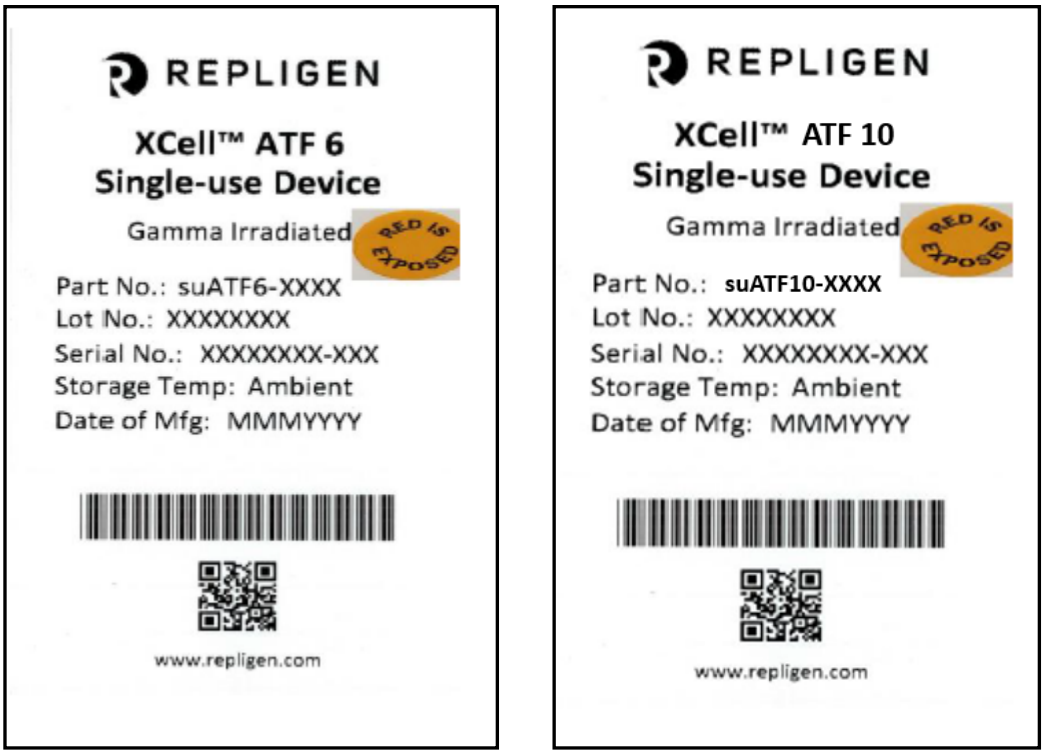
3.7 Packaging, Documentation and Gamma Irradiation for XCell ATF 6 and 10 Products

The packaging configuration and certificates provided with the XCell ATF6 and ATF10 Single-use Devices and the associated tube set kits are described below:

Single-use Devices:

1. Device finished good label includes a round gamma irradiation indicator sticker (**Figure 9**).
2. Primary packaging: 2 x 6 mil poly double bagged with a finished good label; the finished good label is on the first layer of poly bag and includes a round gamma irradiation indicator sticker. The disposable aseptic connectors and the A2C line are bubble wrapped to ensure that components do not tear the primary or secondary bag.
3. Secondary Packaging: Polyethylene die cut foam insert fitted in a corrugated cardboard box. Box label includes a round gamma irradiation indicator sticker.
4. Box Dimensions (L x W x H):
   XCell ATF 6 Device - 41.5” x 16.125” x 15.375”
   XCell ATF 10 Device - 48.125” x 26.625” x 21.75”

Figure 8: XCell ATF 6 and 10 Single-use Device Labels



Each XCell ATF Single-Use Device is labeled with the following information:

- Part number
- Lot number
- Serial number
- Date of manufacturing

Figure 9: XCell ATF 6 and 10 Single-use Device tube set kit Labels

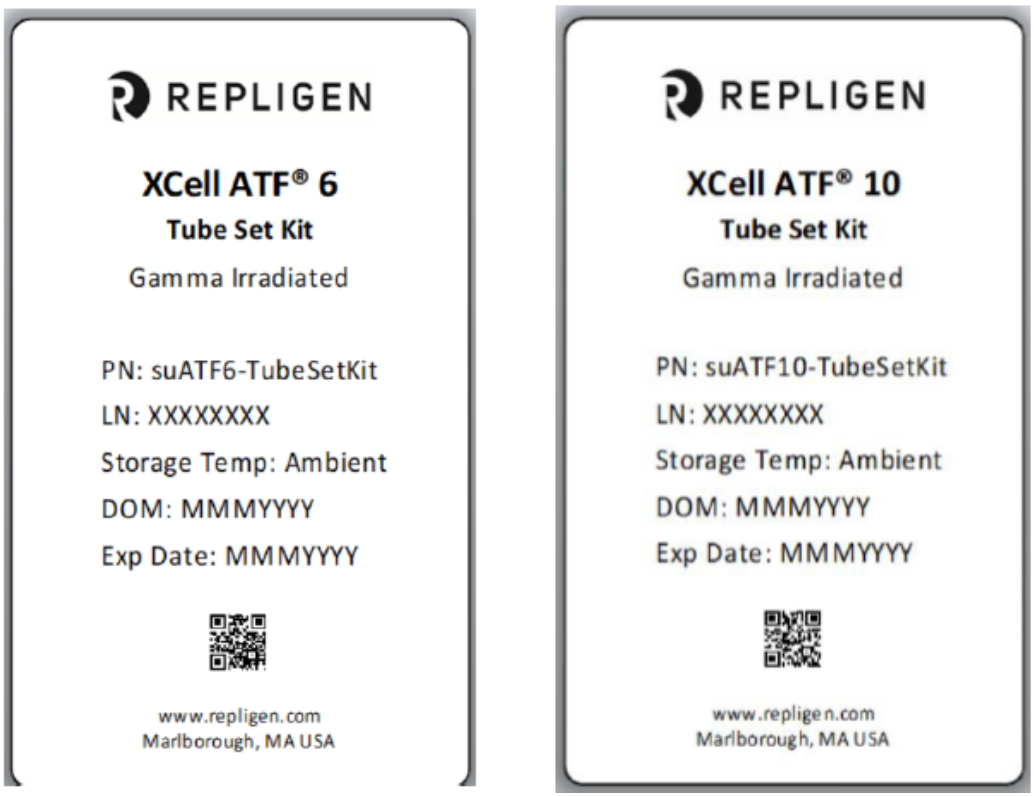


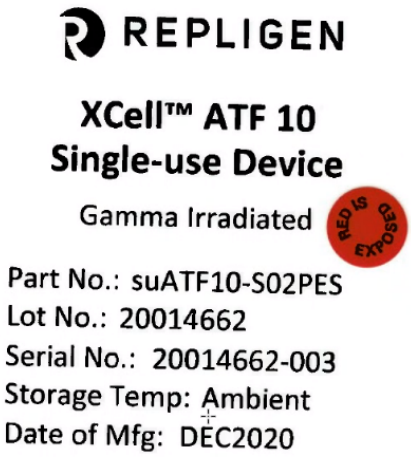
Figure 10. Primary packaging of the XCell ATF 6 Single-use Device

Figure 11. Primary packaging of the XCell ATF 10 Single-use Device

Tube set kits:

1. Tube set kits are manufactured by Advances Scientific Inc (ASI/Thermo, OEM) or Repligen. Tube set components are manufactured to Repligen specifications.
2. The disposable aseptic connector ends of each individual tube set component are bubble wrapped to ensure the components do not tear the primary or secondary packaging.
3. Primary Packaging: Each tube set component is packaged individually in 2 x 4 mil poly double bagging with a component label. The component label is on the first layer of the poly bag.
4. Secondary Packaging: 2 x 4 mil poly double bagging with finished good tube set kit labels. The finished good label includes a round gamma irradiation indicator sticker.
5. Tertiary Packaging: The tube set kit is shipped in a cardboard box that includes a finished good label and a gamma indicator sticker.

Figure 12. Example Gamma Irradiation Sticker Color Change to Red



The fluid path of XCell ATF Singe-use devices has been validated following ANSI/AAMI/ISO 11137 guidelines for VDmax25 to provide a minimum Sterility Assurance Level (SAL) of 10-6 for an established irradiation dose of 25.0 – 40.0 kGy.

The fluid path of this Tube Set Kits has been validated following ANSI/AAMI/ISO 11137 guidelines for VDmax25 to provide a minimum Sterility Assurance Level (SAL) of 10-6 for an established irradiation dose of 25.0 – 45.0 kGy.

The round gamma irradiation indicator sticker changes color from orange to red when exposed to gamma irradiation (Figure). Thus, this sticker is used to visually indicate completion of the gamma irradiation device sterilization procedure. The Certificate of Quality (CoQ) is accompanied by the Certificate of Processing (CoP) provided by the gamma irradiation vendor and serves as proof of gamma irradiation (Appendix B).

3.8 Storage conditions

Store in original packaging at ambient conditions protected from moisture, extreme temperatures, and light.

4. Safety Information

4.1 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 ensure 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.

4.2 Extractables strategy

Repligen conducted extractables testing for several of the polymeric components of the XCell ATF Single-use Devices. The testing was performed at NSF's Health Science Services and was based on the white paper established by the BPOG E&L Working Group. The NSF data tables were pared down to only depict extractables detected above the quantitation limit for each analytical technique. Where possible, the source of the detected extractable was linked to a chemical ingredient in the device components. Identifications of all observed extractables were attempted from the mass spectra. Identifications were made using NSF's Health Science Services' expert interpretation of mass spectral data assisted by library matching, when available.

4.2.1 XCell ATF extractables testing summary

Repligen performed an extractables risk assessment for the polymer components used to construct the device (Appendix C). The device consists of elastomeric polymer components commonly used in bioprocessing. Each device component was assessed based on its material of construction, vendor supplied information/data concerning the material, and the conditions of use (processing streams, time, temperature) in typical bioprocessing applications. Five device components were identified as having a moderate extractables risk, which warranted additional extractables testing. These components included:

- Polycarbonate Components: Device housing (tube), XCell ATF pump components and aseptic connectors
- Silicone diaphragm: XCell ATF pump diaphragm
- Silicone gaskets
- Silicone O-rings
- Adhesive: used to adhere ports to the device housing and pump hemisphere

The Repligen approach to extractables and leachables (E&L) assessment has two parts:

1. It is the responsibility of the product technology vendor to provide a technical extractable package for the components of the product considered to be product contact.
2. The assessment of leachables is considered to be process specific and therefore this assessment is the responsibility of the end user to define with specific process solutions.

With this strategy, Repligen designed an extractables program to produce a robust data package by conducting extractables testing based on the BioPhorum Operations Group (BPOG) standardized protocol for the evaluation of extractables from single-use bioprocessing systems. After surveying the applications of our clients, we have concluded that the following BPOG solvents most accurately model the solvating properties of the processing streams used with the XCell ATF Single-use Devices:

- Water for Injection (WFI)
- Ethanol/Water (50:50)
- 1% Polysorbate 80 in Water

Each device component was gamma-sterilized prior to extraction as the product is supplied gamma-sterilized. The extractions were performed at 40° C with agitation for 7, 21, and 72 days. The extracts were analyzed for volatiles by headspace GC/MS, semi-volatiles by GC/MS, and non-volatiles by LC/UV/MS. In some cases, a given extractable can be detected by multiple analytical techniques. When this occurred, the extractable was reported for each method. The inorganic extractables were evaluated by ICP/MS. The organic anionic extractables were also determined by ion chromatography. The following elements were screened for in each extract:

Scandium, Yttrium, Palladium, Indium, Terbium, Thorium, Gold, Mercury, Boron, Lithium, Sodium, Potassium, Iron, Calcium, Magnesium, Aluminum, Antimony, Arsenic, Barium, Beryllium, Bismuth, Cadmium, Cerium, Cesium, Chromium, Cobalt, Copper, Dysprosium,

Erbium, Europium, Gadolinium, Gallium, Germanium, Hafnium, Holmium, Iridium, Lanthanum, Lead, Lutetium, Manganese, Molybdenum, Neodymium, Nickel, Niobium, Phosphorus, Platinum, Praseodymium, Rhenium, Rhodium, Rubidium, Ruthenium, Samarium, Selenium, Silver, Strontium, Tantalum, Tellurium, Thallium, Thulium, Tin, Titanium, Tungsten, Uranium, Vanadium, Ytterbium, Zinc, Zirconium, Silicon

4.3 Safety Data Sheet (SDS)

XCell ATF Single-use devices are made from plastic components only and, therefore, no Safety Data Sheet (SDS) is needed.

5. Quality Documentation

5.1 Product certification

Repligen supplies certificates of quality for released manufacturing lots (Appendix A). Upon advanced request, you can receive certificates of quality for individual devices. Certificates of quality are substantiated with data appropriate to each product type.

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

5.2 Animal-free origin

Repligen manufactures the XCell ATF product line 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 the XCell ATF product line is free of transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE)Al. l product contact materials of construction are compliant with EMA/410/01 guidelines.

5.3 Additive-free statement

Repligen does not intentionally add the following items during the XCell ATF product Line manufacturing processes. Additionally, Repligen does not specifically test for the presence of these items in its XCell ATF products:

- Aflatoxin
- Gluten
- Lactose
- Porcine
- GMO
- Allergens
- Genotoxic
- Antibiotics
- Pesticide
- Latex
- Herbicide

5.4 Melamine statement

Regulatory guidance on melamine contamination is with regards to food or pharmaceutical components that contain nitrogen or are derived from milk, in particular to food products with protein. Filters and single-use fluid management products are not considered within the scope of this regulatory guidance as they are not pharmaceutical drug components. Repligen does not have information for the presence of melamine in XCell ATF products and does not test for melamine or nitrogen content in XCell ATF products.

5.5 Latex specific statement

Regulatory guidance on latex is with regards to medical devices or pharmaceutical drugs, and the packaging and labeling of these products.
Filters and single-use fluid management products are not considered within the scope of this regulatory guidance as they are not medical products or pharmaceutical drugs and are not intended to be used as packaging.
Repligen does not have information for the presence of latex in XCell ATF products.

5.6 BPA statement

Regulatory guidance on Bisphenol A (BPA) is with regards to food contact products. Products used in pharmaceutical applications are not considered within the scope of this regulatory guidance.

5.7 ISO and USP Class VI statements

All product contact materials of construction meet USP Class VI and/or ISO 10993 biosafety requirements.

5.8 Sterility Assurance Level Validation Summary for ATF Single-use product family

5.8.1 Executive summary

Repligen XCell ATF Single-use products were developed and validated in accordance with ANSI/AAMI/ISO 11137-2: Sterilization of Health Care Products – Radiation – Establishing the sterilization dose – Method VDmax. The study was conducted to substantiate a minimum sterilization dose of 25 kGy and to verify a Sterility Assurance Level (SAL) of 10^{-6} or no more than one nonsterile unit for each one million units sterilized.

Preliminary bioburden results (Table 19) demonstrate 2 - 3 folds lower than 1000 cfu/device and are acceptable for VDmax25 dose substantiation. The commonality of the raw materials, manufacturing environment, and manufacturing personnel will also ensure that types of microorganisms on the ATF2 product are representative of those found on the ATF6 and ATF10 versions. The AFT2 product was therefore used for this study. The pre-sterilization bioburden level was determined for three independent lots of SU-ATF2 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 in the ANSI/AAMI/ISO 11137-2. This study supports the release of SU-ATF products for which exposure to the minimum dose of 25 kGy is demonstrated using calibrated dosimeters. In accordance with ANSI/AAMI/ISO 11137-2: Method VDmax, 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 following Single-Use ATF Family.

5.8.2 Method

Finished routine production units of the suATF Assembly in standard final packaging were sampled before sterilization. The Sample Item Proportion (SIP) used for all testing was one (1.0). A bioburden recovery validation was performed and utilized for this study. Bioburden testing was performed on the three independent lots for determination of the verification dose. An additional thirteen nonsterile, final packaged samples were exposed to the verification dose. These samples were subjected to test of sterility and method suitability (bacteriostasis/ Fungistasis) tests. All testing methods and procedures were in accordance with AAMI Standards. The method utilized for this study was ANSI/AAMI/ISO 11137-2: Sterilization of Health Care Products – Radiation – Establishing the sterilization dose – Method VDmax.

5.8.3 Results

Efficiency of Recovery Factor (Bioburden Recovery Validation)
The bioburden recovery validation was performed on five devices using the exhaustive recovery method. The efficiency of recovery factor (ERF) was determined and utilized for the bioburden results, and the determination of the verification dose. Testing was performed in accordance with ANSI/AAMI/ISO 11737-1.

5.8.3.1 Bioburden Testing

The methodology used to obtain the bioburden count for calculating the verification dose for each lot was the same. Table 2 summarizes the results for the three lots of AFT2 product and is reported as colony forming units (cfu) per device: Product Lot Number Total Bioburden

Table 19. SUATF Bioburden Results reported as colony forming units (CFU) per device

Product	Lot Number	Total Theoretical Bioburden (cfu/device)
suATF2	SA161639	295.7
suATF2	SA161640	105.4
suATF2	SA161708	238.7
Overall Average		213.3

5.8.3.2 Verification Dose

The appropriate verification dose for this validation was determined using the bioburden information provided on the bioburden test reports for each lot. The overall average of 213.3 cfu per device was utilized since no single lot average was more than twice the overall average. Using 213.3 cfu per device, the verification dose was determined from Table 9 in the ANSI/AAMI/ISO 11137-2 guidelines. The verification dose for this validation and future dose audits is 8.7 kGy.

5.8.3.3 Bioburden Method Suitability (Bacteriostasis/ Fungistasis)

Method suitability (bacteriostatic or fungistatic) characteristics were not shown to be associated with the sterility cultures of the test article when challenged with Bacillus subtilis, Candida albicans, and Aspergillus niger.

5.8.3.4 Test of Sterility

After the verification dose was applied to the verification samples, they were placed on test of sterility. Testing was performed in accordance with ANSI/AAMI/ISO 11137-2. The results of the sterility test are summarized in Table 14. There were no positive samples on the test of sterility. This was within the acceptance criteria of no more than one positive sample per ten verification dose samples.

Table 20: Verification dose testing

Product	Number of Units Tested	Number of Units Positive
suATF2	10	0

5.8.4 Analysis

In accordance with ANSI/AAMI/ISO 11137-2: Method VDmax, statistical verification was successfully completed since not more than one positive sterility test culture was observed after irradiation at the determined verification dose for the lot tested. The average bioburden was less than 1,000 organisms and statistical verification of the bioburden resistance was accepted and therefore the

sterilization dose of 25 kGy will be accepted as the 10-6 SAL dose for the Single-Use ATF Family. Routine sterilization of subsequent manufacturing lots will require demonstration, through dosimetry, that this 10-6 sterility assurance dose has been achieved at the point of minimum absorbed dose in each irradiation carrier load. To substantiate the continued validity of 25 kGy dose as a 10-6 SAL dose, verification dose audits will be performed according to an established schedule, as specified in ANSI/AAMI/ISO 11137-1.

5.9 XCell ATF Single-use Device Shelf-Life Stability Assessment

5.9.1 Background

Real time, ambient temperature and accelerated, higher temperature stability studies to determine the shelf life of the XCell ATF Single-use devices, with the goal of demonstrating a two-year shelf life for the product in its final form, have been completed. The stability studies were executed with XCell ATF 6 Single-use devices (Part Numbers: suATF6-S02PES and suATF6-G02PS). Independent Design FMEAs/Risk Assessments concluded that the XCell ATF 10 Single-use devices (Part Numbers: suATF10-S02PES and suATF10-G02PS) and the XCell ATF 2 Single-use devices (Part Numbers: suATF2-S02PS and suATF2-G02PES) are similar in form, fit and function (including design, components, materials of construction, manufacturing procedures, and packaging), and therefore that the suATF 6 device stability study and associated conclusions are applicable to the entire ATF single-use product line.

The real time stability study was executed at ambient temperature (22°C), the intended and recommended storage temperature for the devices. The accelerated stability study was executed at 55°C, and using an Arrhenius equation, a calculated or predicted stability at ambient storage temperature was determined. Devices used for the shelf-life stability assessment were stored in their final product form for the duration of each study. The shelf-life stability was assessed by evaluating the physical integrity, the mechanical integrity, and the performance of the device from each study time point. An overview of the test methods used to assess the integrity and performance is provided in Table 20. All real time stability test time points have been executed. These results are summarized in Table 21. In addition, the accelerated stability test is complete. These results are summarized in Table 22.

Table 21. Summary of XCell ATF Single-use Device Test Methodologies

Measurement	Descriptions
Sterility	Device is filled with cell culture media (growth promoting) and held at 30°for 14 days. Growth is then assessed.
Diaphragm Integrity Test	The device is pressurized above the diaphragm to 25psi, and pressure decay is measured.
Assembly Integrity Test	The device is pressurized below and above the diaphragm to 25psi and pressure decay is measured.
Maximum Pressure Integrity Test	The device is pressurized below and above the diaphragm to 50psi and pressure decay is measured.
Filter Integrity	The hollow fiber filter is wetted, and the diffusion flow rate is assessed at 10psi.
Assembly Cycle Test	The XCell ATF device is operated at an ATF rate of 17.2LPM with 40°C water to 100,000 diaphragm (Pressure and Exhaust) cycles.

Table 22: Summary of Real Time Device Stability Study Design and Results Obtained

	Test Method	Sterility Assessment	Diaphragm Integrity Test	Assembly Integrity Test	Filter Integrity	Assembly Cycle Test
	Specifi-cation	No growth obtained in 14 day media hold	< 0.42psi decay/25min	< 0.42psi decay/25min	< 75mL/min (<30SCCM)	> 100,000 Cycles Achieved
Device Lot/Serial Number	Real Time Stability Time Point (Months at 22°C)					
SA1614580009	1.5	No growth observed	-0.09/25min	-0.13/25min	13.9mL/min	120422 cycles achieved
SA1614580004	12	No growth observed	-0.27/25min	-0.21/25min	13.2mL/min	115256 cycles achieved
SA1614580003	18	No growth observed	-0.12/25min	-0.09/25min	11.9mL/min	110570 cycles achieved
SA1614590004	24	No growth observed	-0.35/25min	0.07/25min	13.2mL/min	116312 cycles achieved
SA1614580006	27	No growth observed	0.2/25min	0.19/25min	12.6mL/min	136758 cycles achieved

NOTE: Prior to the AIT/DIT assessments, each device was exposed to -10psi vacuum and then 50psi positive pressure for 30 minutes, the same condition used for the maximum pressure, thus demonstrating the integrity of the device to negative pressure and to twice the 25psi pressure rating claim.

Table 23. Summary of Device Accelerated Stability Study Design and Results Obtained

		Test Method	Sterility Assessment	Diaphragm Integrity Test	Assembly Integrity Test	Maximum Pressure Integrity Test	Filter Integrity	Assembly Cycle Test
		Specific-ation	No growth obtained in 14 day media hold	< 0.42psi decay/25min	< 0.42psi decay/25min	< 2.0psi decay/60min	< 75mL/min (<30SCCM)	> 100,000 Cycles Achieved
Device Lot/Serial Number	Accelerated Stability Time Point (Weeks at 55°C)	Equivalent Ambient Shelf Life Stability (Weeks / Months)						
SA1614580001	2.5	25 / 5.7	No growth observed	-0.33/25min	-0.20/25min	-0.72/60min	14.1mL/min	146258 cycles achieved
SA1614580010	8	79 / 18.4	No growth observed	-0.29/25min	-0.26/25min	-0.71/60min	17.1mL/min	162996 cycles achieved
SA1614580002	12	118 / 27.6	No growth observed	-0.29/25min	-0.38/25min	-0.60/60min	14.3mL/min	142444 cycles achieved

5.9.2 Conclusions

The shelf-life stability of the XCell ATF 6 Single-use device has been assessed with storage at ambient temperature (22°C) for 27 months. Five independent measurements, designed to assess the physical integrity, the mechanical integrity, and the performance of the device, were performed when the device was removed from storage. All measurements passed all required specifications. These

results indicate that the XCell ATF 6 Single-use devices are stable for up to 24 months when stored at ambient temperature. A risk assessment indicated equivalence of form, fit and function of the ATF 2, ATF 6, and ATF 10 single-use devices, thus a shelf-life stability of 24 months can be set for the entire product line.

The shelf-life stability of the XCell ATF 6 Single-use device was also assessed with three accelerated shelf-life stability time points. Six independent measurements, designed to assess the physical integrity, mechanical integrity, and the performance of the device, were performed after each high temperature storage time was achieved. All measurements at all time points passed all required specifications. This result indicates that the XCell ATF 6 Single-use devices and the XCell ATF 10 Single-use devices, in their final product form, are stable for 12 weeks at 55°C. Using an Arrhenius Equation (Q=2), this accelerated stability can be equated to 118 weeks or 27.6 months of product stability at ambient storage temperature. Thus, it can be concluded that based on accelerated stability data, the devices are stable to the target of 24 months storage at room/ambient temperature. The accelerated stability data can be used to support the claims of the real time stability study.

Table 24: Shelf-Life Statement for SU ATF6 and ATF10 Device and Tubing Sets

Product Number	Shelf Life
XCell ATF6 Single-use Device	2 years from date of manufacture
XCell ATF10 Single-use Device	2 years from date of manufacture
XCell ATF6 Single-use Tubing set	2 years from date of manufacture
XCell ATF10 Single-use Tubing set	2 years from date of manufacture

The expiration date of the product is listed as the date of expiration date on the product label.

5.10 Shipping and packaging validation

Two studies were 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. One study included three XCell ATF6 Single-use devices and the other included three ATF10 devices. Both studies were tested per ISTA-2A with Environmental Conditioning. The studies concluded that packaging and product configurations were subjected to typical hazards encountered in the shipping and distribution. Upon their return to Repligen, the devices were visually inspected for damage and subjected to Assembly Integrity Test (AIT): 50 psi stress test, AIT: -10 psi stress test, AIT: 25 psi pressure hold test, and Diaphragm Integrity Test (DIT): 25 psi pressure hold test to validate that the devices are still functional. All devices passed the visual inspection as well as all testing stated above. As a result, the shipping boxes for the single-use ATF devices were sufficient to protect them from damage during transport. Packaging and product integrity were maintained for all applicable test conditions.

5.10.1.1 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.

5.11 Chemical Compatibility

Chemical solutions that are not compatible with the materials of construction of hollow fiber filter modules can damage the filter module or significantly decrease filtration performance. 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. The device should not be exposed to high pH solutions (pH>7.5), such as sodium hydroxide. Devices can be decontaminated with sodium hydroxide or potassium hydroxide solutions with concentrations between 0.5 and 1.0N for thirty minutes if needed.

6. Frequently asked questions

What do I do if a vent filter accidentally becomes wet during the wetting process?

Vent filters are made of hydrophobic membrane. Wetting solution contacting vent filters for short duration (< 15 minutes) does not impact the integrity and sterility of vent filter and XCell ATF 6 or XCell ATF 10 Devices. We recommend purging the vent filter to remove the residual solution.

What do I do if a leak is detected during the off-line wetting procedure?

Each individual device is pressure tested at 25 psi to ensure the integrity of the entire assembly. However, if a leak is detected during the wetting process, immediately stop the peristaltic pump and identify the location of the leak. Please ensure that the sterile connectors and tubing clamps are appropriately installed at proper locations. Clamping the wrong tubing sets during wetting procedure pressurizes the device and leads to leakage. If no faults were found in setup, please contact a local FAS or customer service for further support.

How do I ensure the sterility of an XCell ATF 6 and XCell ATF 10 Device?

The wetting solution collected from off-line wetting procedure can be incubated in a shake flask at 37° C for 24 hours to assess the sterility of a device.

How long can the XCell ATF 6 and XCell ATF 10 Devices be stored in a wet condition before connecting to a bioreactor?

After completing the wetting procedure, the tubing segment leading to the vent filters on the A2B, and the top permeate tubing segments must be clamped to avoid filter drying. The device can be stored in a wet condition for one week before installing the device for cell culture processing.

What do I do if the device fails pre-use integrity testing?

Please ensure that the tubing clamps on the retentate side are properly installed. Generally, if the filter integrity test fails by small percentage (acceptance criteria: 30 SCCM/m^2), it is recommended to wet the filter again using the same procedure. If a gross leak is detected during integrity, please contact a local sales manager or customer service for further support.

Do the XCell ATF 6 and XCell ATF 10 Devices perform similarly to XCell ATF 6 and XCell ATF 10 stainless-steel devices?

Yes, the filter used in the XCell ATF 6 and XCell ATF 10 Device is same as the one which is being used in the XCell ATF 6 and XCell ATF 10 stainless-steel devices. In addition, the single-use device is operated using the same XCell Controller as stainless-steel without modifying any parameters and the pumps between the stainless-steel and single-use equipment are identical.

7. Appendix A: Example Certificates of Quality (COQ) for XCell ATF 6 and 10 Single-use Devices and Tube Set Kits

7.1 Example CoQ for Single-Use ATF 6 PES Devices

Certificate of Quality

Product: XCell ATF® 6 Single-use Device
Product Description: XCell ATF® 6 Single-use Device with a 0.2µm PES Hollow Fiber Cartridge Cartridge: 0.2µm pore size, 1mm lumen, nominal 2.53m² surface area
Part Number: suATF6-S02PES
Lot Number: XXXXXXXX
Date of Manufacture: MMMYYYY
Date of Expiration: MMMYYYY

This document certifies that the XCell ATF® 6 Single-use Device is manufactured, tested and compliant to the following Repligen quality standards:

1) The device was manufactured in certified ISO Class 7 clean room.
2) The fluid path materials of construction for the suATF device are as follows:

• Housing and Pump Components	Polycarbonate
• Aseptic Connectors	Polycarbonate and Platinum Cured Silicone
• Hollow Fiber Filter Cartridge	Polyethersulfone , Polysulfone, Polyurethane, and Polypropylene
• Port Adhesive	Acrylated urethane
• Pump Diaphragm and Gaskets	Silicone
• Fittings	Polyvinylidene fluoride

3) All product contact materials of construction meet USP Class VI and/or ISO 10993 biosafety requirements and do not contain any substances derived from animal products or are compliant with EMA 410/01 guidelines.

4) The fiber lot used to manufacture the hollow fiber cartridge was sample tested to verify pore size, water flux rate and burst pressure. Each hollow fiber cartridge has been integrity tested against specifications in accordance with the procedures of the cartridge manufacturer. The filter surface area is within ± 10% of the noted value.

5) Each device has been visually inspected and integrity tested for acceptance in accordance with Repligen Quality Control procedures.

6) Each device has lot traceability on materials, assembly, and test.

7) The fluid path of the suATF device has been validated following ANSI/AAMI/ISO 11137 guidelines for VDmax25 to provide a minimum Sterility Assurance Level (SAL) of 10-6 for an established irradiation dose of 25.0 – 40.0 kGy.

8) Intended for single use.

9) Store in original packaging at ambient conditions protected from moisture, extreme temperatures, and light.

10) Manufactured under ISO 9001:2015 quality system in the United States of America.

Quality Assurance Date

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Document Number:QS-5027 Revision: 1 Effective Date: 9/22/2023 Legacy Document #: QA-FM-10376
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7.2 Example CoQ for Single-Use ATF 6 PS Devices

Certificate of Quality

Product: XCell ATF® 6 Single-use Device
Product Description: XCell ATF® 6 Single-use Device with a 0.2µm PS Hollow Fiber Cartridge
Cartridge: 0.2µm pore size, 1mm lumen, nominal 2.1m^2 surface area
Part Number: suATF6-G02PS
Lot Number: XXXXXXXX
Date of Manufacture: MMMYYYY
Date of Expiration: MMMYYYY

This document certifies that the XCell ATF® 6 Single-use Device is manufactured, tested and compliant to the following Repligen quality standards:

1) The device was manufactured in certified ISO Class 7 clean room.

2) The fluid path materials of construction for the suATF device are as follows :

- Housing and Pump Components — Polycarbonate
- Aseptic Connectors — Polycarbonate and Platinum Cured Silicone
- Hollow Fiber Filter Cartridge — Polysulfone , Polyethylene, Epoxy, and Polypropylene
- Port Adhesive — Acrylated Urethane
- Pump Diaphragm and Gaskets — Silicone
- Fittings — Polyvinylidene fluoride

3) All product contact materials of construction meet USP Class VI and/or ISO 10993 biosafety requirements and do not contain any substances derived from animal products or are compliant with EMA 410/01 guidelines.

4) The fiber lot used to manufacture the hollow fiber cartridge was sample tested to verify water flux rate. Each hollow fiber cartridge has been integrity tested against specifications in accordance with the procedures of the cartridge manufacturer.

5) Each device has been visually inspected and integrity tested for acceptance in accordance with Repligen Quality Control procedures.

6) Each device has lot traceability on materials, assembly, and test.

7) The fluid path of the suATF device has been validated following ANSI/AAMI/ISO 11137 guidelines for VDmax25 to provide a minimum Sterility Assurance Level (SAL) of 10-6 for an established irradiation dose of 25.0 – 40.0 kGy.

8) Intended for single use.

9) Store in original packaging at ambient conditions protected from moisture, extreme temperatures, and light.

10) Manufactured under ISO 9001:2015 quality system in the United States of America.

Quality Assurance Date

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7.3 Example CoQ for Single-Use ATF 10 PES Devices

Certificate of Quality

Product:	XCell ATF® 10 Single-use Device
Product Description:	XCell ATF® 10 Single-use Device with a 0.2µm PES Hollow Fiber Cartridge Cartridge: 0.2µm pore size, 1mm lumen, nominal 11.0m^2 surface area
Part Number:	suATF10-S02PES
Lot Number:	XXXXXXXX
Date of Manufacture:	MMMYYYY
Date of Expiration:	MMMYYYY

This document certifies that the XCell ATF® 10 Single-use Device is manufactured, tested and compliant to the following Repligen quality standards:

1) The device was manufactured in certified ISO Class 7 clean room.

2) The fluid path materials of construction for the suATF device are as follows:

- Housing and Pump Components — Polycarbonate
- Aseptic Connectors — Polycarbonate and Platinum Cured Silicone
- Hollow Fiber Filter Cartridge — Polyethersulfone , Polysulfone, Epoxy, and Polypropylene
- Port Adhesive — Acrylated Urethane
- Pump Diaphragm and Gaskets — Silicone
- Fittings — Polyvinylidene fluoride

3) All product contact materials of construction meet USP Class VI and/or ISO 10993 biosafety requirements and do not contain any substances derived from animal products or are compliant with EMA 410/01 guidelines.

4) The fiber lot used to manufacture the hollow fiber cartridge was sample tested to verify pore size, water flux rate and burst pressure. Each hollow fiber cartridge has been integrity tested against specifications in accordance with the procedures of the cartridge manufacturer. The filter surface area is within ± 10% of the noted value.

5) Each device has been visually inspected and integrity tested for acceptance in accordance with Repligen Quality Control procedures.

6) Each device has lot traceability on materials, assembly, and test.

7) The fluid path of the suATF device has been validated following ANSI/AAMI/ISO 11137 guidelines for VDmax25 to provide a minimum Sterility Assurance Level (SAL) of 10-6 for an established irradiation dose of 25.0 – 40.0 kGy.

8) Intended for single use.

9) Store in original packaging at ambient conditions protected from moisture, extreme temperatures, and light.

10) Manufactured under ISO 9001:2015 quality system in the United States of America.

Quality Assurance Date

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7.4 Example CoQ for Single-Use ATF 6 Tube Set Kits

Certificate of Conformance

Part No:	**suATF6-TUBESETKIT**	**Manufactured Date:**	**MMMYYYY**
Revision:	**B**	**Expiration Date:**	**2 Years DOM**
Description:	**XCELL ATF6 SINGLE-USE TUBING SET**	**Irradiation Dose:**	**25.0 – 45.0 kGy**
Lot Number:	**TBD**		

Sample Certificate of Conformance - Issued 15JUL24, HLS

Biological:	The fluid path of this single use fluid transfer system has passed USP Class VI (USP<88>) and/or ISO 10993 testing.
TSE/BSE:	The fluid path of this single use fluid transfer system conforms to European guidance EMA/410/01.
Endotoxin:	The fluid path of a representative single use system is routinely tested in periodic validations for the presence of endotoxin in accordance with current USP Bacterial Endotoxin Test (USP<85>). Aqueous extracts contained <0.25 EU/mL as determined by the Limulus Amebocyte Lysate test (LAL).
Particulate:	The fluid path of a representative single use system is routinely tested in periodic validations in accordance with current USP Particulate Matter in Injections Microscopic Particle Count Test (USP<788>).
Sterility:	The fluid path of the single use system has been validated following ANSI/AAMI/ISO 11137 guidelines for VDmax[25] to provide a minimum Sterility Assurance Level (SAL) of 10^{-6} for an established irradiation dose.
Inspection:	This lot has been 100% visually inspected for acceptance in accordance with product specifications and Repligen Quality Control procedures.
Manufacturing:	Repligen is an ISO 9001 certified company and products are manufactured meeting Repligen's quality management system. This product was assembled in an ISO Class 7 cleanroom.
Storage:	Store in original packaging at ambient conditions protected from moisture, extreme temperatures, and light.

Quality Assurance **Issue Date**

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7.5 Example CoQ for Single-Use ATF 10 Tube Set Kits

Certificate of Conformance

Part No:	**suATF10-TUBESETKIT**	**Manufactured Date:**	**MMMYYYY**
Revision:	**B**	**Expiration Date:**	**2 Years DOM**
Description:	**XCELL ATF10 SINGLE-USE TUBING SET**	**Irradiation Dose:**	**25.0 – 45.0 kGy**
Lot Number:	**TBD**		

Sample Certificate of Conformance - Issued 15JUL24, HLS

Biological:	The fluid path of this single use fluid transfer system has passed USP Class VI (USP<88>) and/or ISO 10993 testing.
TSE/BSE:	The fluid path of this single use fluid transfer system conforms to European guidance EMA/410/01.
Endotoxin:	The fluid path of a representative single use system is routinely tested in periodic validations for the presence of endotoxin in accordance with current USP Bacterial Endotoxin Test (USP<85>). Aqueous extracts contained <0.25 EU/mL as determined by the Limulus Amebocyte Lysate test (LAL).
Particulate:	The fluid path of a representative single use system is routinely tested in periodic validations in accordance with current USP Particulate Matter in Injections Microscopic Particle Count Test (USP<788>).
Sterility:	The fluid path of the single use system has been validated following ANSI/AAMI/ISO 11137 guidelines for VDmax^{25} to provide a minimum Sterility Assurance Level (SAL) of 10^{-6} for an established irradiation dose.
Inspection:	This lot has been 100% visually inspected for acceptance in accordance with product specifications and Repligen Quality Control procedures.
Manufacturing:	Repligen is an ISO 9001 certified company and products are manufactured meeting Repligen's quality management system. This product was assembled in an ISO Class 7 cleanroom.
Storage:	Store in original packaging at ambient conditions protected from moisture, extreme temperatures, and light.

Quality Assurance **Issue Date**

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8. Appendix B: Example Certificates of Processing (COP) for XCell ATF 6 and ATF 10 Single-use Devices and Tube Sets

Note: suATF6 and suATF10 devices can be sterilized in the same gamma irradiation run.

8.1 Example COP for XCell ATF 6 Single-use Device

Certificate Of Processing

STERIS

Prepared for **REPLIGEN CORP**

Gamma Process Run ID **124629B**

Product Code	Product Lot Number	Quantity	UOM
suATF10-S02PES	20003973	3	CS
suATF6-S02PES	20003714	2	CS
suATF6-S02PES	20003856	9	CS
suATF6-S02PES	20003861	1	CS

PO Number: 4004179

Processing Run Start Date/Time: 03-Apr-2020 08:01:00 am Approx. Downtime (hours): 0.00

Processing Run End Date/Time: 03-Apr-2020 09:25:00 am

Minimum Specified Dose (kGy): 25.0 **Minimum Delivered Dose (kGy):** 27.1

Maximum Specified Dose (kGy): 38.0 **Maximum Delivered Dose (kGy):** 36.6

Product meets Customer specifications; zero nonconformities occurred during this irradiation run.

Signature Manifest

Reviewed and E-Signed By

Robin Hinckley (QS/RC Analyst)

Document Content Revision: 1

Signed On 4/3/2020 at 2:18 PM

UTC / GMT Offset (hh:mm): -4:00

Processing Location:
STERIS
435 Whitney Street
Northborough, MA 01532
Phone: 508-393-9323
Fax: 844-698-9776

Operating facilities are in compliance with applicable state and federal regulations (FDA, NRC, EPA, and OSHA) and provide services under a quality system which meets the requirements of FDA QSR, EN/ISO 13485, and in alignment with the applicable standard, EN ANSI/AAMI/ISO 11137 or EN ANSI/AAMI/ISO 11135. For items processed with gamma irradiation, STERIS certifies that these items received the indicated doses within the precision and accuracy of the dosimetry system used.

WI-00034/01354/01369 Last Rev In Rel. 3.6.5.1 Release Date: 05-Jun-2017 Page 1 of 1

8.2 Example COP for XCell ATF 10 Single-use Device

Certificate Of Processing

STERIS

Prepared for **REPLIGEN CORP**

Gamma Process Run ID **124629A**

Product Code	Product Lot Number	Quantity	UOM
suATF10-S02PES	20003862	8	CS
suATF10-S02PES	20003973	1	CS

PO Number: 4004179

Processing Run Start Date/Time:	03-Apr-2020 06:21:00 am	Approx. Downtime (hours):	0.00
Processing Run End Date/Time:	03-Apr-2020 07:45:00 am		

Minimum Specified Dose (kGy):	**25.0**	**Minimum Delivered Dose (kGy):**	**26.8**
Maximum Specified Dose (kGy):	**38.0**	**Maximum Delivered Dose (kGy):**	**37.3**

Product meets Customer specifications; zero nonconformities occurred during this irradiation run.

Signature Manifest

Reviewed and E-Signed By
Robin Hinckley (QS/RC Analyst)
Document Content Revision: 1

Signed On 4/3/2020 at 4:07 PM
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435 Whitney Street
Northborough, MA 01532
Phone: 508-393-9323
Fax: 844-698-9776

Operating facilities are in compliance with applicable state and federal regulations (FDA, NRC, EPA, and OSHA) and provide services under a quality system which meets the requirements of FDA QSR, EN/ISO 13485, and in alignment with the applicable standard, EN ANSI/AAMI/ISO 11137 or EN ANSI/AAMI/ISO 11135. For items processed with gamma irradiation, STERIS certifies that these items received the indicated doses within the precision and accuracy of the dosimetry system used.

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8.3 Example COP for XCell ATF 6 Tube Set Kits

Note: suATF Tube Set Kits are OEM manufactured to Repligen specifications by ASI, thus the irradiation is managed by ASI

Certificate Of Processing

STERIS

Prepared for **ADVANCED SCIENTIFICS INC**

Gamma Process Run ID **103320A**

Product Code	Product Lot Number	Quantity	UOM
GROUP 7	04.625 / 986YX-0000	10	CS
GROUP 7	B102346-I / 98465-0000	10	CS
GROUP 7	B104308-I / 9846B-0000	1	CS
GROUP 7	B107777-I / 9875L-0000	1	CS
GROUP 7	B108162-I / 9846A-0000	1	CS
GROUP 7	B108827-I / 987CM-0000	4	CS
GROUP 7	B110621-I / 986JJ-0000	1	CS
GROUP 7	B112264-I / 987WS-0000	1	CS
GROUP 7	B114196-I / 98730-0000, -0001, -0002, -0003, -0004, -0005, -0006	24	CS
GROUP 7	B115781-I / 987KW-0000	7	CS
GROUP 7	CO-0362 / 986SR-0000	5	CS

Processing Run Start Date/Time:	17-Aug-2019 03:34:00 pm	Approx. Downtime (hours):	0.00
Processing Run End Date/Time:	17-Aug-2019 05:02:00 pm		

Minimum Specified Dose (kGy):	**27.5**	**Minimum Delivered Dose (kGy):**	**30.3**
Maximum Specified Dose (kGy):	**45.0**	**Maximum Delivered Dose (kGy):**	**41.4**

Product meets Customer specifications; zero nonconformities occurred during this irradiation run.

Signature Manifest

Reviewed and E-Signed By
Caitlin Davies (QS/RC Technician)
Document Content Revision: 1

Signed On 8/20/2019 at 9:46 AM
UTC / GMT Offset (hh:mm): -4:00

Processing Location:
STERIS
9 Apollo Drive
Whippany, NJ 07981
Phone: 973-887-2754
Fax: 973-887-6591

Operating facilities are in compliance with applicable state and federal regulations (FDA, NRC, EPA, and OSHA) and provide services under a quality system which meets the requirements of FDA QSR, EN/ISO 13485, and in alignment with EN ANSI/AAMI/ISO 11137. STERIS certifies that these processed items received the indicated doses within the precision and accuracy of the dosimetry system used.

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8.4 Example COP for XCell ATF 10 Tube Set Kits

Note: suATF Tube Set Kits are OEM manufactured to Repligen specifications by Advanced Scientifics Inc, a part of Thermo Fisher Scientific. The irradiation is managed by ASI.

Certificate Of Processing

Prepared for **ADVANCED SCIENTIFICS INC**

STERIS

Gamma Process Run ID **226191B**

Product Code	Product Lot Number	Quantity	UOM
GROUP 503	B108433-I / 98CK8-0000	12	CS
GROUP 8	B106114-I / 98AHH-0000	24	CS
GROUP 8	B106114-I / 98EUZ-0000	10	CS
GROUP 8	B110701-I / 98AVY-0000	14	CS
GROUP 8	B112093-I / 98C3M-0000	19	CS
GROUP 8	B114197-I / 98AND-0000	6	CS
GROUP 8	HM00319-I / 98CBU-0000	6	CS

Processing Run Start Date/Time:	13-Jan-2020 04:18:49 pm	Approx. Downtime (hours):	0.37
Processing Run End Date/Time:	13-Jan-2020 07:01:17 pm		

Minimum Specified Dose (kGy):	**27.5**	**Minimum Delivered Dose (kGy):**	**29.5**
Maximum Specified Dose (kGy):	**45.0**	**Maximum Delivered Dose (kGy):**	**42.0**

Product meets Customer specifications; zero nonconformities occurred during this irradiation run.

Signature Manifest

Reviewed and E-Signed By
Arocho, Rogelio (QS/RC Technician)
Document Content Revision: 1

Signed On 1/14/2020 at 9:22 AM
UTC / GMT Offset (hh:mm): -5:00

Processing Location:
STERIS
23 Elizabeth Drive
Chester, NY 10918
Phone: 845-469-4087
Fax: 845-469-7512

Operating facilities are in compliance with applicable state and federal regulations (FDA, NRC, EPA, and OSHA) and provide services under a quality system which meets the requirements of FDA QSR, EN/ISO 13485, and in alignment with EN ANSI/AAMI/ISO 11137. STERIS certifies that these processed items received the indicated doses within the precision and accuracy of the dosimetry system used.

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