User Requirement Specification (URS) for Tangential Flow Filtration (TFF) System

VERSION 1
November 14, 2023

Revision History

Revision Number	Date	Description of Changes
0	June 12, 2023	Original Version
1	Nov. 14, 2023	Final Version

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1 Purpose and Scope

The purpose of this User Requirements Specification (URS) is to specify a single pass tangential flow filtration (TFF) system in accordance with its technical requirements and applicable current local and regulatory, environmental, health, and safety, and automation standards.

The intent is to define the critical aspects (CAs) and critical process parameters (CPPs) on which the system qualification will be based. This document also details performance requirements and various design criteria for the equipment to be used in the pharmaceutical environment under cGMP conditions. However, it is not the intent of this document to detail all mechanical, electrical and control requirements. The vendor shall supply all subordinate components necessary to meet the performance requirements established herein. Should the vendor find it necessary to deviate from the specific design and performance requirements detailed in this document, the vendor shall clearly state all the deviations in the proposal and give the reason(s) for each deviation.

The TFF system will be referred to as "system" in this document. The system will be used in a continuous purification process for manufacture of biopharmaceutical products (e.g. monoclonal antibody production). The system will operate continuously for twenty-eight (28) days. During this time a constant stream of feed material will be supplied to the system. The system will perform a first concentration step followed by buffer exchange and a second concentration of the biopharmaceutical product. The equipment will be installed in a cGMP environment, specifically in non-hazardous Grade C or Grade D clean room with temperature control (15-25°C).

The system will be used for a 500-Liter, 2,000-Liter, and 4,000-Liter perfusion process over a range of titers. Multiple single-use flow paths will be required to cover this range.

The single-use, product contact flow path assembly is specified in the requirements section of this document. Feed product bags, final product collection bags, buffer solution totes and tangential flow filtration membrane cassettes or cartridge will be connected to this system to operate the Ultrafiltration Diafiltration (UFDF) steps. The requirements for the feed and final product bags, buffer totes and filtration cassettes are not within the scope of this URS.

2 Area of Application

This URS applies to the following systems:

Item	Description	Tag Number
1	TFF System	TFF001

3 Responsibilities

Function	Purpose of Signature
Local User	I am signing on behalf of the user and confirm that this document accurately reflects the technical user requirements.
Project Engineering	I am signing/authorizing this document and agree that the technologies specified in this document are correct and in line with current technical concepts and that each requirement is specific and measurable for requirements affecting Product Quality.
Automation	I am authorizing this document and agree that the automation requirements specified in this document are correct and in line with current technical concepts.
Health, Safety and Environment	I am authorizing this document and agree that the requirements specified in this document are in line with current health, safety and environmental standards.
Quality	I am signing on behalf on the Quality Unit and confirm that the content of this document is compliant with relevant internal and external cGMP standards.

4 Process

The single pass tangential flow filtration system will be used for diafiltration and concentration of the drug product intermediate. These processes exchange the upstream process buffer for the final drug substance buffer and concentrate the product within the final drug substance concentration range.

First, an ultrafiltration step is performed to concentrate product to a target (ex. 60 g/L) with three tangential flow filters in series to perform single pass tangential flow filtration (SPTFF), as shown in Figure 1. Next, a three stage diafiltration step is performed followed by a final concentration step across a single SPTFF membrane, as shown in Figure 2.

Figure 1. Initial ultrafiltration step.

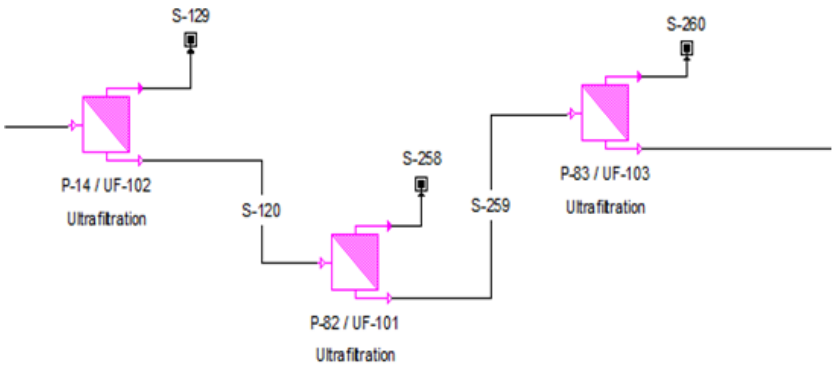
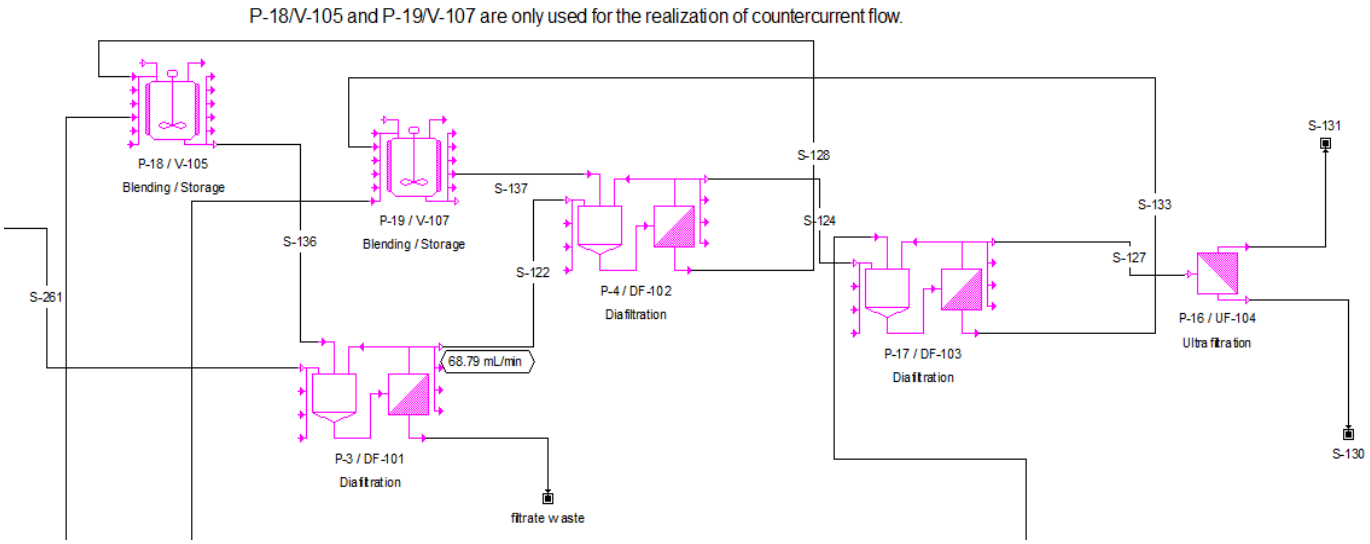


Figure 2. Diafiltration and second concentration steps.



The diafiltration step consists of three stages of single pass TFF membranes (DF-101, DF-102, DF-103). Buffer exchange of over 99.75% or higher (equivalent to 6 diavolumes) can be achieved with a series of three dilution and concentration steps[1]. A single TFF stage (UF-104) can concentrate the product >10-fold without recirculation of the material (actual concentration factors used in a process to achieve diafiltration targets will vary but are expected to be within 5X to 10X). Dilution of the product with the final drug substance buffer is performed prior to each of the three single pass TFF membranes. As a result, the

feed material entering into each TFF membrane is dilute and the drug product leaving the 3rd section is concentrated.

Example (note 10X is used for demonstration purposes only, actual concentration factors are expected to be between 5X-10X):

Diafiltration Stage	Dilution Factor	Concentration Factor	% Buffer Exchange	Outlet Concentration
1	10X	10X	90%	60 mg/ml
2	10X	10X	99%	60 mg/ml
3	10X	10X	99.9%	60 mg/ml

For reference, a traditional TFF step (not specified in this URS) recirculates material to and from a feed tank and a TFF membrane. For this system, the retentate is not recirculated back to the TFF membrane.

In order to reduce buffer volume requirements, the process may be operated in a counter current manner. Permeate buffer from the second and third sections will be fed to the first and second sections, respectively, to dilute the concentrated product. Figure 2 illustrates this process and another illustration of this is shown in Figure 2 below[2].

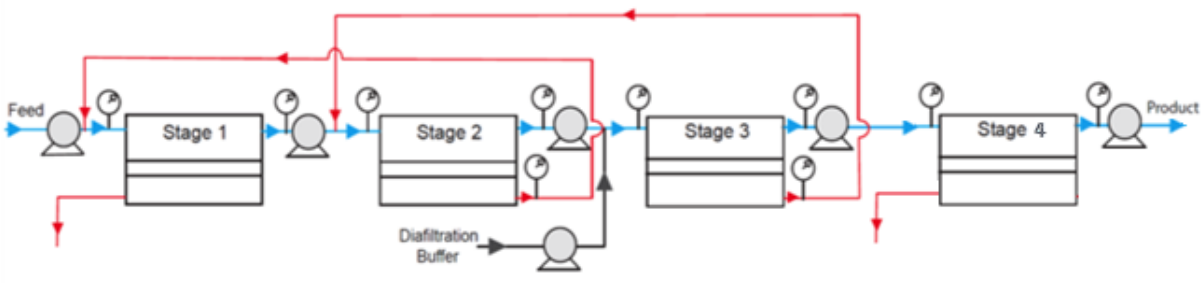


Figure 3

The process steps shall consist of the following:

1. Pre-use equilibration with water or process buffer to check system operation (leaks, valves open/close, pumps on/off).
2. Pre-use sanitization with 1.0N sodium hydroxide.
3. Pre-use equilibration with process buffer.
4. Introduction of product and steady state operation.
5. Post-use flush of product with equilibration buffer.
6. Post-use sanitization of membranes with 1.0N sodium hydroxide.
7. Storage of membranes with 0.1 N sodium hydroxide.

5 Requirements

5.1 Product Quality Critical Assessment

An assessment has been performed to determine which requirements listed in this specification are critical to product quality. Where a requirement is deemed to be product quality critical, "Yes" is stated. If a requirement has been determined - as non-critical to product quality, one of the following justifications is provided as its rationale:

(1) **Health, safety, and environment critical** (for personnel and/or equipment only).
(2) **Business critical** (productivity, operations, process efficiency).
(3) **Technical requirement** with indirect or no impact on product quality, patient safety, and CGMP data integrity.
(4) **Non-product contact** (applies to equipment that is not in direct contact with the product).
(5) **Critical** but quality critical requirement is covered by another requirement in this URS. Reference is provided to the critical requirement.

The justifications (1 to 5) above are applicable for the entire document. At least one justification shall be stated per requirement.

5.2 General Requirements

Reference the General Equipment URS for details.

5.3 Functional Requirements

ID	Requirement	Product Quality Critical (Yes/No)	Comments / Questions
FNC-01	System shall perform a first concentration step to 60-90 g/L (5-10X concentration factor) , a diafiltration step at 60-90 g/L (with 5-10X concentration factors across SPTFF membranes), and a second concentration step to 90-180 g/L, as needed (1.5-2.5X concentration factor).	Y	
FNC-02	The diafiltration step shall be a three-stage process with single pass TFF membranes and the ability to perform counter current flow of diafiltration buffer. The decision to operate in countercurrent mode will be decided on a per use basis by the end user.	Y	
FNC-03	System shall have operating time of up to 28 days.	Y	
FNC-04	Membranes/cartridges shall be disposable and are expected to be replaced every week.	Y	

FNC-05	System dimensions shall not exceed 34'' x 60'' x 72'' (WxLxH) to ensure fit through standard doorways. Accessories may exceed these dimensions.	N	1
FNC-06	System to use a single use product contact flow path.	N	2
FNC-07	The system shall provide connections for seven (7) single pass TFF membranes. Three (3) TFF membranes are used for initial concentration, three (3) TFF membranes are used for diafiltration and (1) TFF membrane is used for final concentration.	Y	
FNC-08	The system shall be equipped with a minimum of one equilibration buffer inlet, one sanitization buffer inlet, one storage buffer inlet, and one water inlet. The system shall be configured to allow for pre-use flush, sanitization, equilibration, and storage of all TFF stages of the system.	Y	
FNC-09	The system shall be equipped with one feed inlet, one permeate line and one retentate line for each of seven (7) TFF membranes. System shall be equipped with one diafiltration buffer inlet for each of the three (3) diafiltration TFF membranes.	Y	
FNC-10	Concentration factors across TFF membranes may be controlled by either (1) a feed and retentate pump on a single membrane or (2) a feed pump and a back pressure control valve. System shall include a minimum of three (3) feed/retentate pumps. These pumps may be multi-channel pumps for steps that operate at the same flow rate, such as the three diafiltration TFF steps.	Y	
FNC-11	System shall include a minimum of one (1) diafiltration buffer pump. A multi-channel pump may be used.	Y	
FNC-12	System shall include a minimum of ten (10) pressure sensors: - one (1) pressure sensor upstream and downstream of the set of concentration 1 TFF membranes (no pressure sensors between the three (3) membranes) - one (1) pressure sensor upstream and downstream of each of four (4) diafiltration and concentration 2 TFF membranes	Y	
FNC-13	System to allow for TMP control on each membrane.	Y	
FNC-14	Pumps speed to be controlled to flow rate set point.	Y	
FNC-15	Flow rate set points to be adjustable during operations.	Y	
FNC-16	Pump flow rates to be controlled (on/off/slower/faster) based on feed and retentate vessel level (with option to select feed or retentate).	Y	
FNC-17	System will pause due to high pressure at any point in the flow path (>60 psi or other membrane/system limitation specified by user).	N	1
FNC-18	System shall have weigh scales that measure the mass of retentate with accuracy of balance to 0.1kg.	Y	
FNC-19	Retentate vessel target working volumes shall be the following- 500 L Scale - 1 to 5 L 2000 L Scale -4 to 20 L 4000 L Scale -– 8 to 40 L	Y	

FNC-20	The equipment shall measure feed flow rate to the filters.	Y	
FNC-21	The equipment shall measure conductivity of the retentate.	Y	
FNC-22	The equipment shall measure permeate flow rate.	Y	
FNC-23	The equipment shall operate with hollow fibre cartridges or flat sheet membrane cassettes.	Y	
FNC-24	The retentate vessels shall be stirred.	Y	
FNC-25	Drain valve shall be at lowest point of system to maximize product recovery.	Y	
FNC-26	Single-use flow path assembly shall be able to withstand pressures of 4 bar.	N	1
FNC-27	The system shall be designed so that there is a minimum retentate hold up of < 5 L.	N	2
FNC-28	Permeate flux of 10 LMH (±50%).	Y	
FNC-29	Membrane capacity shall be 1680 L/m^2.	Y	
FNC-30	System will perform diafiltration buffer addition at rate of approximately 5-10X the concentrated product volume.	Y	
FNC-31	The system will be designed for a facility with an upstream continuous perfusion bioreactor range of 500L to 4000L working volume. Multiple single-use flow paths of different IDs will be required to cover this range. The TFF system requirements to cover the range are as follows: Concentration 1 to have three membranes of equal size connected in series. Membrane size: 500 L Scale - 0.114 m^2 2000 L Scale - 0.679 m^2 4000 L Scale - 1.565 m^2 Diafiltration to have three membranes of equal size. Diafiltration Step Membrane size: 500 L Scale - 0.37 m^2 2000 L Scale - 3.13 m^2 4000 L Scale - 6.23 m^2 Concentration 2 Membrane size (one membrane): 500 L Scale - 0.027 m^2 2000 L Scale - 0.224 m^2 4000 L Scale - 0.446 m^2	Y	
FNC-32	Concentration 1 feed and retentate flow rate targets (flow rate range to be ±50%): <u>500 L Scale</u> - 66.07 mL/min (stage 1 feed) -->; 46.99 mL/min (stage 1 retentate, stage 2 feed) -->; 27.93 mL/min (stage 2 retentate, stage 3 feed) -->; 8.80 mL/min (stage 3 retentate)	Y	

	2000 L Scale - 414.01 mL/min (stage 1 feed) -> 300.65 mL/min (stage 1 retentate, stage 2 feed) --> 186.9 mL/min (stage 2 retentate, stage 3 feed) --> 74.42 mL/min (stage 3 retentate) 4000 L Scale - 930.47 mL/min (stage 1 feed)--> 654 ml/min (stage 1 retentate, stage 2 feed) --> 406.72 ml/min (stage 2 retentate, stage 3 feed) --> 148.14 mL/min (stage 3 retentate)		
FNC-33	Concentration 1 permeate flow rate target for all three stages (flow rate range shall be ±50% target): 500 L Scale - 19 mL/min (Stage 1) 2000 L Scale - 113 mL/min (Stage 2) 4000 L Scale - 262 mL/min (Stage 3)	Y	
FNC-34	Diafiltration inlet flow rate target (flow rate range shall be ±50% target): 500 L Scale - 8.80 ml/min 2000 L Scale - 74.42 ml/min 4000 L Scale - 148.14 ml/min	Y	
FNC-35	Diafiltration retentate and concentration 2 feed flow rate target (flow rate range shall be ±50% target): 500 L Scale - 8.82 ml/min 2000 L Scale - 74.55 ml/min 4000 L Scale - 148.42 ml/min	Y	
FNC-36	Diafiltration buffer addition flow rate target (flow rate range shall be ±50% target): 500 L Scale - 61.61 ml/min 2000 L Scale - 520.91 ml/min 4000 L Scale - 1037.0 ml/min	Y	
FNC-37	System to receive signal from SCADA system and provide real-time update of flow rates in response.	Y	
FNC-38	The system shall be capable of automated inline filter integrity testing and system integrity testing.	Y	

5.4 Cleaning, Sanitization and Steaming in Place Requirements

See General Equipment URS for specifications.

5.5 Utility Requirements

ID	Requirement	Product Quality Critical (Yes/No)	Comments / Questions
UTL-01	System shall be able to connect to the following utilities: Instrument air (0 to 7 barg) Water (0 to 6 barg) System to have pressure reducing valve to keep water pressure below safe operating pressure of system.	N	3
UTL-02	The gas inlets of the system shall be equipped with pneumatic quick connects.	N	3
UTL-03	Flow path to system inputs and from system outputs shall be (multi-use) hoses for the following fluids: -Instrument air -Heating/cooling fluid	N	3
UTL-04	The system shall be operable with safety gloves (one or two pairs).	N	1
UTL-05	Vendor shall provide utility connection information, steady state and peak consumption demands.	N	

5.6 Automation Requirements

See General Equipment URS for specifications.

5.7 Metrology Requirements

See General Equipment URS for specifications.

5.8 Electrical Requirements

See General Equipment URS for specifications.

5.9 Health, Safety, and Environment

See General Equipment URS for specifications.

5.10 Maintenance requirements

See General Equipment URS for specifications.

5.11 Flexibility

See General Equipment URS for specifications.

5.12 Scope of required documentation

See General Equipment URS for specifications.

6 Abbreviations & Acronyms

Abbreviation / Acronym	Description
URS	User Requirement Specification
TFF	Tangential Flow Filtration
SPTFF	Single Pass Tangential Flow Filtration
CGMP	Current Good Manufacturing Practice
UFDF	Ultrafiltration Diafiltration

7 Attachments and References

a. Attachments

#	Title	Doc. No.

b. References

#	Title	Doc. No.
1	Rucker-Pezzini, Joanna, et al. "Single pass diafiltration integrated into a fully continuous mAb purification process." *Biotechnology and bioengineering* 115.8 (2018): 1949-1957.	N/A
2	Nambiar, Anirudh MK, Ying Li, and Andrew L. Zydney. "Countercurrent staged diafiltration for formulation of high value proteins." *Biotechnology and bioengineering* 115.1 (2018): 139-144.	N/A