Stainless Steel XCell® ATF Housings

User Guide

For Use with:

- XCell® ATF 2 Housing
- XCell® ATF 4 Housing
- XCell® ATF 6 Housing
- XCell® ATF 10 Housing

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Abbreviations

µm	micrometer/micron
A2B	ATF to bioreactor
ATF	Alternating Tangential Flow
DAC	disposable aseptic connector
FAS	Field Application Specialist
H	height
HFF	hollow fiber filter
hr	hour
IPA	isopropyl alcohol
kDa	kilodalton
L	length
lb-ft	pound-foot
m	meter
MF	microfiltration
MU	multi-use
NaOH	sodium hydroxide
PA	pump air side
PES	polyethersulfone
PL	pump liquid side
ppm	parts per million
PS	polysulfone
psi	pounds per square inch
psig	pounds per square inch, gauge
sccm	standard cubic centimeters per minute
SIP	steam in place
SS	stainless steel
SSB	stainless steel bioreactor
SU	single-use
SUB	single-use bioreactor
UF	ultrafiltration
W	width

California Proposition 65 Warning

Warning This product can expose you to chemicals including lead, which isknown to the State of California to cause cancer and birth defects or other reproductive harm. For more information, go to www.P65Warnings.ca.gov/product.

1. Introduction

XCell® ATF Technology uses alternating tangential flow (ATF) to intensify upstream processes by retaining cells in suspension cultures, such as mammalian cell culture. An innovative diaphragm pump creates alternating tangential flow, leading to high viable cell densities and increased throughput with lower cost of goods. Typical applications include intensification of the following processes:

- N-1 and high density seed of fed-batch
- Long-term continuous perfusion
- Vaccine and virus production
- Gene and cell therapies

Repligen's broad range of stainless steel formats XCell ATF 2, XCell ATF 4, XCell ATF 6, and XCell ATF 10 Housings enable production of high density, high viability cell culture applications with linear flux and low shear for scale-up from bench scale to manufacturing scale, up to 5000+ L. The stainless steel product line includes stainless steel housings, XCell Lab and LS Controllers, software, tubing set kits, pressure sensors, and accessories. The hollow fiber filters (HFF) used in XCell ATF Technology are made of polyethersulfone (PES) or polysulfone (PS) and are available in 0.2µm and 0.5µm and 50kD pore size and 1 mm inner diameter lumen and are scalable across the entire device range.

Single-use tubing set kits and accessories are available for the connection of ATF 2, ATF 4, ATF 6, and ATF 10 Stainless Steel Housings to both stainless steel and single-use bioreactors, simplifying preparation and connectivity and allowing for the proper exchange of cell culture material. XCell Lab and XCell LS Controllers operate the diaphragm pump. The housings and tubing set kits are also compatible with legacy C24 and C410 Controllers. Additional information on the use of the controllers and XCell ATF Technology can be found in XCell Lab Controller User Guide and XCell LS Controller User Guide.

This document describes the major components, set-up, connectivity, and preparation of the stainless steel XCell ATF 2, ATF 4, ATF 6, and ATF 10 Housings and hollow fiber filters. Users should possess a basic level of skill in the areas of aseptic technique and fluid handling.

For further support in optimizing or troubleshooting, please contact your local Repligen Field Applications Specialist (FAS).

2. Description of XCell ATF Housings

Stainless steel XCell ATF Technology includes a variety of filter housings and compatible tubing set kits to support a fully scalable process. An integrated diaphragm pump provides alternating tangential flow through a hollow fiber filter, which retains large components (i.e., cells), while removing waste or harvesting product components (via permeate/filtrate).

2.1 Components

- **Filter housing:** stainless steel housing containing hollow fiber filter
- **Diaphragm pump:** spherical housing in which a silicone diaphragm membrane is inflated and deflated by pressurized air or vacuum, creating alternating flow
- **XCell ATF to bioreactor (A2B) connection:** tubing set kit connecting the housing to a bioreactor
- **Bioreactor adapter:** adapter between the connection assembly and bioreactor port. Typical fittings for stainless steel bioreactors include Ingold® or Tri-Clamp. Single-use bioreactors (SUB) use disposable, aseptic connectors.

Note: *Bioreactor adapter is not provided.*

- **Hollow fiber filter (HFF):** 0.2 or 0.5 µm or 50 kD pore size filter, positioned between the bioreactor and the diaphragm pump
- **Permeate/harvest tubing:** sterile tubing and fittings connecting the housing to the collection vessel. Compatible with a permeate/harvest pump.

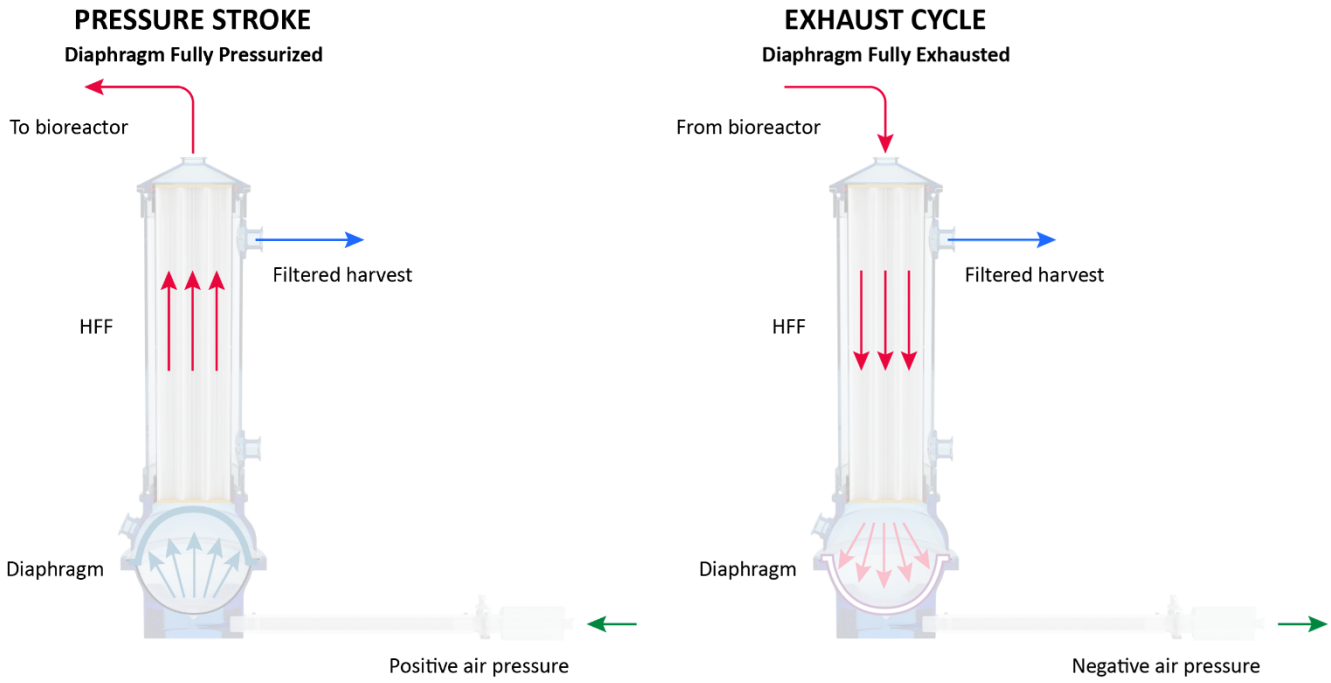
Note: *Permeate/harvest tubing and pump are not provided.*

2.2 XCell ATF Housing Pump Cycle

The diaphragm pump of the XCell ATF Device generates alternating tangential flow (ATF) through hollow fiber filters. ATF is a continuous, low shear, pulsating, and bi-directional flow of cell suspension between a bioreactor and a diaphragm pump (Figure 1). Cells move back and forth through the lumen of the hollow fiber filters. Two strokes of the diaphragm pump, the Pressure stroke (P-stroke) and the Exhaust stroke (E-stroke), complete each back-and-forth cycle.

Delivery of positive air pressure to the base of the diaphragm by the pressure control valve in the controller initiates the P-stroke. Positive air pressure pushes the diaphragm up from the *air-side* hemisphere of the device, driving liquid from the diaphragm pump through the lumen of the hollow fiber filters and back to the bioreactor. Replacement of the positive pressure under the diaphragm pump with a vacuum initiates the E-stroke. The vacuum pulls the diaphragm down from the *liquid-side* hemisphere of the device, pulling liquid from the bioreactor through the hollow fiber lumens and towards the diaphragm pump.

Figure 1. Pressure and Exhaust Strokes



Note: *XCell ATF Housings 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 Housing operation.*

3. About This Document

Several user attention phrases are used throughout this manual. Each phrase should draw the following level of attention:

Table 1. Explanation of User Attention Phrases

Phrase	Description
Note:	Points out useful information
IMPORTANT	Indicates information necessary for proper instrument operation
CAUTION	Cautions users regarding potentially hazardous situations regarding user injury or damage to the instrument if the information is not heeded
WARNING!	Warns users that serious physical injury can result if warning precautions are not heeded

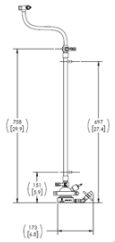
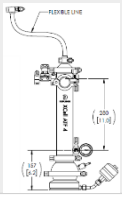
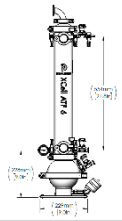
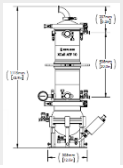
4. Safety Precautions

Table 2. Explanation of Symbols

Symbol		Description
Caution		Risk of danger. Consult Operating Instructions for nature of hazard and corrective actions. Potentially hazardous situation which, if not avoided, may result in property/equipment damage
Safety Alert Symbol		Hazard to personnel is present, the safety alert symbol is omitted when the hazard is related to property/equipment damage only

5. Specifications

Table 3. Dimensions

Filtration Assembly	Dimensions[1] H, W	Base Plate/L x W	Drawings with Dimensions (cm[in])
SS XCell ATF 2 Housing	30 in, 5 in	3 in x 3 in	
SS XCell ATF 4 Housing	24 in, 6 in	6 in x 10 in	
SS XCell ATF 6 Housing	44 in, 10 in	8 in x 12 in	
SS XCell ATF 10 Housing	44 in, 14 in	14 in x 20 in	

[1]Indicated dimensions are estimates for the filtration assembly, as the connections to the bioreactor and accessories can affect height and effective area.

Housing selection depends on the perfusion rate or total volume throughput in addition to other process conditions.

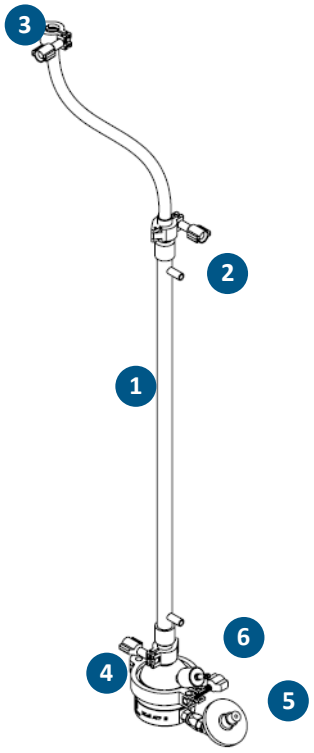
Table 4. Standard Length of ATF to Bioreactor (A2B) Connection – Reach out to Repligen FAS for More Information

Housing	Length
XCell ATF 2	14 in
XCell ATF 4	14 in
XCell ATF 6	31 in
XCell ATF 10	46 in

6. XCell ATF 2 Stainless Steel Housing

XCell ATF 2 Stainless Steel Housing (Figure 2) is recommended for use with 2 – 10 L bioreactors. The assembly of the housing and accessories includes installing the diaphragm into the housing, connecting the hollow fiber filter to the housing, and connecting the filter to the bioreactor and the harvest vessel. The system is prepared for use by filter wetting, integrity testing, and autoclaving.

Figure 2. XCell ATF 2 Stainless Steel Housing



1. Hollow fiber membrane
2. Permeate/harvest
3. Retentate
4. Diaphragm pump
5. Air inlet
6. Drain port

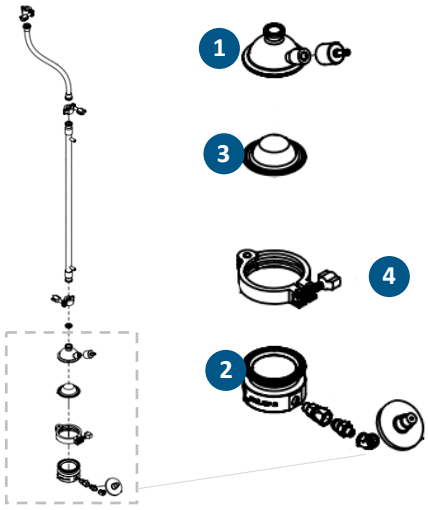
6.1 Stainless Steel XCell ATF 2 Housing Assembly

XCell ATF 2 Stainless Steel Housing assembly includes installation of the diaphragm and hollow fiber filter and connection of the tubing from the housing to the bioreactor and the housing to the harvest vessel.

6.1.1 Installing the Diaphragm

Important: The silicone diaphragm must be replaced after each run and prior to sterilization. To avoid premature failure, it is important to ensure that the diaphragm is seated in the correct orientation. Use with aqueous liquids only. For use with other fluids contact Repligen for a technical discussion. When used as instructed, the diaphragm is designed to last over one million pressure/exhaust cycles.

Figure 3. Orientation of Silicone Diaphragm in XCell ATF 2 Stainless Steel Housing



1. Pump liquid-side hemisphere
2. Pump air-side hemisphere
3. Diaphragm
4. Clamp

6.1.2 XCell ATF 2 Device Diaphragm Placement

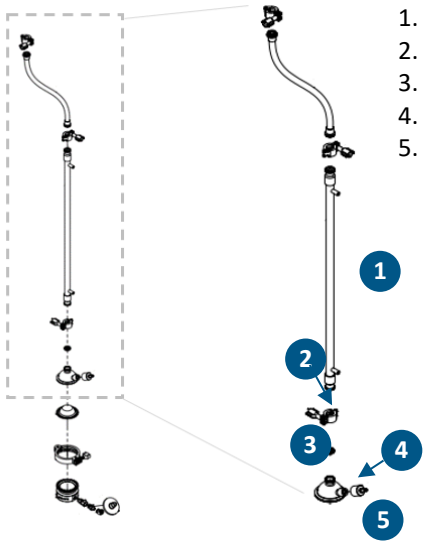
Important: The silicone diaphragm must be replaced after each run, prior to sterilization.

1. Set the pump air-side (PA) hemisphere (Figure 3, 2) on a flat surface with the open (concave) side of the hemisphere facing up.
2. Place diaphragm (3) with the convex side oriented up onto the PA hemisphere, and place the PL hemisphere, wide opening down, on top of the diaphragm.
3. Assure the diaphragm gasket O-ring is positioned uniformly around the periphery of the pump O-ring groove. Place the pump liquid-side (PL) hemisphere (1) on top. The two hemispheres, with diaphragm in between, should be equally spaced.
4. Clamp (4) the two hemispheres together.

6.1.3 XCell ATF 2 Stainless Steel Housing Hollow Fiber Filter Installation

XCell ATF 2 Stainless Steel Housing accommodates a variety of hollow fiber modules (HFM). For selection support, please contact your local Repligen Field Applications Specialist (FAS).

Figure 4. XCell ATF 2 Stainless Steel Housing Installation of Hollow Fiber Filter



1. Hollow fiber module (not included)
2. Clamp
3. Gasket
4. PL hemisphere
5. Drain port

1. Place a sanitary gasket (Figure 4, 3) into the sanitary groove on top of the Pump Liquid-side (PL) hemisphere (4).
2. Connect the HFM (1) to the pump housing by aligning it with the sanitary gasket on the top of the PL hemisphere (4).
3. Secure the connection tightly with a ¾" tri-clamp (2).

6.2 Filter Preparation

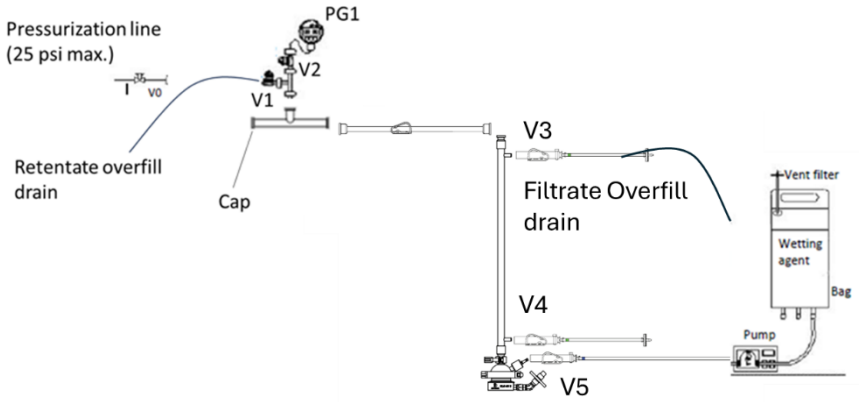
To prepare the filter for use, the assembled housing should be wetted, integrity tested, and autoclaved.

6.2.1 Filter Wetting

Hollow fiber filters require wetting after installation. Rinsing filters prior to use is a standard practice within the industry and the pre-autoclave integrity test requires a fully wetted cartridge. The following wetting liquids should be used with the indicated filters and are intended as single-use-pass through the filter to disposal. It is recommended that the filter be flushed with appropriate wetting agent until a permeate volume of 2 mL/cm^2 of surface area is reached:

- **Micro-filtration (MF) 0.1 – 0.65 µm**: use WFI or buffer as wetting agent.
- **Ultra-filtration (UF) 10 – 750 kDa**: use 10 – 25% isopropyl alcohol (IPA).

Figure 5. XCell ATF 2 System Filtration Assembly Prepared for Wetting and Integrity Testing



1. Assemble the XCell ATF Device according to Figure 5. Slight variations in assembly are possible depending on the configuration of equipment purchased and its intended use. For more detailed assembly instructions contact Repligen.
2. Connect the container with the wetting solution volume of ≥2.6 L and place tuning into peristaltic pump. Direct feed from WFI drop may also be used, provided there is a means to modulate the pressure and flow to satisfy requirements.
3. Close V2 and V4. Keep V1, V3, and V5 open.
4. Pump the liquid into the system from bottom up at a rate of ≤0.2 L/min (for UF membranes, use 10 psi feed pressure). Ensure that no air enters the system. (Flow should occur from bottom to top as this naturally removes the air from the system. Top to bottom can result in trapped air, which may lead to incomplete filter wetting and a failed integrity test result).
5. Continue filling the system until the first sign that liquid begins to flow from V1. Stop the pump.
6. Close V1. Keep V3 and V5 open.
7. Start the peristaltic pump to wet the filter at 0.2 LPM (for UF membranes, use 10 psi feed pressure).
8. Once liquid begins to flow from V3, tilt the ATF 20° away from V3 to facilitate air removal from the top of the filtrate compartment until no more air flows through.
9. After wetting is complete (≥2.6 L is collected in filtrate), stop the peristaltic pump.
10. Close V3 and V5 and allow the UF filter to soak in the wetting solution for at least one hour (step not needed for MF filters).
11. Remove the liquid from the system, both the filtrate and retentate chambers, Open V3 (remove the harvest line) to drain the filtrate side by gravity. Open V1 and V5 and slowly run the peristaltic pump in reverse to drain the retentate side.

Note: *If IPA is used for wetting, repeat the above procedure at least three times with WFI to thoroughly remove the IPA. Soaking is not required for these additional WFI flushes to maximize removal of liquid from the system, the diaphragm must be pushed up by slowly adding air through the 0.2 µm air inlet filter (F1) up to 2 psi, ensuring not to overinflate the diaphragm. Tilt the XCell ATF towards V4 by 20° to facilitate drainage. Leaving a small amount of WFI (i.e., milliliters) inside the pump is acceptable for autoclaving.*

6.2.2 Integrity Testing Pre-Autoclaving

Note: *Repligen strongly recommends the practice of integrity testing pre-autoclaving for XCell ATF 4, 6, and 10 to ensure a proper assembly prior to autoclaving.*

1. Refer to Figure 5 for proper set up. Equipment must be at ambient temperature.
2. Close V1, V4, and V5. Keep V3 open.
3. Connect air pressurization line to V1.
4. Open V2 to monitor the pressure on PG1.
5. Open the pressurization line at V0.
6. Carefully regulate V1 to pressurize the retentate chamber to 10 psi for MF membranes and 20 psi for UF membranes. Close V1 rapidly to hold the pressure.
7. Allow for a 1-minute equilibration period prior to taking either pressure or flow readings.
8. Record PG1 initial values.
9. Monitor the pressure decay rate on PG1: Record PG1 at one minute intervals for 5 minutes.
10. Calculate the average pressure decay rate over 5 min. The calculated pressure decay rate should not exceed 0.5 psi/min.

Note: *The air diffusion rate may also be used for integrity assessment by monitoring the flow rate from V3 using a digital mass flow meter (diffusion rate should be ≤2.6 mL/min). Integrity test instruments may also be used to test the integrity of filters.*

6.2.3 Autoclaving

The XCell ATF 2 Stainless Steel Housing Assembly is autoclaved either before or after integrity testing. XCell ATF 2 comprises a small-diameter, self-contained hollow fiber filter connected to a diaphragm pump and can be autoclaved using a pre-programmed liquid cycle at 121°C for 30 minutes. Refer to Appendix A for complete instructions.

6.3 Connecting XCell ATF 2 Stainless Steel Housing to a Bioreactor

XCell ATF 2 Stainless Steel Housing is generally connected to the bioreactor prior to autoclaving.

Fluid management for XCell ATF 2 Stainless Steel Housings includes retentate (A2B) tubing set kits and accessories that connect the housing with the bioreactor, ensuring proper exchange of cell culture material. The A2B tubing connects to XCell ATF 2 with a tri-clamp. The bioreactor end of the tubing is available with either a tri-clamp or an AseptiQuik® or Readymate™ disposable aseptic connector. The tubing is connected to the headplate (Table 5) and feeds into a dip tube (P/N TC-DIP-LAB-.25/.5-250). Permeate tubing connects to the housing with a hose barb and should be sterilized by autoclave or attached to the harvest vessel with a tubing welder or disposable sterile coupling. The permeate tubing should be compatible with the permeate/harvest pump. Tubing is also provided for the bottom permeate and drain ports, both of which connect with a hose barb.

Table 5. Headplate Fitting Part Numbers

Head Plate Fitting	Bioreactor
HP:APP-M19	3 L Applikon
HP:APP-M26	5 – 10 L Applikon
HP:BBI-M26	Sartorius/BBI
HP:PG13.5L	Millipore Mobius® CellReady
HP-PG13.3	Generics Sartorius UniVessel® SU

6.3.1 XCell ATF 2 Stainless Steel Tubing Set Kits and Accessories

Several components are required to connect the XCell ATF 2 Stainless Steel Housing to a bioreactor. XCell ATF 2 Autoclavable Tubing Set Kits (Table 6) are available in three configurations depending on the type of bioreactor in use and the preferred connectors. All tubing set kits have a pressure rating of 25 psi. Additional accessories (Table 7) are required, regardless of the chosen tubing set.

Table 6. XCell ATF 2 Tubing Set Kit Options

Tube Set Part Number	Tubing Connection	Use
ATF2-A2B-TC	Tri-Clamp/Tri-Clamp	ATF to bioreactor
ATF2-A2B-RMTC	Cytiva ReadyMate/Tri-Clamp	ATF to bioreactor
ATF2-A2B-TCAQ	AseptiQuik/Tri-Clamp	ATF to bioreactor
ATF2-A2B-AQ	AseptiQuik S/AseptiQuik S	ATF to bioreactor

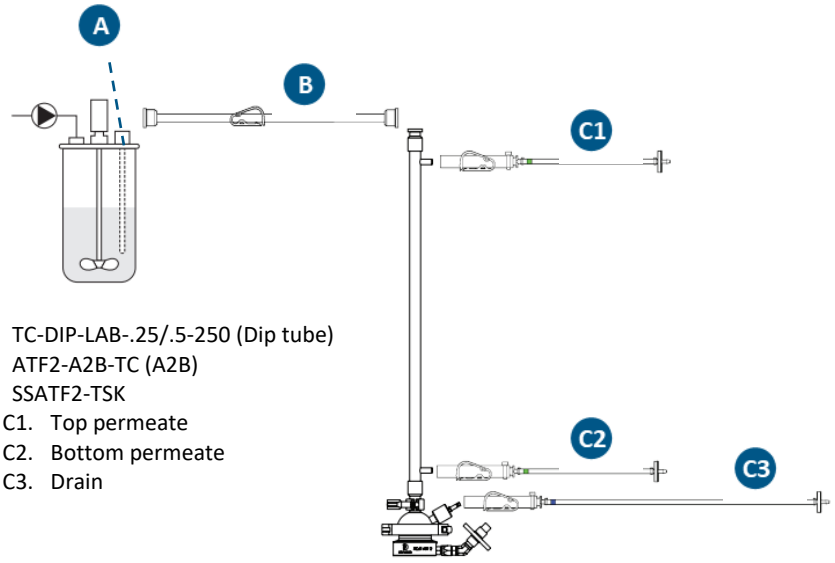
Table 7. XCell ATF 2 Optional Accessory

Description	Part Number	Single/Multi-use	Pressure Rating	ID	Material of Construction
Top and bottom permeate and drain	SSATF2-PSK	SU	25 psi	0.25"	Platinum-cured silicone

6.3.2 Tubing Set Kit for XCell ATF 2 Stainless Steel Housing Connected to Glass Bioreactor

Assembly of the housing, tubing set, and accessories is completed prior to autoclaving.

Figure 6. XCell ATF 2 Stainless Steel Housing Connection to Glass Bioreactor (Tri-Clamp)

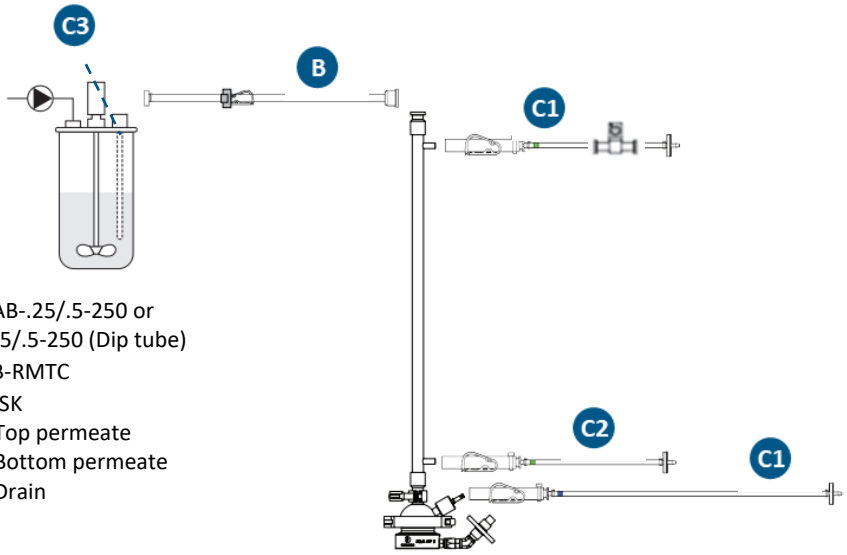


A. TC-DIP-LAB-.25/.5-250 (Dip tube)
B. ATF2-A2B-TC (A2B)
C. SSATF2-TSK
   C1. Top permeate
   C2. Bottom permeate
   C3. Drain

Connection instructions (Figure 6):

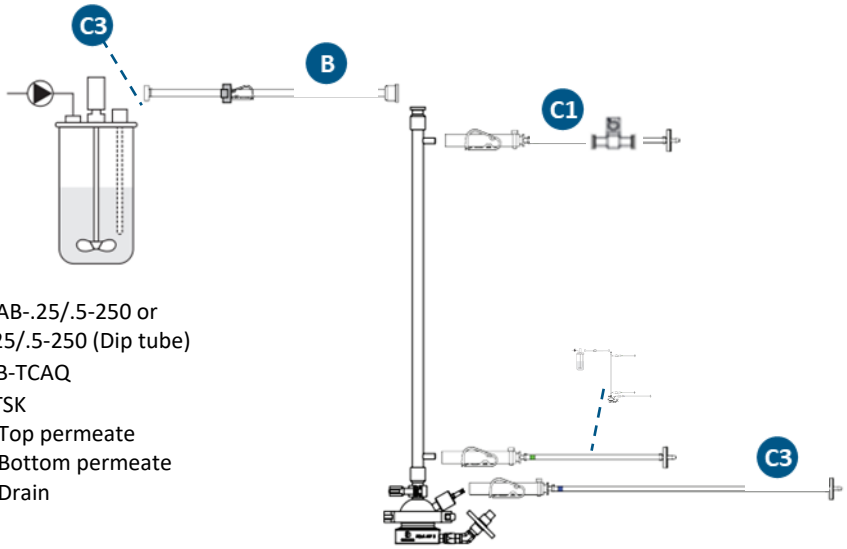
1. Ensure dip tube (A) is attached to head plate of bioreactor.
2. Attach A2B tubing (B) to XCell ATF 2 and bioreactor head plate.
3. Attach top permeate (C1) to hose barb.
4. Attach bottom permeate (C2) to hose barb.
5. Attach drain (C3) to hose barb. Autoclave.

Figure 7. XCell ATF 2 Stainless Steel Housing Connection to Single-Use Bioreactor (ReadyMate)



A. TC-DIP-LAB-.25/.5-250 or TC-DIP-.25/.5-250 (Dip tube)
B. ATF2-A2B-RMTC
C. SSATF2-TSK
   C1. Top permeate
   C2. Bottom permeate
   C3. Drain

Figure 8. XCell ATF 2 Stainless Steel Housing Connection to Single-Use Bioreactor (AsepticQuik)



A. TC-DIP-LAB-.25/.5-250 or TC-DIP-.25/.5-250 (Dip tube)
B. ATF2-A2B-TCAQ
C. SSATF2-TSK
   C1. Top permeate
   C2. Bottom permeate
   C3. Drain

Connection instructions (Figure 7, Figure 8):

1. Ensure dip tube (A) is attached to head plate fitting. Attach a ¾" sanitary genderless AseptiQuik S connector (AQS33012HT) or ReadyMate DAC Mini TC (28936695) connector to diptube. Autoclave separately and insert in single-use bioreactor in a BSC.
2. Attach A2B tubing (B) to XCell ATF 2.

Note: *Bioreactor adapter tubing not provided*.

3. Attach top permeate (C1) to hose barb.
4. Attach bottom permeate (C2) to hose barb.
5. Attach drain (C3) to hose barb. Autoclave.
6. Attach A2B tubing (B) to sterile connector on single-use bioreactor after autoclave.

6.4 Disassembly and Maintenance

6.4.1 Removing the Housing From the Bioreactor

1. Stop the permeate/harvest pump and disconnect the harvest bag from the housing.
2. Stop and disconnect the A2C line from the diaphragm pump.
3. Close or disconnect compressed air and vacuum services from the pneumatic enclosure.
4. Disconnect sensors from the filtration assembly to pneumatic enclosure.
5. If necessary, remove the pneumatic enclosure from the filtration assembly.
6. Close valves connecting the filtration assembly to the vessel.
7. Drain liquid from the connection.
8. Optionally, purge the connection with water, steam, or some other medium.
9. Disconnect the filtration assembly from vessel.
10. Remove the filtration assembly to an appropriate work area.

6.4.2 HFF Removal

1. Drain the system into an appropriate waste vessel or drain.
2. Remove all sensors from the housing.
3. Remove air inlet filter connected to the diaphragm pump and any other connections to the XCell ATF Housing.
4. Open the clamp that connects the filter to the diaphragm pump and separate.
5. Open the clamp that connects the filter to the A2B tubing and separate.
6. Remove the gasket at the exposed end of the HFF.
7. Press the HFF in the opposite direction to remove.
8. Prepare filter housing for cleaning and reuse.

6.4.3 Decontaminating the HFF for Disposal

1. Rinse the HFF two times with water to remove residual cells and debris.
2. Decontaminate with either 0.5M NaOH, potassium hydroxide, or bleach for 2 – 24 hours.

Note: *5.25% chlorine is equivalent to 52,500 parts per million (ppm). If household chlorine bleach is used, two working solutions are generally recommended: 5000 – 6000 ppm for initial decontamination of organic spill material, and 500 – 600ppm for disinfection of cleaned surfaces.*

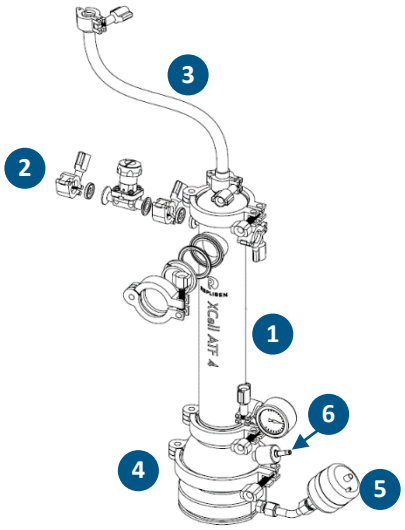
6.4.4 Pump Air Inlet Filter, O-Rings, Gaskets, and Quick Connects

All consumable items are single use.

7. Stainless Steel XCell ATF 4 Housing

XCell ATF 4 Housing (Figure 9) is recommended for use with 10 – 50 L bioreactors. The assembly of the housing and accessories includes installing the diaphragm and hollow fiber filter into the housing, connecting the tubing set kit to the bioreactor, and connecting the harvest line to the housing. The system is prepared for use by pressure testing, filter wetting, integrity testing, and autoclaving.

Figure 9. XCell ATF 4 Housing



1. Housing
2. Permeate/Harvest
3. Retentate
4. Diaphragm pump
5. Air inlet
6. Drain Port

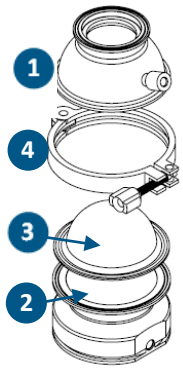
7.1 Stainless Steel XCell ATF 4 Housing Assembly

XCell ATF 4 Housing assembly includes installation of the diaphragm and hollow fiber filter and assembly of the tubing set kit that will connect the housing and the bioreactor and the tubing that will connect the housing and the harvest vessel.

7.1.1 Installing the Diaphragm

Important: The silicone diaphragm must be replaced after each run and prior to sterilization. To avoid premature failure, it is important to ensure that the diaphragm is seated in the correct orientation. Use with aqueous liquids only. For use with other fluids contact Repligen for a technical discussion. When used as instructed, the diaphragm is designed to last over one million pressure/exhaust cycles.

Figure 10. Orientation of Silicone Diaphragm in XCell ATF 4 Housing



1. Housing assembly, pump liquid-side (PL) hemisphere
2. Housing assembly, pump air- side (PA) hemisphere
3. Diaphragm
4. Clamp

7.1.2 XCell ATF 4 Housing Diaphragm Placement

1. Set the pump air-side (PA) hemisphere (Figure 10,2) on a flat surface with the open (concave) side of the hemisphere facing up.
2. Place diaphragm (3) with the convex side oriented up onto the PA hemisphere, and place the PL hemisphere, wide opening down, on top of the diaphragm.
3. Assure the diaphragm gasket O-ring is positioned uniformly around the periphery of the pump O-ring groove. The two hemispheres, with diaphragm in between, should be equally spaced.
4. Clamp (4) the two hemispheres together. Hand tightening is sufficient with the supplied clamps.

7.1.3 XCell ATF 4 Housing Hollow Fiber Filter Installation

XCell ATF 4 Housing accommodates a variety of hollow fiber filters. For support in selecting hollow fiber filters, please contact your local Repligen Field Applications Specialist (FAS).

1. Stand the filter housing vertically, with harvest port down.
2. Insert the HFF into the housing
3. Insert one O-ring into the groove between HFF and housing end-ferrule wall.
4. Place the 2½" TC sanitary gasket onto the diaphragm pump.
5. Carefully place the filter housing onto gasket of the diaphragm pump, forcing the O-ring deeper into the groove.
6. Clamp the filter housing to the diaphragm pump. Hand tightening is sufficient with the supplied clamps.
7. On the other end of the filter housing, place the second O-ring into the groove between HFF and housing end-ferrule.
8. Place the2 ½" TC sanitary gasket followed by the reducer onto the end, forcing the O-ring into the groove.
9. Clamp the reducer to the housing, compressing the O-ring against the HFF. A seal is formed between the housing, reducer and HFF. Hand tightening is sufficient with the supplied clamps.
10. Assemble the rest of the XCell ATF Housing, including tubing set kits (Figure 9).

7.2 Filter Preparation

To prepare the filter for use, the assembled housing should be pressure tested, wetted, integrity tested, and autoclaved.

7.2.1 Pressure Testing

Pressure testing ensures that the XCell ATF 4 Housing assembly is free of leaks and can withstand the required operating pressures. The assembly can be pressure tested with or without a filter module, before or after sterilization. Ideally, the test is performed with a filter prior to autoclaving. Slight variations in the configuration of the external connections are possible depending on the configuration of the equipment purchased and the connections being made to the bioreactor.

Figure 11. XCell ATF 4 System Filtration Assembly Prior to Pressure Test

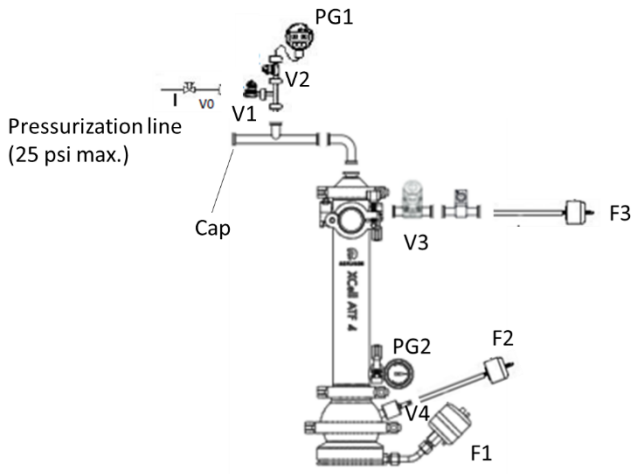


Table 8. XCell ATF 4 Vent Filter Required Surface Area

F1[1]	F2	F3	F4	F5	F5a
≥0.15 m^2	≥0.05 m^2	≥0.05 m^2	≥0.05 m^2	≥0.15 m^2	≥0.05 m^2

[1]F1 – F5 correspond to vent filter locations shown in Figure 11, Figure 12, and Figure 32.

1. Assemble the XCell ATF System according to Figure 11.
2. Prepare a regulated ~22psi/1.5 bar, dry, oil-free air source.
3. Close all valves. Attach pressurization line to V1. Secure all connections.

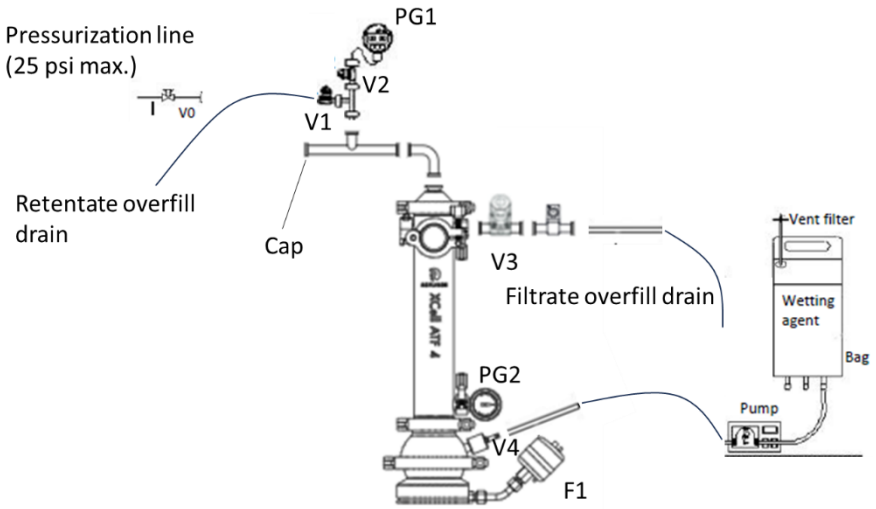
4. While monitoring the pressurization rate on PG1 and PG2, open V2 and slowly regulate opening of V1 to pressurize the retentate side. Equalize pressure on the filtrate side.
5. Once the XCell ATF Filtration unit is pressurized to about 20 psi, close V0 and V1.
6. Wait five minutes for the pressure in the XCell ATF system to stabilize.
7. Record the values for both the retentate and filtrate pressure gauges, PG1 and PG2.
8. After 60 minutes, record these pressure values again.
9. Any drop in pressure should not exceed 1 psi.
10. If the Pressure Test has failed, find the leak and repeat steps 4 through 9 again.
11. To depressurize the system, disconnect the pressurization line and slowly open V3 to depressurize the filtrate side first, then open V4 to depressurize the retentate side.

7.2.2 Filter Wetting

After the filter cartridge is installed and the pressure test confirms an integral assembly, the filter must be wetted prior to autoclaving. Rinsing filters prior to use is a standard practice within the industry and the pre-autoclave integrity test requires a fully wetted cartridge. The following wetting liquids should be used with the indicated filters and are intended as single-use pass-through the filter to disposal. It is recommended that the filter be flushed with appropriate wetting agent until a permeate volume of 2 mL/cm^2 of surface area is reached:

- **Micro-filtration (MF) 0.1 – 0.65 µm**: Use WFI or buffer as wetting agent.
- **Ultra-filtration (UF) 10 – 750 kDa**: Use 10 – 25% isopropyl alcohol (IPA).

Figure 12. XCell ATF 4 System Filtration Assembly Prepared for Wetting and Integrity Testing



1. Assemble the XCell ATF Device according to Figure 12. Slight variations in assembly are possible depending on the configuration of equipment purchased and its intended use. For more detailed assembly instructions contact Repligen.
2. Connect the container with the wetting solution volume of ≥15.4 L and place the tubing into a peristaltic pump. Direct feed from WFI drop may also be used, provided there is a means to modulate the pressure and flow to satisfy requirements.
3. Close V2, keep V1, V3, and V4 open.
4. Pump the liquid into the system from bottom up at a rate of ≤1 L/min (for UF membranes, use 10 psi feed pressure). Ensure that no air enters the system. (Flow should occur from bottom to top as this naturally removes the air from the system. Top to bottom can result in trapped air, which may lead to incomplete filter wetting and a failed integrity test result).
5. Continue filling the system until the first sign that liquid begins to flow from V1. Stop the pump.
6. Close V1. Keep V3 and V4 open.

7. Start the peristaltic pump to wet the filter at 1 LPM (for UF membranes, use 10 psi feed pressure).
8. Once liquid begins to flow from V3, tilt the ATF 20° away from V3 to facilitate air removal from the top of the filtrate compartment until no more air flows through.
9. After wetting is complete (≥15.4 L is collected in filtrate), stop the peristaltic pump.
10. Close V3 and V4 and allow the UF filter to soak in the wetting solution for at least 1 hour (step not needed for MF filters).
11. Remove the liquid from the system, both the filtrate and retentate chambers: Open V3 (remove the harvest line) to drain the filtrate side by gravity; then, open V1 and V4, and slowly run the peristaltic pump in reverse to drain the retentate side.

Note: *If IPA is used for wetting, repeat the above procedure at least three times with WFI to thoroughly remove the IPA. Soaking is not required for these additional WFI flushes to maximize removal of liquid from the system, the diaphragm must be pushed up by slowly adding air through the 0.2 µm air inlet filter (F1) up to 2 psi, ensuring not to overinflate the diaphragm. Tilt the XCell ATF towards V4 by 20° to facilitate drainage. Leaving a small amount of WFI (i.e. milliliters) inside the pump is acceptable for autoclaving.*

7.2.3 Integrity Testing Pre-Autoclaving

Note: *Repligen strongly recommends the practice of pre-autoclaving integrity testing to ensure a proper assembly prior to autoclaving.*

1. Refer to Figure 12 for proper setup. Equipment must be at ambient temperature.
2. Close V1 and V4. Keep open V3.
3. Connect air pressurization line to V1.
4. Open V2 to monitor the pressure on PG1.
5. Open the pressurization line at V0.
6. Carefully regulate V1 to pressurize the retentate chamber to 10 psi for MF membranes and 20 psi for UF membranes. Close V1 rapidly to hold the pressure.
7. Allow for a one-minute equilibration period prior to taking either pressure or flow readings.
8. Record PG1 and PG2 initial values.
9. Monitor the pressure decay rate on PG1: Record PG1 and PG2 pressure at one minute intervals for 5 minutes.

Note: *PG2 should remain at zero.*

10. Calculate the average pressure decay rate over 5 minutes. The calculated pressure decay rate should not exceed 0.29 psi/min.

Note: *The air diffusion rate may also be used for integrity assessment by monitoring the flow rate from V3 using a digital mass flow meter (diffusion rate should be ≤15.4 mL/min). Integrity test instruments may also be used to test the integrity of filters.*

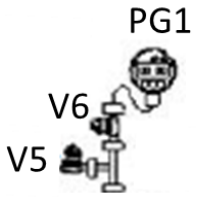
7.2.4 Autoclaving

The XCell ATF 4 Housing assembly is autoclaved either before or after integrity testing. The cycle sequence presented is strongly recommended to ensure sterility and to retain filter integrity and performance. The procedure includes three pre-vacuum pulses, which provide proper chamber evacuation for a faster and more consistent ramp to the required temperature. Please refer to Appendix A for complete instructions.

7.2.5 Integrity Testing Post Autoclaving

Post-autoclaving integrity testing is required only if testing was not performed pre-autoclaving.

Figure 13. Vent Tee for Post-Autoclaving Integrity Testing



1. Add setup in Figure 13 to F4 on either single-use or stainless steel bioreactor setup (Figure 32). Equipment must be at ambient temperature.
2. Clamp retentate tubing with a C-clamp to create a dead end if no bi-valve is present.
3. Close V4 (also close V1 and V1a if using bivalve). Open V2, V3, and V6.
4. Pressurize retentate-side by introducing air through sterile vent filter F4 up to 10 psi for MF membranes and 20 psi for UF membranes by opening V5 connected to pressure source.
5. Close V5 rapidly to hold the pressure.
6. For Pressure Decay, monitor pressure from pressure gauge PG1 at one-minute intervals for 5 minutes. The calculated decay rate should not exceed 0.44 psi/min.
7. For diffusion rate, monitor diffusion rate by attaching digital flow meter to sterile vent filter F3. The diffusion rate should not exceed 23.1 mL/min.

Note: *The post-autoclave maximum levels are elevated above the pre-autoclave levels as the membranes may partially dry out during the autoclave cycle.*

7.3 Connecting XCell ATF 4 Housing to a Bioreactor

Two types of connections between the housing 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 single-use connectors such as AseptiQuik, and Readymate DAC and are connected to the housing prior to autoclaving.

Fluid management for XCell ATF 4 Housings includes retentate (A2B) tubing set kits and accessories that connect the housing 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 housing 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 permeate/harvest pump.

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

7.3.1 Stainless Steel XCell ATF 4 Tubing Set Kits and Accessories

Several components are required to connect the XCell ATF 4 Housing to a bioreactor. XCell ATF 4 Autoclavable Tubing Set Kits (Table 9) are available in three configurations depending on the type of bioreactor in use and the preferred connectors. All tubing set kits have a pressure rating of 25 psi. Additional accessories (Table 10) are required, regardless of the chosen tubing set.

Table 9. XCell ATF 4 Tubing Set Kit Options

Tube Set Part Number	Bioreactor Type	Tubing Connection
ATF4-A2B-TC	Stainless steel	Tri-clover
SSATF4-SUB-A2B-RM	Single-use	Cytiva ReadyMate
ATF4-A2B-TCAQ		AseptiQuik G

Table 10. XCell ATF 4 Required Accessories

Description	Part Number	Single/Multi-use	Pressure Rating	ID	Material of Construction
Vent filter	F46-AIR-LSC	SU	25 psi	NA	PVDF
Permeate Pressure Sensor	SSATF-LSC-PSK	SU	25 psi	3/4 in	Polycarbonate
Vent tee (Single-use bioreactor only)	ATF4-OPT2	MU	45 psi	3/8 in	Stainless steel

In addition, use of a SSB requires bivalve assemblies (Table 11), which can be steamed in place.

Table 11. XCell ATF 4 Required Stainless Steel Bioreactor Accessory

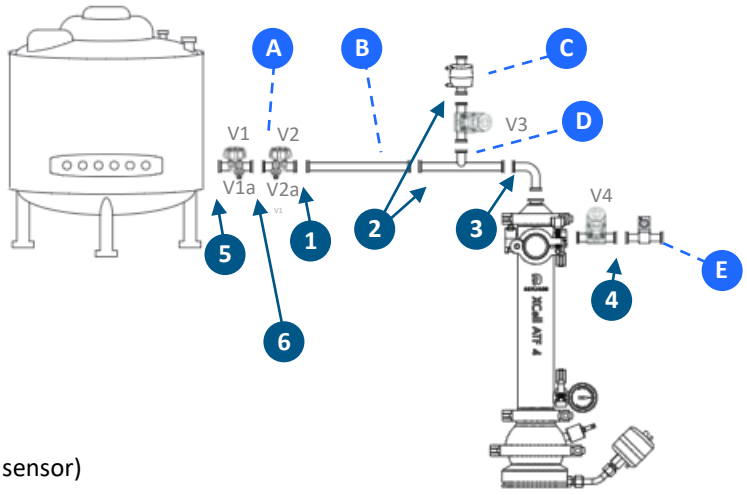
Description	Part Number	Single-/ Multi-use	Pressure Rating	ID	Material of Construction
Bivalve assembly	ATF4-VLV-KIT	MU	45 psi	3/8 in	Stainless steel

7.3.2 Tubing Set Kit Assembly for XCell ATF 4 Connected to Stainless Steel Bioreactor

Assembly of the housing, tubing set, and accessories is completed prior to autoclaving. Hard connection between the tubing set kit and the stainless steel bioreactor consists of the following parts, available as a unit:

- Two isolation bivalves: one attached to the bioreactor, and one attached to the housing
- A flexible hose between the main branches of the two valves
- A steam inlet: a side valve on one bivalve
- Condensate drain: a side valve on the other bivalve; lowest of the available valves

Figure 14. XCell ATF 4 Connection to Stainless Steel Bioreactor



A. ATF4-VLV-KIT (bivalve)
B. ATF4-A2B-TC (A2B)
C. F46-AIR-LSC (vent filter)
D. ATF4-OPT2 (vent tee)
E. SSATF-LSC-PSK (pressure sensor)

Following assembly of the housing, tubing set, and accessories, the right side of the system is autoclaved. Simultaneously, the right-facing bivalve is steamed in place so that when the autoclave cycle is complete, that section can be attached to the bioreactor and another steam-in-place cycle can be performed.

Connection instructions (Figure 14):

1. Attach left-facing bivalve (A) to tubing set (B).
2. Attach vent filter (C) to vent tee (D). Connect vent tee (D) to A2B tubing (B).
3. Connect ATF4 Housing to vent tee (D).

4. Attach permeate pressure sensor (E) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of pressure sensor. Open V2, V2a, V3,V4, and V5. Autoclave the entire assembly. Close V2, V2a, V4, and V5.
5. Attach the right-facing bivalve (A) to the bioreactor. Open valve V1a and attach trap. Open valve V1. Steam in place. Close V1.
6. Connect bivalves to each other. Open valves V1a and V2a. Valves V1 and V2 are closed. SIP the bivalve connection. Close valves V1a and V2a. Open valves V1 and V2 and close V3 for operation.

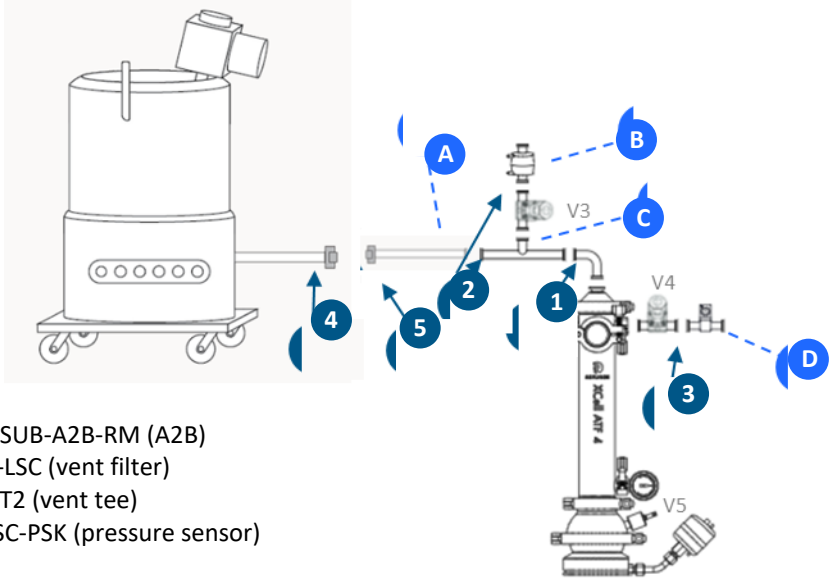
The following steam-in-place procedure is recommended for hard connections:

1. Attach a steam trap to the condensate valve and connect to a drain.
2. Close steam inlet and condensate drain valves.
3. Securely connect a regulated steam source to the steam inlet valve.
4. Open steam service.
5. Slowly open steam inlet valve.
6. Slowly open steam condensate valve.
7. Sterilize connection for about 20 minutes at 121°C and ~16 psi.
8. Cool down.
9. Close the condensate valve.
10. Rapidly close the steam inlet valve and immediately open the main valve into the filtration assembly to minimize a pressure drop in the connection.

7.3.2.1 Tube Set Kit Assembly for XCell ATF 4 Connected to Single-Use Bioreactor Using ReadyMate Tubing Set

Assembly of the housing, tubing set, and accessories, on the right side of the system is completed prior to autoclaving.

Figure 15. XCell ATF 4 Connection to Single-Use Bioreactor (ReadyMate)



A. SSATF4-SUB-A2B-RM (A2B)
B. F46-AIR-LSC (vent filter)
C. ATF4-OPT2 (vent tee)
D. SSATF-LSC-PSK (pressure sensor)

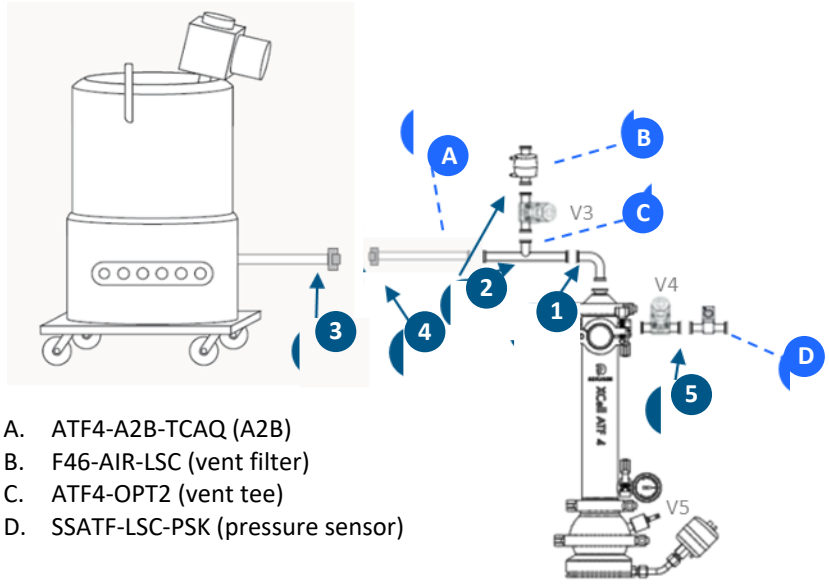
Connection instructions (Figure 15):

1. Connect ATF4 housing to vent tee (C).
2. Attach vent filter (B) to vent tee (C). Connect A2B tubing (A) to vent tee (C).
3. Attach permeate pressure sensor (D) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of the pressure sensor. Open all valves. Autoclave the assembly. Close all valves.
4. Determine the recommended aseptic connector for SUB. Connect adapter tubing (not supplied) to SUB must have ID ≥3/8", Length ≤10". Clamp sterile tubing.
5. Connect assembly to bioreactor.

7.3.2.2 Tube Set Kit Assembly for XCell ATF 4 Connected to Single-Use Bioreactor Using AseptiQuik Tubing Set

Assembly of the housing, tubing set, and accessories, on the right side of the system is completed prior to autoclaving.

Figure 16. XCell ATF 4 Connection to Single-Use Bioreactor (AseptiQuik)



A. ATF4-A2B-TCAQ (A2B)
B. F46-AIR-LSC (vent filter)
C. ATF4-OPT2 (vent tee)
D. SSATF-LSC-PSK (pressure sensor)

Connection instructions (Figure 16):

1. Connect ATF 4 housing to vent tee (C).
2. Attach vent filter (B) to vent tee (C). Connect A2B tubing (A) to vent tee (C).
3. Attach permeate pressure sensor (D) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of the pressure sensor. Open all valves. Autoclave the assembly.
4. Determine the recommended aseptic connector for SUB. Connect adapter tubing (not supplied) to SUB must have ID ≥3/8", Length ≤10". Clamp sterile tubing.
5. Connect assembly to bioreactor.

7.4 Disassembly and Maintenance

7.4.1 Removing the Housing From the Bioreactor

1. Stop the permeate/harvest pump and disconnect the harvest bag from the housing.
2. Stop and disconnect the A2C line from the diaphragm pump.
3. Close or disconnect compressed air and vacuum services from the pneumatic enclosure.
4. Disconnect sensors from the filtration assembly to pneumatic enclosure.
5. If necessary, remove the pneumatic enclosure from the filtration assembly.
6. Close both bivalves connecting the filtration assembly to the vessel.
7. Drain liquid from the connection.
8. Optionally, purge the connection with water, steam, or some other medium.
9. Disconnect the filtration assembly from vessel between the two bivalves.
10. Remove the filtration assembly to an appropriate work area.

7.4.2 HFF Removal

1. Drain the system into an appropriate waste vessel or drain.
2. Remove all sensors from the housing.
3. Remove air inlet filter connected to the diaphragm pump and any other connections to the XCell ATF Housing.

4. Open the clamp that connects the filter housing to the diaphragm pump and separate.
5. Open the clamp that connects the reducer to the filter housing and separate.
6. Remove the HFF from housing by firmly pressing it from one end.
7. Remove the O-ring at the exposed end of the HFF.
8. Press the HFF in the opposite direction to remove.
9. Prepare filter housing for cleaning and reuse.

7.4.3 Decontaminating the HFF for Disposal

1. Rinse the HFF two times with water to remove residual cells and debris.
2. Decontaminate with either 0.5M NaOH, potassium hydroxide, or bleach for 2 – 24 hours.

Note: *5.25% chlorine is equivalent to 52,500 parts per million (ppm). If household chlorine bleach is used, two working solutions are generally recommended: 5000-6000 ppm for initial decontamination of organic spill material, and 500 – 600 ppm for disinfection of cleaned surfaces.*

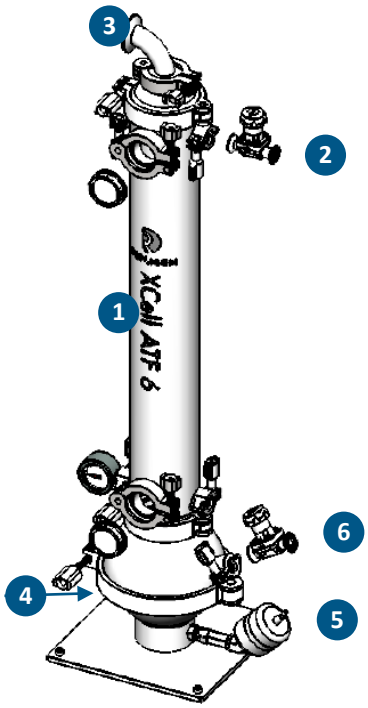
7.4.4 Pump Air Inlet Filter, O-Rings, Gaskets, and Quick Connects

All consumable items are single use.

8. Stainless Steel XCell ATF 6 Housing

XCell ATF 6 Housing (Figure 17) is recommended for use with 50 – 200 L bioreactors. The assembly of the housing and accessories includes installing the diaphragm and hollow fiber filter into the housing, connecting the tubing set kit to the bioreactor, and connecting the harvest line to the housing. The system is prepared for use by pressure testing, filter wetting, integrity testing, and autoclaving.

Figure 17. XCell ATF 6 Housing



1. Housing
2. Permeate/Harvest
3. Retentate
4. Diaphragm pump
5. Air inlet
6. Drain Port

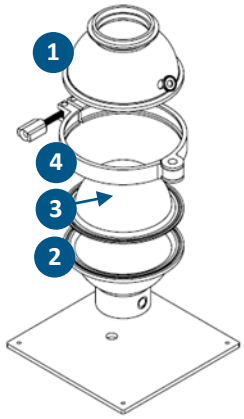
8.1 Stainless Steel XCell ATF 6 Housing Assembly

XCell ATF 6 Housing assembly includes installation of the diaphragm and hollow fiber filter and assembly of the tubing set kit that will connect the housing and the bioreactor and the tubing that will connect the housing and the harvest vessel.

8.1.1 Installing the Diaphragm

Important: The silicone diaphragm must be replaced after each run and prior to sterilization. To avoid premature failure, it is important to ensure that the diaphragm is seated in the correct orientation. Use with aqueous liquids only. For use with other fluids contact Repligen for a technical discussion. When used as instructed, the diaphragm is designed to last over one million pressure/exhaust cycles.

Figure 18. Orientation of Silicone Diaphragm in Pump Housing XCell ATF 6



1. Housing assembly, pump liquid-side (PL) hemisphere
2. Housing assembly, pump air-side (PA) hemisphere
3. Diaphragm
4. Clamp

8.1.1.1 XCell ATF 6 Housing Diaphragm Placement

1. Set the pump air-side (PA) hemisphere (Figure 18, 2) on a flat surface with the open (concave) side of the hemisphere facing up.
2. Place diaphragm (3) with the convex side oriented up onto the PA hemisphere, and place the PL hemisphere, wide opening down, on top of the diaphragm.
3. Assure the diaphragm gasket O-ring is positioned uniformly around the periphery of the pump O-ring groove. The two hemispheres, with diaphragm in between, should be equally spaced.
4. Clamp (4) the two hemispheres together. Hand tightening is sufficient with supplied clamps.
5. Secure the diaphragm pump to the stand.

8.1.2 XCell ATF 6 Housing Hollow Fiber Filter Installation

XCell ATF 6 Housing accommodates a variety of hollow fiber filters. For support in selecting hollow fiber filters, please contact your local Repligen Field Applications Specialist (FAS).

1. Stand the filter housing vertically, with harvest port down.
2. Insert the HFF into the housing
3. Insert one O-ring into the groove between HFF and housing end-ferrule wall.
4. Carefully place the filter housing onto the diaphragm pump, forcing the O-ring deeper into the groove.
5. Clamp the filter housing to the diaphragm pump. Hand tightening is sufficient with supplied clamps.
6. On the other end of the filter housing, place the second O-ring into the groove between HFF and housing end-ferrule.
7. Place the reducer onto the end, forcing the O-ring into the groove.
8. Clamp the reducer to the housing, compressing the O-ring against the HFF. A seal is formed between the housing, reducer and HFF. Hand tightening is sufficient with supplied clamps.
9. Assemble the rest of the XCell ATF Housing, including tubing set kits (Figure 17).

8.2 Filter Preparation

To prepare the filter for use, the assembled housing should be pressure tested, wetted, integrity tested and autoclaved.

8.2.1 Pressure Testing

Pressure testing ensures that the XCell ATF 6 Housing assembly is free of leaks and can withstand the required operating pressures. The assembly can be pressure tested with or without a filter module, before or after sterilization. Ideally, the test is performed with a filter prior to autoclaving. Slight variations in the configuration of the external connections are possible depending on the configuration of the equipment purchased and the connections being made to the bioreactor.

Figure 19. XCell ATF 6 System Filtration Assembly Prior to Pressure Test

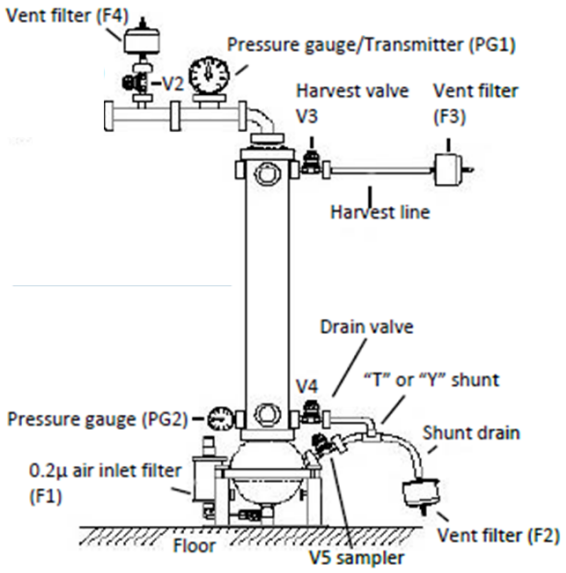


Table 12. XCell ATF 6 Vent Filter Required Surface Area

F1[1]	F2	F3	F4	F5	F5a
≥0.15 m^2	≥0.15 m^2	≥0.05 m^2	≥0.15 m^2	≥0.15 m^2	≥0.05 m^2

[1]F1 – F5 correspond to vent filter locations in Figure 19, Figure 20, and Figure 33.

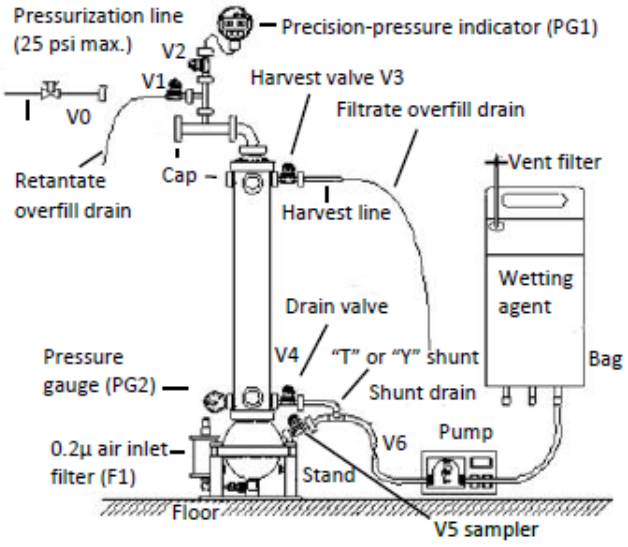
1. Assemble the XCell ATF System according to Figure 19. Ensure an end cap is placed on vent tee.
2. Prepare a regulated ~22 psi/1.5 bar, dry, oil-free air source.
3. Close all valves. Attach pressurization line to shunt line (V4/V5). Secure all connections.
4. While monitoring the pressurization rate on PG1 and PG2, slowly regulate opening of V5 to pressurize the retentate side first, then slowly open V4 to equalize the pressure on the filtrate side.
5. Once the XCell ATF Device is pressurized to about 20 psi, close all valves.
6. Wait five minutes for the pressure in the XCell ATF system to stabilize.
7. Record the values for both the retentate and filtrate pressure gauges, PG1 and PG2.
8. After 60 minutes, record these pressure values again.
9. Any drop in pressure should not exceed 1 psi.
10. If the Pressure Test has failed, find the leak and repeat steps 4 through 9 again.
11. To depressurize the system, disconnect the pressurization line and slowly open V4 to depressurize the filtrate side first, then open V5 to depressurize the retentate side.

8.2.2 Filter Wetting

After the filter cartridge is installed and the pressure test confirms an integral assembly, the filter must be wetted prior to autoclaving. Rinsing filters prior to use is a standard practice within the industry and the pre-autoclave integrity test requires a fully wetted cartridge. The following wetting liquids should be used with the indicated filters and are intended as single-use pass-through the filter to disposal. It is recommended that the filter be flushed with appropriate wetting agent until a permeate volume of 2 mL/cm^2 of surface area is reached:

- **Micro-filtration (MF) 0.1 – 0.65 µm** – use WFI or buffer as wetting agent.
- **Ultra-filtration (UF) 10 – 750 kDa** – use 10-25% isopropyl alcohol (IPA).

Figure 20. XCell ATF 6 System Filtration Assembly Prepared For Wetting and Integrity Testing



1. Assemble the XCell ATF Device according to Figure 20. Slight variations in assembly are possible depending on the configuration of equipment purchased and its intended use. For more detailed assembly instructions contact Repligen.
2. Connect the container with the wetting solution volume of ≥50 L and place the tubing into a peristaltic pump. Direct feed from WFI drop may also be used, provided there is a means to modulate the pressure and flow to satisfy requirements.
3. Close V2 and V4, keep V1, V3, and V5 open.
4. Pump the liquid into the system from bottom up at a rate of ≤4 L/min (for UF membranes, use 10 psi feed pressure). Ensure that no air enters the system. (Flow should occur from bottom to top as this naturally removes the air from the system. Top to bottom can result in trapped air, which may lead to incomplete filter wetting and a failed integrity test result).
5. Continue filling the system until the first sign that liquid begins to flow from V1. Stop the pump.
6. Close V1. Keep V3 and V5 open.
7. Start the peristaltic pump to wet the filter at 4 LPM (for UF membranes, use 10 psi feed pressure).
8. Once liquid begins to flow from V3, tilt the ATF 20° away from V3 to facilitate air removal from the top of the filtrate compartment until no more air flows through.
9. After wetting is complete (≥50 L is collected in filtrate), stop the peristaltic pump.
10. Close V3 and V5 and allow the UF filter to soak in the wetting solution for at least one hour (step not needed for MF filters).
11. Remove the liquid from the system, both the filtrate and retentate chambers: Open V4 and V3 (remove the harvest line) to drain the filtrate side by gravity; then, open V1 and V5, and slowly run the peristaltic pump in reverse to drain the retentate side.

Note: *If IPA is used for wetting, repeat the above procedure at least three times with WFI to thoroughly remove the IPA. Soaking is not required for these additional WFI flushes to maximize removal of liquid from the system, the diaphragm must be pushed up by slowly adding air through the 0.2 µm air inlet filter (F1) up to 2 psi, ensuring not to overinflate the diaphragm. Tilt the XCell ATF towards V4 by 20° to facilitate drainage. Leaving a small amount of WFI (i.e., milliliters) inside the pump is acceptable for autoclaving.*

8.2.3 Integrity Testing Pre-Autoclaving

Note: *Repligen strongly recommends the practice of pre-autoclaving integrity testing to ensure a proper assembly prior to autoclaving.*

1. Refer to Figure 20 for proper setup. Equipment must be at ambient temperature.
2. Close V1, V4 and V5. Keep V3 open.
3. Connect air pressurization line to V1.
4. Open V2 to monitor the pressure on PG1.
5. Open the pressurization line at V0.
6. Carefully regulate V1 to pressurize the retentate chamber to 10 psi for MF membranes and 20 psi for UF membranes. Close V1 rapidly to hold the pressure.
7. Allow for a 1-minute equilibration period prior to taking either pressure or flow readings.
8. Record PG1 and PG2 initial values.
9. Monitor the pressure decay rate on PG1. Record PG1 and PG2 pressure at one minute intervals for 5 minutes.

Note: *PG2 should remain at zero.*

10. Calculate the average pressure decay rate over 5 min. The calculated pressure decay rate should not exceed 0.31 psi/min.

Note: *The air diffusion rate may also be used for integrity assessment by monitoring the flow rate from V3 using a digital mass flow meter (diffusion rate should be ≤50 mL/min). Integrity test instruments may also be used to test the integrity of filters.*

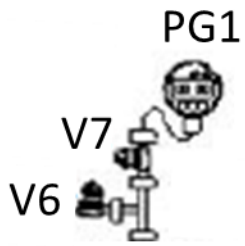
8.2.4 Autoclaving

The XCell ATF 6 Housing assembly is autoclaved either before or after integrity testing. The cycle sequence presented is strongly recommended to ensure sterility and to retain filter integrity and performance. The procedure includes three pre-vacuum pulses, which provide proper chamber evacuation for a faster and more consistent ramp to the required temperature. Please refer to Appendix A for complete instructions.

8.2.5 Integrity Testing Post Autoclaving

Post-autoclaving integrity testing is required only if testing was not performed pre-autoclaving.

Figure 21. Vent Tee for Post-Autoclaving Integrity Testing



1. Add setup in Figure 21 to F4 on either single-use or stainless steel bioreactor (Figure 33). Equipment must be at ambient temperature.
2. Clamp retentate tubing with a C-clamp to create a dead end if no bi-valve is present.

3. Close V4 and V5 (also close V1 and V1a if using bivalve). Open V2, V3, and V7.
4. Pressurize retentate-side by introducing air through sterile vent filter F4 up to 10 psi for MF membranes and 20 psi for UF membranes by opening V6 connected to pressure source.
5. Close V6 rapidly to hold the pressure.
6. For Pressure Decay, monitor pressure from pressure gauge PG1 at one-minute intervals for 5 minutes. The calculated decay rate should not exceed 0.47 psi/min.
7. For diffusion rate, monitor diffusion rate by attaching digital flow meter to sterile vent filter F3. The diffusion rate should not exceed 75 mL/min.

Note: *The post-autoclave maximum levels are elevated above the pre-autoclave levels as the membranes may partially dry out during the autoclave cycle.*

8.3 Connecting XCell ATF 6 Housing to a Bioreactor

Two types of connections between the housing 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 single-use connectors such as AseptiQuik and Readymate DAC and are connected to the housing prior to autoclaving.

Fluid management for XCell ATF 6 Housings includes retentate (A2B) tubing set kits and accessories that connect the housing 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 housing 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 permeate/harvest pump.

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

8.3.1 Stainless Steel XCell ATF 6 Tubing Set Kits and Accessories

Several components are required to connect the XCell ATF 6 Housing to a bioreactor. XCell ATF 6 Autoclavable Tubing Set Kits (Table 13) are available in three configurations depending on the type of bioreactor in use and the preferred connectors. All tubing set kits have a pressure rating of 25 psi. Additional accessories (Table 14) are required, regardless of the chosen tubing set.

Table 13. XCell ATF 6 Tubing Set Kit Options

Tube Set Part Number	Bioreactor Type	Tubing Connection
SSATF6-SSB-A2B-TC	Stainless steel	Tri-clover
SSATF6-SUB-A2B-RM	Single-use	ReadyMate
SSATF6-SUB-A2B-AQG		AseptiQuik G

Table 14. XCell ATF 6 Required Accessories

Description	Part Number	Single/Multi-use	Pressure Rating	ID	Material of Construction
Vent filter	F46-AIR-LSC	SU	25 psi	NA	PVDF
Permeate Pressure Sensor	SSATF-LSC-PSK	SU	25 psi	3/4 in	Polycarbonate
Vent tee (Single-use bioreactor only)	ATF6-OPT2	MU	45 psi	1 in	Stainless steel

In addition, use of a SSB requires bivalve assemblies (Table 15), which can be steamed in place.

Table 15. XCell ATF 6 Required Stainless Steel Bioreactor Accessory

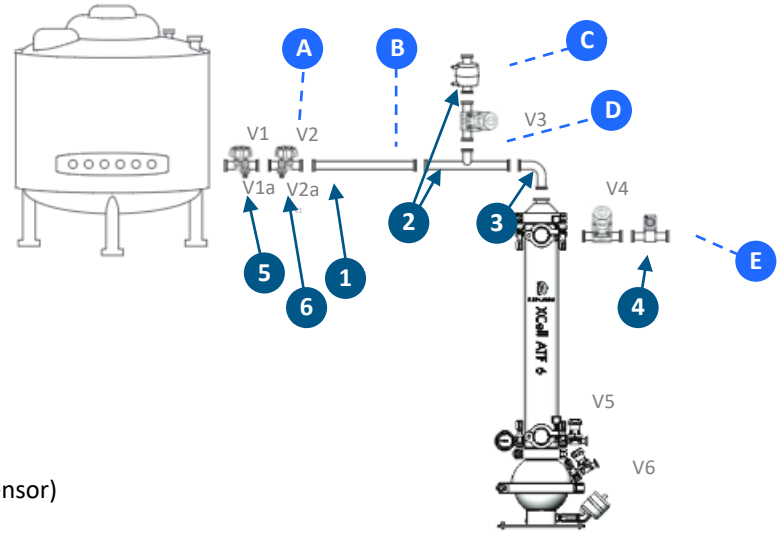
Description	Part Number	Single/Multi-use	Pressure Rating	ID	Material of Construction
Bivalve assembly	ATF6-VLV-KIT	MU	45 psi	1.5 in	Stainless steel

8.3.2 Tube Set Kit Assembly for XCell ATF 6 Connected to Stainless Steel Bioreactor

Assembly of the housing, tubing set, and accessories is completed prior to autoclaving. Hard connection between the tubing set kit and the stainless steel bioreactor consists of the following parts, available as a unit:

- Two isolation bivalves: one attached to the bioreactor, and one attached to the housing
- A flexible hose between the main branches of the two valves
- A steam inlet: a side valve on one bivalve
- Condensate drain: a side valve on the other bivalve; lowest of the available valves

Figure 22. XCell ATF 6 Connection to Stainless Steel Bioreactor



A. ATF6-VLV-KIT (bivalve)
B. SSATF6-SSB-A2B-TC (A2B)
C. F46-AIR-LSC (vent filter)
D. ATF6-OPT2 (vent tee)
E. SSATF-LSC-PSK (pressure sensor)

Following assembly of the housing, tubing set, and accessories, the right side of the system is autoclaved. Simultaneously, the right-facing bivalve is steamed in place so that when the autoclave cycle is complete, that section can be attached to the bioreactor and another steam-in-place cycle can be performed.

Connection instructions (Figure 22):

1. Attach left-facing bivalve (A) to tubing set (B).
2. Attach vent filter (C) to vent tee (D). Connect vent tee (D) to A2B tubing (B).
3. Connect housing to vent tee (D).
4. Attach permeate pressure sensor (E) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of the pressure sensor. Open V2, V2a, V3,V4, V5, and V6. Autoclave the entire assembly. Close V2, V2a, V4, V5, and V6.
5. Attach the right-facing bivalve (A) to the bioreactor. Open valve V1a and attach trap. Open Valve V1. Steam in place. Close V1.
6. Connect bivalves to each other. Open valves V1a and V2a. Valves V1 and V2 are closed. SIP the bivalve connection. Close valves V1a and V2a. Open valves V1 and V2 and close V3 for operation.

The following steam-in-place procedure is recommended for hard connections:

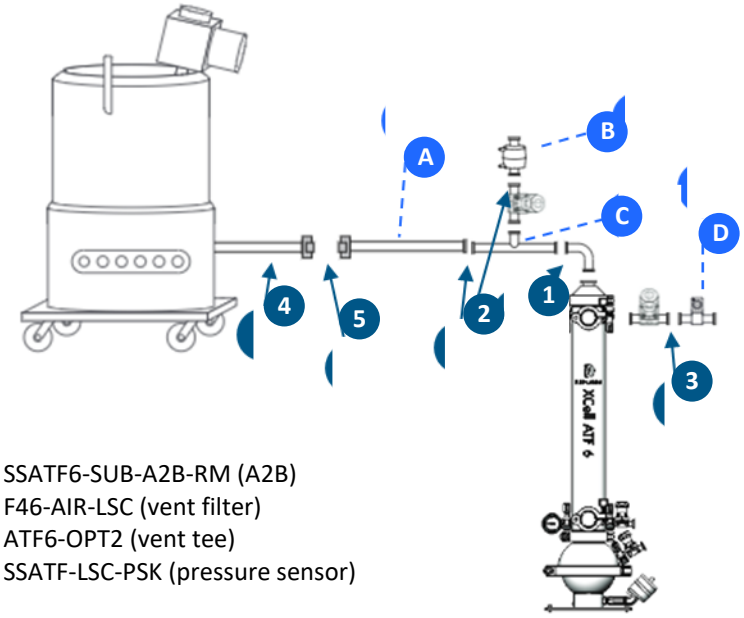
1. Attach a steam trap to the condensate valve and connect to a drain.
2. Close steam inlet and condensate drain valves.
3. Securely connect a regulated steam source to the steam inlet valve.
4. Open steam service.

5. Slowly open steam inlet valve.
6. Slowly open steam condensate valve.
7. Sterilize connection for about 20 minutes at 121°C and ~16 psi.
8. Cool down.
9. Close the condensate valve.
10. Rapidly close the steam inlet valve and immediately open the main valve into the filtration assembly to minimize a pressure drop in the connection.

8.3.2.1 Tube Set Kit Assembly for XCell ATF 6 Connected to Single-Use Bioreactor Using ReadyMate Tubing Set

Assembly of the housing, tubing set, and accessories is completed prior to autoclaving.

Figure 23. XCell ATF 6 Connection to Single-Use Bioreactor (ReadyMate)



A. SSATF6-SUB-A2B-RM (A2B)
B. F46-AIR-LSC (vent filter)
C. ATF6-OPT2 (vent tee)
D. SSATF-LSC-PSK (pressure sensor)

Connection instructions (Figure 23):

1. Connect housing to vent tee (C).
2. Attach vent filter (B) to vent tee (C). Connect vent tee (C) to A2B tubing (A).
3. Attach permeate pressure sensor (D) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of the pressure sensor. Open all valves. Autoclave the assembly.
4. Determine the recommended aseptic connector for SUB. Connect adapter tubing (not supplied) to SUB must have ID ≥3/4", Length ≤10". Clamp sterile tubing.
5. Connect assembly to bioreactor.

8.4 Disassembly and Maintenance

8.4.1 Removing the Housing From the Bioreactor

1. Stop the permeate/harvest pump and disconnect the harvest bag from the housing.
2. Stop and disconnect the A2C line from the diaphragm pump.
3. Close or disconnect compressed air and vacuum services from the pneumatic enclosure.
4. Disconnect sensors from the filtration assembly to pneumatic enclosure.
5. If necessary, remove the pneumatic enclosure from the filtration assembly.
6. Close both bivalves connecting the filtration assembly to the vessel.

7. Drain liquid from the connection.
8. Optionally, purge the connection with water, steam, or some other medium.
9. Disconnect the filtration assembly from vessel between the two bivalves.
10. Remove the filtration assembly to an appropriate work area.

8.4.2 HFF Removal

1. Drain the system into an appropriate waste vessel or drain.
2. Remove all sensors from the housing.
3. Remove air inlet filter connected to the diaphragm pump and any other connections to the XCell ATF Housing.
4. Open the clamp that connects the filter housing to the diaphragm pump and separate.
5. Open the clamp that connects the reducer to the filter housing and separate.
6. Remove the HFF from housing by firmly pressing it from one end.
7. Remove the O-ring at the exposed end of the HFF.
8. Press the HFF in the opposite direction to remove.
9. Prepare filter housing for cleaning and reuse.

8.4.3 Decontaminating the HFF for Disposal

1. Rinse the HFF two times with water to remove residual cells and debris.
2. Decontaminate with either 0.5M NaOH, potassium hydroxide, or bleach for 2 – 24 hours.

Note: *5.25% chlorine is equivalent to 52,500 parts per million (ppm). If household chlorine bleach is used, two working solutions are generally recommended: 5000-6000 ppm for initial decontamination of organic spill material, and 500-600 ppm for disinfection of cleaned surfaces.*

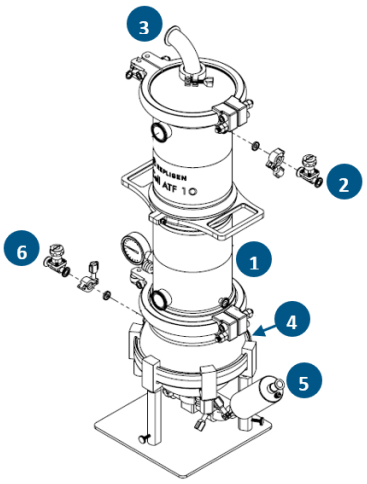
8.4.4 Pump Air Inlet Filter, O-Rings, Gaskets, and Quick Connects

All consumable items are single use.

9. Stainless Steel XCell ATF 10 Housing

XCell ATF 10 Housing (Figure 24) is recommended for use with 200 – 5000+ L bioreactors. The assembly of the housing and accessories includes installing the diaphragm and hollow fiber filter into the housing, connecting the tubing set kit to the bioreactor, and connecting the harvest line to the housing. The system is prepared for use by pressure testing, filter wetting, integrity testing, and autoclaving.

Figure 24. XCell ATF 10 Housing



1. Housing
2. Permeate/Harvest
3. Retentate
4. Diaphragm pump
5. Air inlet
6. Drain Port

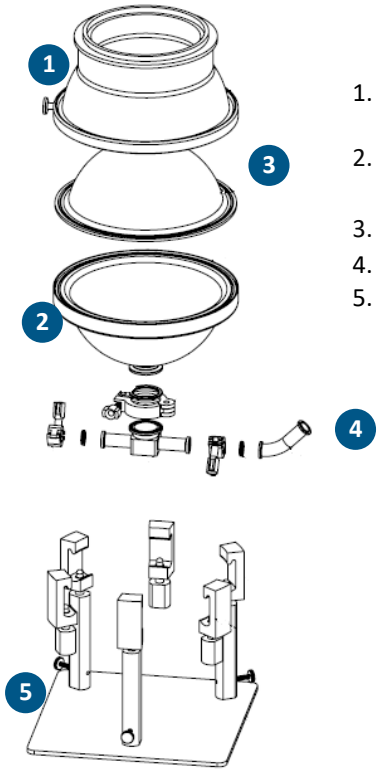
9.1 Stainless Steel XCell ATF 10 Housing Assembly

XCell ATF 10 Housing assembly includes installation of the diaphragm and hollow fiber filter and assembly of the tubing set kit that will connect the housing and the bioreactor and the tubing that will connect the housing and the harvest vessel.

9.1.1 Installing the Diaphragm

Important: The silicone diaphragm must be replaced after each run and prior to sterilization. To avoid premature failure, it is important to ensure that the diaphragm is seated in the correct orientation. Use with aqueous liquids only. For use with other fluids contact Repligen for a technical discussion. When used as instructed, the diaphragm is designed to last over one million pressure/exhaust cycles.

Figure 25. Orientation of Silicone Diaphragm in Pump Housing XCell ATF 10



1. Housing assembly, pump liquid-side (PL) hemisphere
2. Housing assembly, pump air- side (PA) hemisphere
3. Diaphragm
4. Air inlet
5. Stand

9.1.1.1 XCell ATF 10 Housing Diaphragm Placement

1. Set the pump air-side (PA) hemisphere (Figure 25, 2) on a flat surface with the open side of the hemisphere facing up.
2. Place diaphragm (3) with the convex side oriented up onto the PA hemisphere, and place the PL hemisphere, wide opening down, on top of the diaphragm.
3. Assure the diaphragm gasket O-ring is positioned uniformly around the periphery of the pump O-ring groove. The two hemispheres, with diaphragm in between, should be equally spaced.
4. Clamp the two hemispheres together.
    a. Use the long clamps first. Space them 120° apart around the circumference of the pump assembly. Uniformly and sequentially tighten (torque to 30 lb-ft) the clamps, so the diaphragm is compressed evenly around the periphery of the spheres.
    b. Add the short clamps in between the long clamps and tighten (torque to 20 – 25 lb-ft) as described in Step 4a.
5. Add the air inlet assembly to the air inlet nozzle on the PA hemisphere.

6. Carefully invert the assembled diaphragm pump place onto the stand.
7. Proceed to installation of the HFF.

9.1.2 XCell ATF 10 Housing Hollow Fiber Filter Installation

XCell ATF 10 Housing accommodates a variety of hollow fiber filters. For support in selecting hollow fiber filters, please contact your local Repligen Field Applications Specialist (FAS). Two people are needed for assembly of ATF 10 Housing.

1. Stand the filter housing vertically, with harvest port down.
2. Insert the HFF into the housing with ridge up.
3. Insert one O-ring into the groove between HFF and housing end-ferrule wall.
4. Carefully place the filter housing onto the diaphragm pump, forcing the O-ring deeper into the groove. Each person holds one handle when turning over and the other hand securing the filter as it is placed onto the diaphragm pump.
5. Clamp the filter housing to the diaphragm pump. Flat section of clamp is aligned to clear port. Use a torque wrench to tighten bolts to 20 ft-lbs.
6. On the other end of the filter housing, place the second O-ring into the groove between HFF and housing end-ferrule.
7. Place the reducer onto the end, forcing the O-ring into the groove.
8. Clamp the reducer to the housing, compressing the O-ring against the HFF. A seal is formed between the housing, reducer and HFF. Use a torque wrench to fasten the bolts to 20 ft-lbs.
9. Assemble the rest of the XCell ATF Housing, including tubing set kits (Figure 24).

9.2 Filter Preparation

To prepare the filter for use, the assembled housing should be pressure tested, wetted, integrity tested and autoclaved.

9.2.1 Pressure Testing

Pressure testing ensures that the XCell ATF 10 Housing assembly is free of leaks and can withstand the required operating pressures. The assembly can be pressure tested with or without a filter module, before or after sterilization. Ideally, the test is performed with a filter prior to autoclaving. Slight variations in the configuration of the external connections are possible depending on the configuration of the equipment purchased and the connections being made to the bioreactor.

Figure 26. XCell ATF 10 System Filtration Assembly Prior to Pressure Test

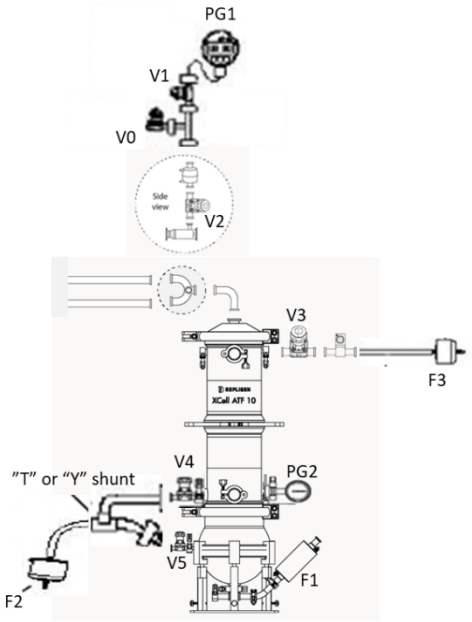


Table 16. XCell ATF 10 Vent Filter Required Surface Area

F1[1]	F2	F3	F4	F5	F5a
≥0.3 m^2	≥0.15 m^2	≥0.15 m^2	≥0.3 m^2	≥0.3 m^2	≥0.05 m^2

[1]F1 – F5 correspond to vent filter locations in Figure 26, Figure 27, and Figure 34.

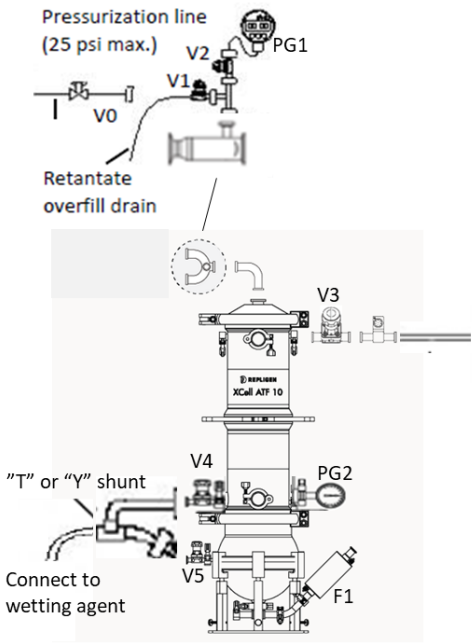
1. Assemble the XCell ATF System according to Figure 26. Ensure an end cap is placed on vent U.
2. Prepare a regulated ~22 psi/1.5 bar, dry, oil-free air source.
3. Close all valves except V1 and V2. Attach pressurization line to shunt line (V4/V5). Secure all connections.
4. While monitoring the pressurization rate on PG1 and PG2, slowly regulate opening of V5 to pressurize the retentate side first, then slowly open V4 to equalize the pressure on the filtrate side.
5. Once the XCell ATF Filtration unit is pressurized to about 20 psi, close all valves except V1 and V2.
6. Wait five minutes for the pressure in the XCell ATF system to stabilize.
7. Record the values for both the retentate and filtrate pressure gauges, PG1 and PG2.
8. After 60 minutes, record these pressure values again.
9. Any drop in pressure should not exceed 1 psi.
10. If the Pressure Test has failed, find the leak and repeat steps 4 through 9.
11. To depressurize the system, disconnect the pressurization line and slowly open V4 to depressurize the filtrate side first, then open V5 to depressurize the retentate side.

9.2.2 Filter Wetting

After the filter cartridge is installed and the pressure test confirms an integral assembly, the filter must be wetted prior to autoclaving. Rinsing filters prior to use is a standard practice within the industry and the pre-autoclave integrity test requires a fully wetted cartridge. The following wetting liquids should be used with the indicated filters and are intended as single-use-pass through the filter to disposal. It is recommended that the filter be flushed with appropriate wetting agent until a permeate volume of 2 mL/cm^2 of surface area is reached:

- **Micro-filtration (MF) 0.1 – 0.65 µm**: use WFI or buffer as wetting agent.
- **Ultra-filtration (UF) 10 – 750 kDa**: use 10 – 25% isopropyl alcohol (IPA).

Figure 27. XCell ATF 10 System Filtration Assembly Prepared For Wetting and Integrity Testing



1. Assemble the XCell ATF Device according to Figure 27. Slight variations in assembly are possible depending on the configuration of equipment purchased and its intended use. For more detailed assembly instructions contact Repligen.
2. Connect the container with the wetting solution volume of ≥220 L and place the tubing into a peristaltic pump. Direct feed from WFI drop may also be used, provided there is a means to modulate the pressure and flow to satisfy requirements.
3. Close V2 and V4, keep V1, V3, and V5 open.
4. Pump the liquid into the system from bottom up at a rate of ≤15 L/min (for UF membranes, use 10 psi feed pressure). Ensure that no air enters the system. Flow should occur from bottom to top as this naturally removes the air from the system. Top to bottom can result in trapped air, which may lead to incomplete filter wetting and a failed integrity test result.
5. Continue filling the system until the first sign that liquid begins to flow from V1. Stop the pump.
6. Close V1. Keep V3 and V5 open.
7. Start the peristaltic pump to wet the filter at 15 LPM (for UF membranes, use 10 psi feed pressure).
8. Once liquid begins to flow from V3, tilt the ATF 20° away from V3 to facilitate air removal from the top of the filtrate compartment until no more air flows through.
9. After wetting is complete (≥220 L is collected in filtrate), stop the peristaltic pump.
10. Close V3 and V5 and allow the UF filter to soak in the wetting solution for at least 1 hour (step not needed for MF filters).
11. Remove the liquid from the system, both the filtrate and retentate chambers: Open V4 and V3 (remove the harvest line) to drain the filtrate side by gravity; then, open V1 and V5, and slowly run the peristaltic pump in reverse to drain the retentate side.

Note: *If IPA is used for wetting, repeat the above procedure at least three times with WFI to thoroughly remove the IPA. Soaking is not required for these additional WFI flushes to maximize removal of liquid from the system, the diaphragm must be pushed up by slowly adding air through the 0.2 µm air inlet filter (F1) up to 2 psi, ensuring not to overinflate the diaphragm. Tilt the XCell ATF towards V4 by 20° to facilitate drainage. Leaving a small amount of WFI (i.e., milliliters) inside the pump is acceptable for autoclaving.*

9.2.3 Integrity Testing Pre-Autoclaving

Note: *Repligen strongly recommends the practice of pre-autoclaving integrity testing to ensure a proper assembly prior to autoclaving.*

1. Refer to Figure 27 for proper setup. Equipment must be at ambient temperature.
2. Close V1, V4 and V5. Keep open V3.
3. Connect air pressurization line to V1.
4. Open V2 to monitor the pressure on PG1.
5. Open the pressurization line at V0.
6. Carefully regulate V1 to pressurize the retentate chamber to 10 psi for MF membranes and 20 psi for UF membranes. Close V1 rapidly to hold the pressure.
7. Allow for a 1-minute equilibration period prior to taking either pressure or flow readings.
8. Record PG1 and PG2 initial values.
9. Monitor the pressure decay rate on PG1. Record PG1 and PG2 pressure at one minute intervals for 5 minutes.

Note: *PG2 should remain at zero.*

10. Calculate the average pressure decay rate over 5 min. The calculated pressure decay rate should not exceed 0.30 psi/min.

Note: *The air diffusion rate may also be used for integrity assessment by monitoring the flow rate from V3 using a digital mass flow meter (diffusion rate should be ≤220 mL/min). Integrity test instruments may also be used to test the integrity of filters.*

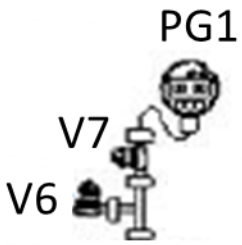
9.2.4 Autoclaving

The XCell ATF 10 Housing assembly is autoclaved either before or after integrity testing. The cycle sequence presented is strongly recommended to ensure sterility and to retain filter integrity and performance. The procedure includes three pre-vacuum pulses, which provide proper chamber evacuation for a faster and more consistent ramp to the required temperature. Please refer to Appendix A for complete instructions.

9.2.5 Integrity Testing Post-Autoclaving

Post-autoclaving integrity testing is required only if testing was not performed pre-autoclaving.

Figure 28. Vent Tee For Post-Autoclaving Integrity Testing



1. Add setup in Figure 28 to F4 on either single-use or stainless steel bioreactor setup (Figure 34). Equipment must be at ambient temperature.
2. Clamp retentate tubing with a C-clamp to create a dead end if no bivalve is present.
3. Close V4 and V5 (also close V1 and V1a if using bivalve). Open V2, V3, and V7.
4. Pressurize retentate-side by introducing air through sterile vent filter F4 up to 10 psi for MF membranes and 20 psi for UF membranes by opening V6 connected to pressure source.
5. Close V6 rapidly to hold the pressure.
6. For Pressure Decay, monitor pressure from pressure gauge PG1 at one-minute intervals for 5 minutes. The calculated decay rate should not exceed 0.45 psi/min.
7. For diffusion rate, monitor diffusion rate by attaching digital flow meter to sterile vent filter F3. The diffusion rate should not exceed 330 mL/min.

Note: *The post-autoclave maximum levels are elevated above the pre-autoclave levels as the membranes may partially dry out during the autoclave cycle.*

9.3 Connecting XCell ATF 10 Housing to a Bioreactor

Two types of connections between the housing 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 single-use connectors such as AseptiQuik and Readymate DAC and are connected to the housing prior to autoclaving.

Fluid management for XCell ATF 10 Housings includes retentate (A2B) tubing set kits and accessories that connect the housing 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 housing 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 permeate/harvest pump.

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

9.3.1 Stainless Steel XCell ATF 10 Tubing Set Kits and Accessories

Several components are required to connect the XCell ATF 10 Housing to a bioreactor. XCell ATF 10 Autoclavable Tubing Set Kits (Table 17) are available in three configurations depending on the type of bioreactor in use and the preferred connectors. All tubing set kits have a pressure rating of 25 psi. Additional accessories (Table 18) are required, regardless of the chosen tubing set.

Table 17. XCell ATF 10 Tubing Set Kit Options

Tube Set Part Number	Bioreactor Type	Tubing Connection
SSATF10-SSB-A2B-TC	Stainless steel	Tri-clover
SSATF10-SUB-A2B-AQX	Single-use	AseptiQuik X
SSATF10-SUB-A2B-AQL		AseptiQuik L

Table 18. XCell ATF 10 Required Accessories

Description	Part Number	Single/Multi-use	Pressure Rating	ID	Material of Construction
Vent filter	F10-AIR-LSC	SU	25 psi	NA	PVDF
Permeate Pressure Sensor	SSATF-LSC-PSK	SU	25 psi	3/4 in	Polycarbonate
U-bend with vent port	ATF10-OPT5	MU	45 psi	1 in	Stainless steel

In addition, use of a SSB requires bivalve assemblies (Table 19), which can be steamed in place.

Table 19. XCell ATF 10 Required Stainless Steel Bioreactor Accessory

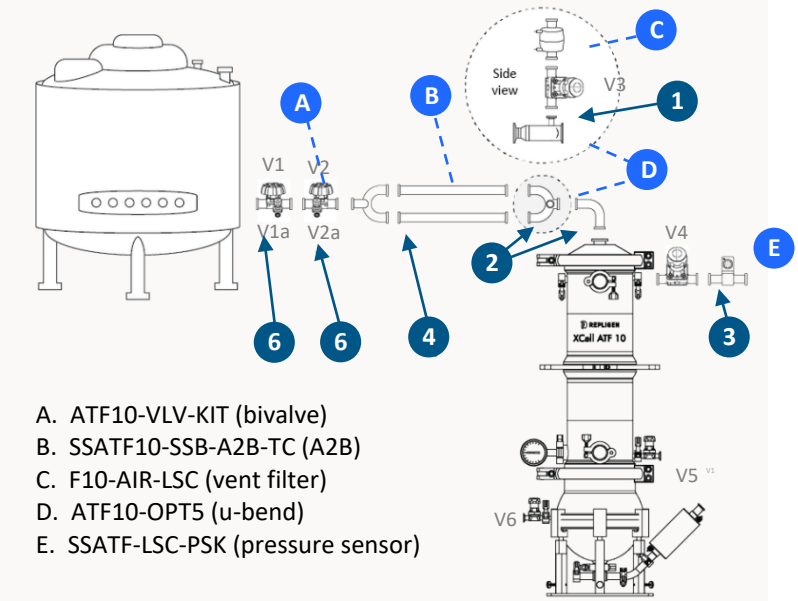
Description	Part Number	Single/Multi-use	Pressure Rating	ID	Material of Construction
Bivalve assembly	ATF10-VLV-KIT	MU	45 psi	1.5 in	Stainless steel

9.3.2 Tube Set Kit Assembly for XCell ATF 10 Connected to Stainless Steel Bioreactor

Assembly of the housing, tubing set, and accessories is completed prior to autoclaving. Hard connection between the tubing set kit and the stainless steel bioreactor consists of the following parts, available as a unit:

- Two isolation bivalves: one attached to the bioreactor, and one attached to the housing
- A flexible hose between the main branches of the two valves
- A steam inlet: a side valve on one bivalve
- Condensate drain: a side valve on the other bivalve; lowest of the available valves

Figure 29. XCell ATF 10 Connection to Stainless Steel Bioreactor



Following assembly of the housing, tubing set, and accessories, the right side of the system is autoclaved. Simultaneously, the right-facing bivalve is steamed in place so that when the autoclave cycle is complete, that section can be attached to the bioreactor and another steam-in-place cycle can be performed.

Connection instructions (Figure 29):

1. Connect vent filter (C) to u-bend (D).
2. Connect u-bend to housing and to A2B tubing set (B).
3. Attach permeate pressure sensor (E) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of the pressure sensor.
4. Attach left-facing bivalve/u-bend (A) to A2B tubing set (B). Open valves V2, V2a, V3, V4, V5, and V6. Autoclave the assembly. Close valves V2, V2a, V4, V5, and V6.
5. Attach the right-facing bivalve (A) to the bioreactor. Open valve V1a and attach trap. Open Valve V1. Steam in place. Close V1.
6. Connect bivalves to each other. Open valves V1a and V2a. Valves V1 and V2 should be closed. SIP the bivalve connection. Close valves V1a and V2a. Open valves V1 and V2 and close V3 for operation.

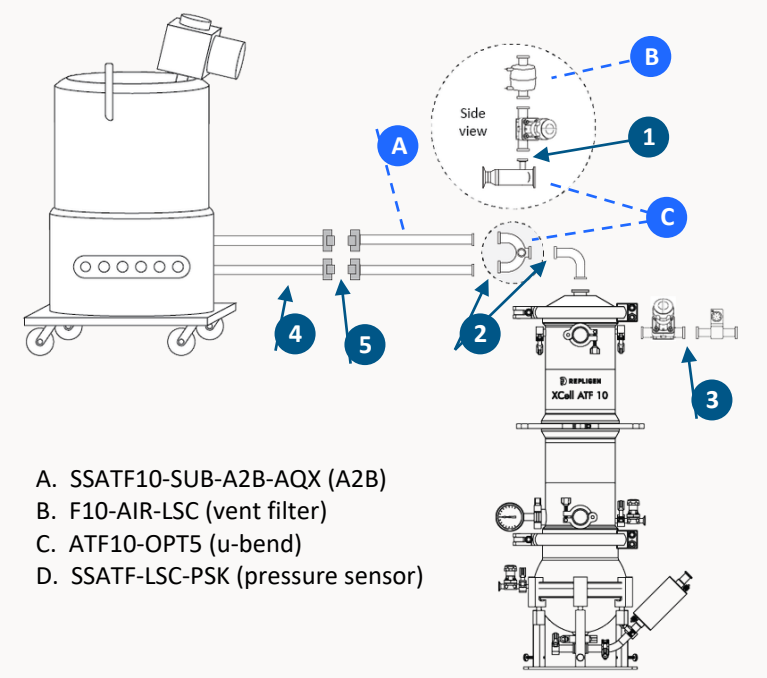
The following steam-in-place procedure is recommended for hard connections:

1. Attach a steam trap to the condensate valve and connect to a drain.
2. Close steam inlet and condensate drain valves.
3. Securely connect a regulated steam source to the steam inlet valve.
4. Open steam service.
5. Slowly open steam inlet valve.
6. Slowly open steam condensate valve.
7. Sterilize connection for about 20 minutes at 121°C and ~16 psi.
8. Cool down.
9. Close the condensate valve.
10. Rapidly close the steam inlet valve and immediately open the main valve into the filtration assembly to minimize a pressure drop in the connection.

9.3.2.1 Tubing Set Kit Assembly for XCell ATF 10 Connected to Single-Use Bioreactor Using AseptiQuik X Tubing Set

Assembly of the housing, tubing set, and accessories, on the right side of the system is completed prior to autoclaving.

Figure 30. XCell ATF 10 Connection to Single-Use Bioreactor (AseptiQuik X)



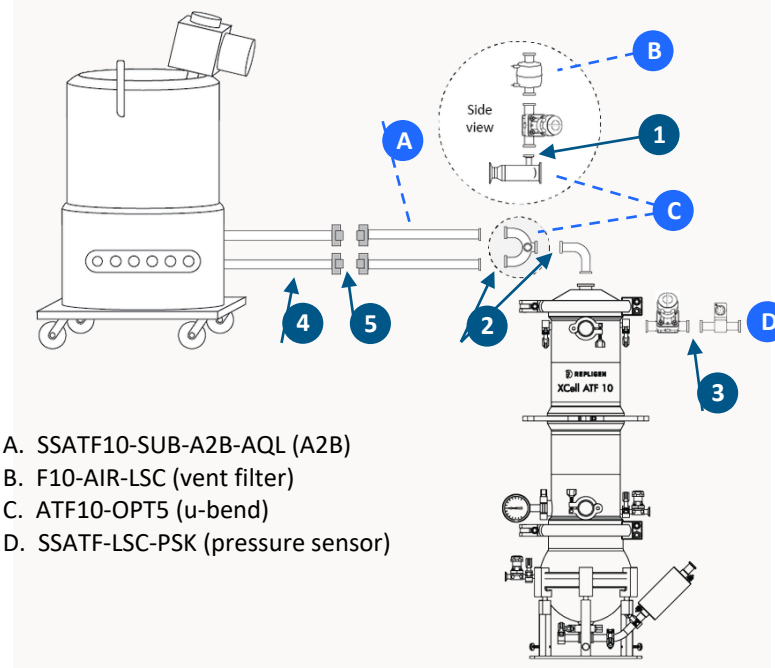
Connection instructions (Figure 30):

1. Connect vent filter (B) to u-bend with vent port (C).
2. Connect u-bend to housing and to A2B tubing set (A).
3. Attach permeate pressure sensor (D) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of the pressure sensor. Open all valves. Autoclave the assembly.
4. Determine the recommended aseptic connector for SUB. Connect the adapter tubing (not supplied) to SUB, both must have ID ≥1", Length ≤10". Clamp sterile tubing.
5. Connect assembly to bioreactor.

9.3.2.2 Tubing Set Kit Assembly for XCell ATF 10 Connected to Single-Use Bioreactor Using AseptiQuik L Tubing Set

Assembly of the housing, tubing set, and accessories, on the right side of the system is completed prior to autoclaving.

Figure 31. XCell ATF 10 Connection to Single-Use Bioreactor (AseptiQuik L)



A. SSATF10-SUB-A2B-AQL (A2B)
B. F10-AIR-LSC (vent filter)
C. ATF10-OPT5 (u-bend)
D. SSATF-LSC-PSK (pressure sensor)

Connection instructions (Figure 31):

1. Connect vent filter (B) to u-bend with vent port (C).
2. Connect u-bend to housing and to A2B tubing set (A).
3. Attach permeate pressure sensor (D) to housing permeate port. Depending on harvest bag port, connect adapter tubing (not supplied) to end of the pressure sensor. Open all valves. Autoclave the assembly.
4. Determine the recommended aseptic connector for SUB. Connect the adapter tubing (not supplied) to SUB, both must have ID ≥1", Length ≤10". Clamp sterile tubing.
5. Connect assembly to bioreactor.

9.4 Disassembly and Maintenance

9.4.1 Removing the Housing From the Bioreactor

1. Stop the permeate/harvest pump.
2. Stop and disconnect diaphragm pump pneumatic line from the pump air inlet filter.
3. Close or disconnect compressed air and vacuum services from the pneumatic enclosure.
4. Disconnect sensors from the filtration assembly to pneumatic enclosure.
5. If necessary, remove the pneumatic enclosure from the filtration assembly.
6. Close and disconnect the permeate line.
7. Close both bivalves connecting the filtration assembly to the vessel.
8. Drain liquid from the connection.
9. Optionally, purge the connection with water, steam, or some other medium.
10. Disconnect the filtration assembly from vessel between the two bivalves.
11. Remove the filtration assembly to an appropriate work area.

9.4.2 HFF Removal

1. Drain the system into an appropriate waste vessel or drain.
2. Remove all sensors from the housing.
3. Remove air inlet filter connected to the diaphragm pump and any other connections to the XCell ATF Housing.
4. Open the clamp that connects the filter housing to the diaphragm pump and separate.
5. Open the clamp that connects the reducer to the filter housing and separate.

6. Remove the HFF from housing by firmly pressing it from one end.
7. Remove the O-ring at the exposed end of the HFF.
8. Press the HFF in the opposite direction to remove.
9. Prepare filter housing for cleaning and reuse.

9.4.3 Decontaminating the HFF for Disposal

1. Rinse the HFF two times with water to remove residual cells and debris.
2. Decontaminate with either 0.5M NaOH, potassium hydroxide, or bleach for 2 – 24 hours.

Note: *5.25% chlorine is equivalent to 52,500 parts per million (ppm). If household chlorine bleach is used, two working solutions are generally recommended: 5000-6000 ppm for initial decontamination of organic spill material, and 500 - 600ppm for disinfection of cleaned surfaces.*

9.4.4 Pump Air Inlet Filter, O-Rings, Gaskets, and Quick Connects

All consumable items are single use.

10. Appendix A: Autoclaving

10.1 Introduction

This guide outlines the proper sequence for the assembly, wetting, pressure/integrity testing and autoclaving of the filters used in Repligen XCell ATF Stainless Steel Housings. Adherence to these procedures ensures sterility and maintains filter integrity and performance.

10.2 Scope

These procedures apply XCell ATF 2, 4, 6, and 10 Stainless Steel Housings and all hollow fiber filters sold by Repligen for use with XCell ATF Technology.

10.3 Safety Requirements

Potential hazards include:

- Steam: Use caution and proper PPE when in contact with housings after autoclaving.
- Pressurized air: Ensure that all components are suitable for use with high pressure and are properly secured. Use safety glasses/face shield.
- Heavy equipment: Use assistance for lifting and assembling.

10.4 Autoclaving Protocols

10.4.1 XCell ATF 2 Stainless Steel Housing Protocols

XCell ATF 2 comprises a small-diameter, self-contained hollow fiber filter connected to a diaphragm pump and can be autoclaved using a pre-programmed liquid cycle at 121˚C for 30 minutes.

1. Attach tubing and vent filters to assembly ports for autoclaving.

Note: *Vent filters must meet surface area requirements (Table 20).*

   a. Attach tubing and a 0.2 µm vent filter to the ventilation port on the pump liquid-side (PL) hemisphere.
   b. Leave the vent port valve open during autoclaving for proper steam penetration.
2. Assemble hollow fiber filter
   a. Attach tubing and a 0.2 µm vent filter to the lower filtrate port on the HFF. Leave open while autoclaving.
   b. Attach the filtrate line (preferably weldable pump tubing) and a 0.2 µm vent filter to the upper filtrate port on the HFF. Leave open while autoclaving.

3. Connect the device to the process vessel if autoclaving together (Figure 6, Figure 7).
4. Install the dip-tube through a compatible bioreactor headplate compression fitting. Position the dip-tube to minimize bubbles from sparger entering the dip-tube as this may affect device operation.
5. Position the Stainless Steel Housing proximal to bioreactor to prevent kinking of the A2B tubing. Do not lay the device on its side.
6. Place the sanitary end of the A2B connector into the tri-clamp groove of the HFM and secure with a ¾" TC clamp.
7. Place the other sanitary end of the A2B connector into the TC groove of the dip tube on the process vessel and secure with a ¾" TC clamp.
8. Autoclave the device and process vessel.
9. If autoclaving the bioreactor with liquid (i.e., WFI or PBS), ensure that the liquid level is below the XCell ATF dip-tube so that liquid is not pulled into the XCell ATF during the autoclave cycle.
10. Place the air inlet assembly, with attached air filter, on the XCell ATF pump air inlet port.
11. Ensure that the path between the ATF and the process vessel is open.
12. Autoclave the entire setup using a pre-programmed liquid cycle with temperature set at 121°C for 30 minutes. Liquid cycle is required for the slow temperature ramping and preventing damage to the filter.
13. Following the autoclave cycle, allow the device to cool slowly to room temperature.
14. Once at room temperature, close the PL hemisphere vent port and clamp the tubing attached to the lower filtrate port on the HFM. Tighten all the clamps.
15. Once at room temperature, close the PL hemisphere vent port and clamp the tubing attached to the lower filtrate port on the HFM. Tighten all the clamps.

10.4.2 XCell ATF 4, 6, and 10 Housings Protocols

The hollow fiber filter is enclosed in the XCell ATF 4, 6, and 10 Stainless Steel Housings. To ensure device sterility and avoid thermal stress that may damage the hollow fiber filter, these larger designs require the use of a complex autoclave sequence (Table 21).

The recommended cycle sequence noted below should be programmed by the customer. Repligen strongly advises adherence to the parameters of the custom program below to ensure satisfactory results. In some cases, it may be necessary to consult with the autoclave manufacturer to assist with the autoclave programming. This procedure includes three pre-vac pulses which provide proper chamber evacuation for a faster and more consistent ramp to the required temperature.

Caution: *Pre-programmed cycles by the autoclave supplier that are based on liquid or dry cycles are not recommended for use on the XCell ATF 4, 6, and 10 Stainless Steel Housings. These cycles may result in sterility failures and damage to the hollow fiber filters.*

Best-practice connection to ATF10: *If the PSK must remain installed through your full ATF cycle, treat it as a limited-cycle and monitor for drift; otherwise, autoclave separately on a PSK-compliant recipe and install aseptically.*

Figure 32. Assembly of XCell ATF 4 System For Autoclave (Left: SUB, Right: SSB)

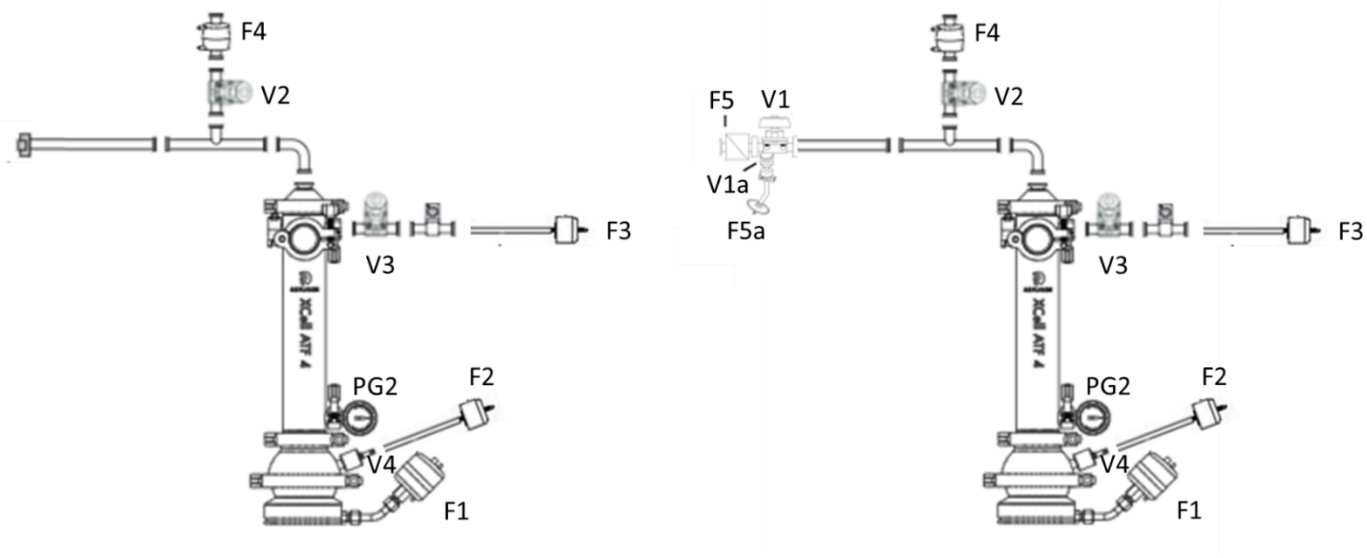


Figure 33. Assembly of XCell ATF 6 System For Autoclave (Left: SUB, Right: SSB)

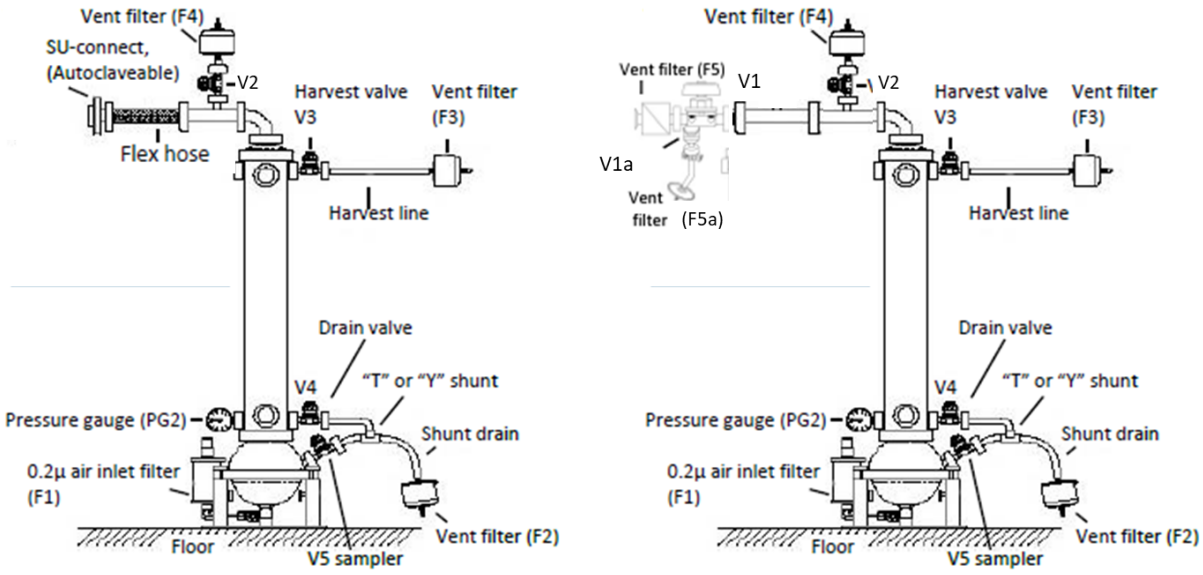
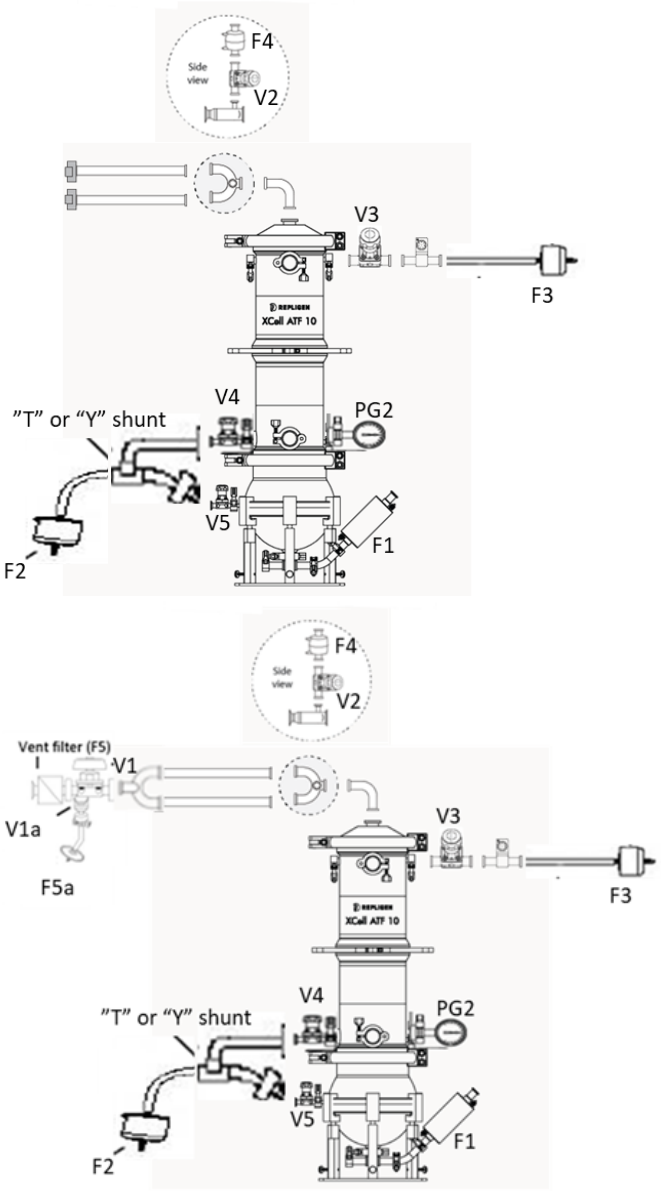


Figure 34. Assembly of XCell ATF 10 System For Autoclave (Left: SUB, Right: SSB)



1. Ensure that the filter has been fully wetted (and IPA removed) and drained of liquid. Prepare the XCell ATF Device with appropriate vent filters, as illustrated in Figure 32, Figure 33, or Figure 34. See Table 20 for filter specifications to ensure adequate gas flow in and out of the assembly during the cycle for each vent filter (F#).
2. Keep all valves open.
3. For XCell ATF 4 and XCell ATF 6, hand-tighten all clamps for autoclaving. For XCell ATF 10, hand-tighten all clamps for autoclaving except for large clamps on filter housing. Ensure that bolts on large clamps on filter housing are tightened to 20 ft-lb.
4. The system should be placed in the autoclave. A vertical fit is preferred, but an angled fit is acceptable (≤30°). Do not place in horizontal position.
5. Follow Autoclave cycle sequence parameters in Table 21.
6. After opening the autoclave door, tighten all connections, especially the large clamps when the ATF temperature reaches 50°C or less. Hand tightening is sufficient for XCell ATF 4 and XCell ATF 6. For XCell ATF 10, hand tightening is sufficient for all clamps besides large filter housing clamps. Bolts on filter housing clamps should be tightened to 30 ft-

lbs. After bolts are tightened, place second set of nuts on bolts to lock in place. Inspect for any damage or other irregularities.

7. Leave all vents open. Close valves only after complete cool-down to ambient room temperature.

Table 20. Vent Filter Surface Area

XCell ATF Housing	Vent Filter Surface Area (m^2)				
	F1	F2	F3	F4	F5
2	0.002	0.002	0.002	N/A	N/A
4	≥0.15	≥0.05	≥0.05	≥0.05	≥0.15
6	≥0.15	≥0.05	≥0.05	≥0.05[1]/≥0.15[2]	≥0.05
10	≥0.3	≥0.15	≥0.15	≥0.3[1]/≥0.15[2]	≥0.3

[1]SUB Connection
[2]SIP (stainless steel bioreactor) Connection

Autoclave cycle sequence parameters:

1. Preheat the XCell ATF Housing 60 – 90 minutes using autoclave jacket heat only (no direct steam) with the load probe positioned in the drain. The filter should reach 60°C due to the convective heat within the chamber.
2. Purge for 5 minutes, not to exceed 6 psig.
3. Vacuum cycles:
    a. Vac #1: Use exhaust rate of -1 psig/min, up to -6 psig. Hold at maximum vacuum for one minute. Apply steam pressure to 6 psig and hold for 20 minutes.
    b. Vac #2: Use exhaust rate of -1 psig/min, up to -6 psig. Hold at maximum vacuum for one minute. Apply steam pressure to 6 psig and hold for 20 minutes.
    c. Vac #3: Use exhaust rate of -1 psig/min, up to -6 psig. Hold at maximum vacuum for one minute. Apply steam pressure to 6 psig and hold for 20 minutes.
    d. Vac #4: Use exhaust rate of -1 psig/min, up to -6 psig. Hold at maximum vacuum for one minute. Apply steam pressure to 6 psig and hold for 20 minutes. Gradually apply steam pressure to reach the sterilization setting of 15 psig / 121 – 123°C, limiting temperature rise to 1°C/min. This sequence should take 30 – 35 minutes.
4. Sterilize for 55 – 60 minutes.
5. Reduce autoclave temperature at rate of 0.5 – 1°C/min to about 0.1 psig or 100°C. A slow rate of cooling is preferred to avoid imposing thermal stress on the filter and to avoid partially drying out the water in the membrane pores.
6. Allow the XCell ATF Stainless Steel Housing to cool at rate of 0.5 – 1.0°C/min until a safe handling temperature is reached (40 – 50°C).

After allowing the housing to reach 50°C, open the autoclave door and tighten all connections, inspect for damage or irregularities. Leave all vents open. Close valves only after a complete cool-down to ambient temperature. If the autoclaved XCell ATF Stainless Steel Housing is to remain unused for more than 12 hours, pressurize the system with air through the vent filter of the shunt line (V4/V5) up to 5 psi until use.

Figure 35. Example Autoclave Cycle

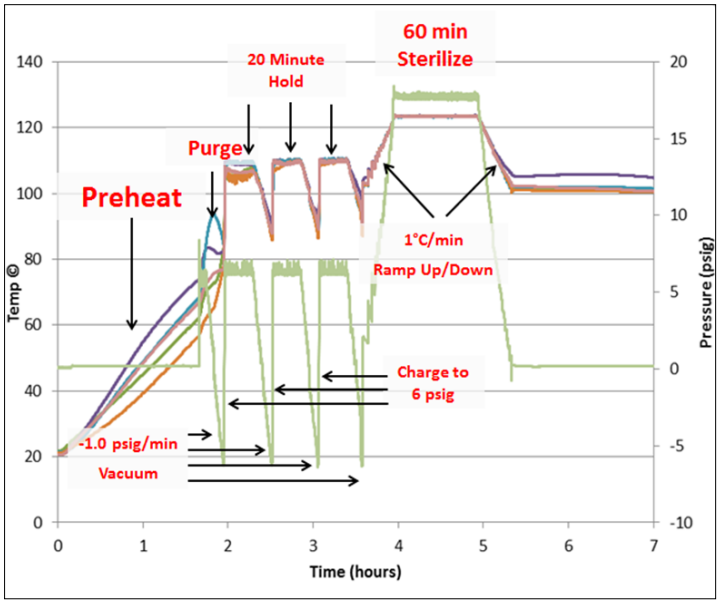


Table 21. Autoclave Cycle Program Parameters

Step #	Stage	Time	Set point	Chamber Temp[1]	Chamber Pressure[1]	Notes
1	Pre-heat	60 – 90 min	60°C	59°C	0.1 psig	Convective heat gently pre-warms the assembly
2	Purge	5 min	6	110°C	6 psig	Steam flow removes chamber air
3a	Vac. #1	12 min	-1 psig/min	85°C	-6 psig (12" Hg vacuum)	Remove air/steam mixture at a controlled rate of change
	Vac. Hold	1 min	<-6 psig (<12" Hg vacuum)	81°C	-6 psig (12" Hg vacuum)	
	Charge	<1 min	6 psig	110°C	6 psig	Steam to a low-pressure setting
	Hold	20 min	6 psig	110°C	6 psig	The 20 min hold allows time for the temperature within the assembly to equilibrate
3b	Vac. #2	12 min	-1 psig/min	85°C	-6 psig (12" Hg vacuum)	Repeated pulses with holds remove air and uniformly warms the assembly
	Vac. Hold	1 min	<-6 psig (<12" Hg vacuum)	85°C	-6 psig (12" Hg vacuum)	
	Charge	<1 min	6 psig	100°C	6 psig	
	Hold	20 min	6 psig	110°C	6 psig	
3c	Vac. #3	12 min	-1 psig/min	85°C	-6 psig (12" Hg vacuum)	
	Vac. Hold	1 min	<-6 psig (<12" Hg vacuum)	85°C	-6 psig (12" Hg vacuum)	
	Charge	<1 min	6 psig	110°C	6 psig	
	Hold	20 min	6 psig	110°C	6 psig	
3d	Vac. #4	12 min	-1 psig/min	85°C	-6 psig (12" Hg vacuum)	
	Vac. Hold	1 min	<-6 psig (<12" Hg vacuum	85°C	-6 psig (12" Hg vacuum)	
	Charge	36 min	1 psig/min	122.6°C	17.1 psig	Gradually increase the steam pressure to the sterilization settings
4	Sterilize	60 min	17 psig	122.6°C	17.1 psig	All areas within the assembly reach the set point. Do not exceed 123°C.
5	Exhaust	17 min	0.5 psig	100°C	0.4 psig	Gently cooling the cartridge is equally critical to avoid thermal shock.
6	Cool	N/A	N/A	50°C	N/A	Continue Step 5 or open door

[1]Indicates the approximate value at end of stage.

10.5 Integrity Testing (Post-autoclave)

1. Assemble the XCell ATF Housing (Figure 13, Figure 21, Figure 28). Equipment must be at ambient temperature.
2. Clamp flex hose with a C-clamp to create a dead end.

Note: *If flex hose is reinforced, a bivalve like V1 must be included in the setup, inline between pressure gauge PG1 and vent F4.*

3. Close V2 and V4. Open V3 and V5.
4. Pressurize retentate side by introducing air through sterile vent filter F2 up to 10 psi for MF membranes and 20 psi for UF membranes. Close V5 rapidly to hold the pressure. Allow a one-minute equilibration period before proceeding.
5. Monitor pressure decay from pressure gauge PG1 at one-minute intervals for 5 minutes. Calculate the average pressure decay rate over 5 minutes. The calculated decay rate should not exceed the established criteria (Table 5).
6. Monitor diffusion rate by attaching a digital flow meter to sterile vent filter F3. The diffusion rate should not exceed established criteria.

Note: *The post-autoclave maximum levels are elevated above the pre-autoclave levels as the membranes may partially dry out during the autoclave cycle.*

Table 22. Post-Autoclave Filter Integrity Test Criteria

XCell ATF Filter	Filter Area	Diffusion Specification	Diffusion Rate	Pressure Decay Rate
2	0.13 m^2	≤30 sccm/m^2	≤3.9 ml/min	≤0.5 psi/min
4	0.77 m^2	≤30 sccm/m^2	≤23.1 ml/min	≤0.5 psi/min
6	2.5 m^2	≤30 sccm/m^2	≤75 ml/min	≤0.5 psi/min
10	11 m^2	≤30 sccm/m^2	≤330 ml/min	≤0.5 psi/min

11. Appendix B: Safety

11.1 Safety

- Repligen XCell ATF Technology is rated for acceptable sound levels (60 dBA).
- Complete system visual inspection for damage or potential risk to the operator, surrounding personnel, or equipment on a semi-annual basis.

Annual safety inspection and maintenance:

- Conduct a vacuum system leak assessment.
- Replace the air filter between the XCell ATF Housing and the XCell LS Controller.
- Inspect air and vacuum connections.
- Inspect the XCell ATF Housing components, especially the internal and sealing surfaces for damage, rust, cracks, scoring.
- Perform a pressure hold test of the XCell ATF Housing.

12. Appendix C: Spare Parts

Table 23. XCell ATF 4 Housing Spare Parts

Item Number	Item Description
ATF4:AIR-ASSY	Assy, Air Inlet, XCell 4
ATF4:PH-AA-AIR	Assy, Pump Hemisphere, air side, XCell 4
ATF4:PHLA-SMP	Assy, Pump Hemisphere, liquid side, XCell 4
SG-2.5-E	Gasket, Sanitary, 2.5 in TC
TC-CAP-3/4	Cap, Sanitary, 3/4 in TC

Table 24. XCell ATF 6 Housing Spare Parts

Item Number	Item Description
A6-BASE	Assy, Base Plate, Pump Hemi, XCell 6
A6-BASE-SHCS	Socket Head Cap (4) & Set Screw (1x)
A6-H1	Assy, Filter Housing, XCell 6
ATF610-TEE	Short Tee, 3/4 in TC x 3/4 in TC x CPM
ATF6:AIR-ASSY	Assy, Air Inlet, XCell 6
ATF6:PH-AA-AIR	Assy, Pump Hemisphere, air side, XCell 6
ATF6:PHLA	Assy, Pump Hemisphere, liquid Side, XCell 6
CS-10650	Legacy Air Connection, ATF 6
SG-1.0-E	Gasket, Sanitary, 1 in TC
TC-BRB1	Adapter, Hose Barb, 3/4 in TC x 1/4 in HB
TC-EL1S	Elbow, 90 Deg, 1.0 in TC
V1-S-0.5N	Sanitary Diaphragm Valve, 1/2 in TC

Table 25. XCell ATF 10 Housing Spare Parts

Item Number	Item Description
A10-STAND	Assy, Stand, XCell 10
A10:C1-LOCK-A	C Clamp Lock A (Long) for XCell 10 pump
A10:C1-LOCK-B	C Clamp Lock B (Short) for XCell 10 pump
A10RF-C3	Assy, ASME Clamp, XCell 10
A10RF-C3-RELIEF	Assy, ASME Clamp w/ Relief, XCell 10
A10RF-HA	Assy, Lifting Handle, XCell 10
ATF10 BOLT-ASSY	Assy, 2 nuts & 1 bolt for XCell 10
ATF10:AIR-ASSY	Assy, Air Inlet, XCell 10
ATF10:PH-AA-AIR	Assy, Pump Hemisphere, air side, XCell 10
ATF10:PHLA	Assy, Pump Hemisphere, liquid side, XCell 10
ATF610-TEE	Short Tee, 3/4 in TC x 3/4 in TC x CPM
SG-05-E	Gasket, Sanitary, 1/2 in TC
SG-075-E	Gasket, Sanitary, 3/4 in TC
SG-1.5-E	Gasket, Sanitary, 1.5 in TC
SG-1.5-S	Gasket, Sanitary, 1.5 in TC-silicone
SG-6.0-SCH5	Sanitary Gasket, 1.5 in TC, Silicone
TC-EL-1.5S	Elbow, 90 Deg, 1.5 in TC

Table 26. Connections Spare Parts

Item Number	Item Description
SC-075	Clamp, Sanitary, 1/2 - 3/4in TC
SC-1.5	Clamp, Sanitary, 1.5 in TC
SC-2.5	Clamp, Sanitary, 2.5 in TC
SC-3L	Clamp, Sanitary, 3 in TC
SC-4.0	Clamp, Sanitary, 4 in TC
SC-6.0	Clamp, Sanitary 6 in TC

13. Index

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