User Requirement Specification (URS) for Continuous Viral Inactivation System

VERSION 0.4
March 28, 2024

NIMBL

Revision History

Revision Number	Date	Description of Changes
0	Oct 31, 2023	Original Version
0.1	Nov 27, 2023	Comments incorporated
0.2	Jan 29, 2024	General requirements removed.
0.3	Mar 12, 2024	Comments incorporated and reformatted
0.4	Mar 28, 2024	1st Gen SME input incorporated

Table of Contents

1 Purpose and Scope

The purpose of this User Requirements Specification (URS) is to specify a continuous viral inactivation (CVI) 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 CVI 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 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.

2 Area of Application

This URS applies to the following systems:

Item	Description	Tag Number
1	CVI System	TBD

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

Continuous Viral Inactivation (CVI) will be used for the inactivation and removal of viruses from the drug substance.

The overall block flow of the CVI is shown below (Figure 1) as well as a more detailed process flow diagram (Figure 2).

Figure 1 CVI Block Flow Diagram

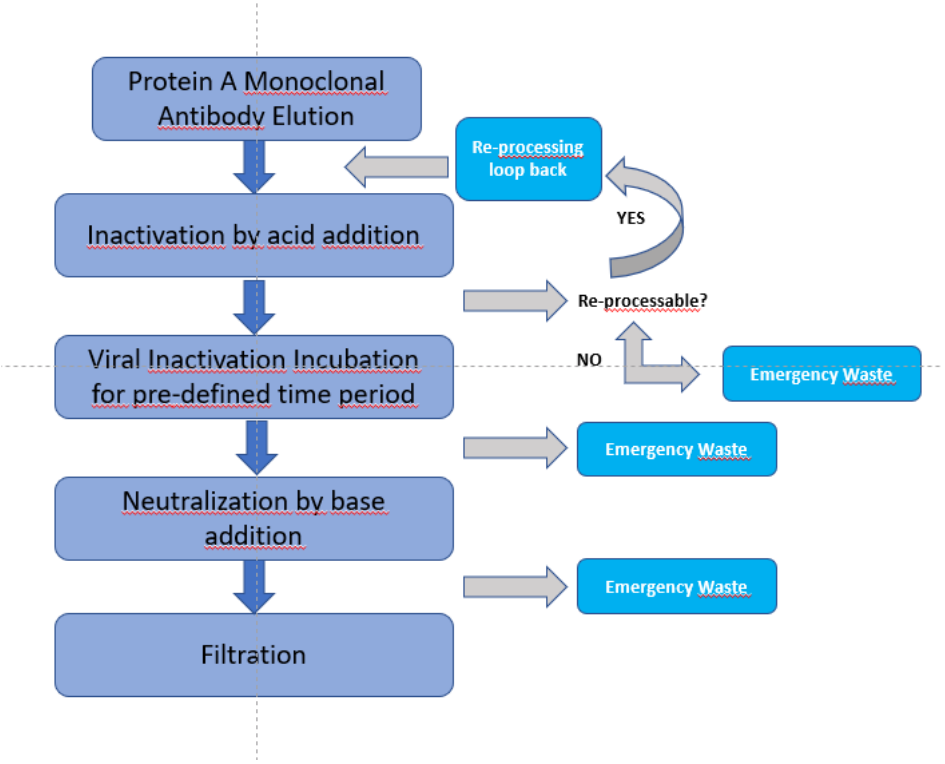
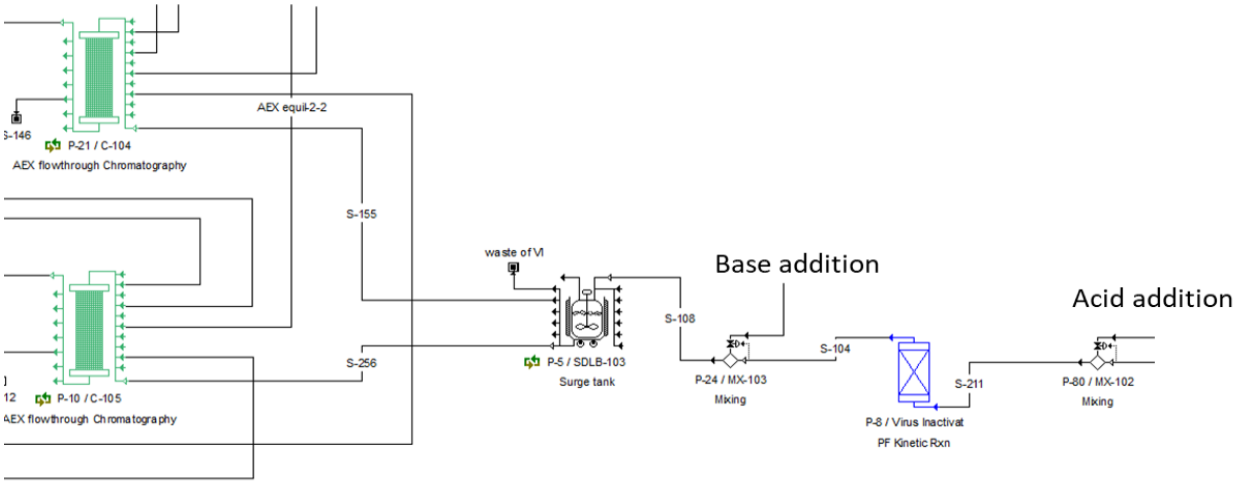


Figure 2 Process Flow Diagram of the CVI system and downstream equipment



The CVI system shall be an integrated system capable of GMP manufacturing over a wide range of process conditions as specified in Section 5 below. The system shall have the overall capability of processing chromatography eluate for low pH viral inactivation by decreasing pH through acid addition, holding for the required time, neutralizing through base addition, and

discharging to downstream users continuously. The CVI system includes an acid injection system including pumps and fluid path, in-line static mixer, inactivation chamber, base injection system including pumps and fluid path and final mixer and surge bag. Flow (and thus calculated residence time) and pH are critically controlled parameters. Temperature and conductivity are also monitored.

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	The CVI system must demonstrate reduction of active enveloped virus particles in a process solution by at least $Log_{10}(5)$ in a time period of 30 minutes after acid addition (low pH inactivation).	Y	
FNC-02	The CVI system must demonstrate clearance of model viruses in comparison to offline non-continuous viral inactivation.	Y	

FNC-03	The CVI system must demonstrate clearance of model viruses with various common buffer compositions and a range of pH conditions.	Y	
FNC-04	The CVI System shall physically integrate with various chromatography system process stream configurations.	Y	
FNC-05	The CVI System shall integrate with the chromatography systems' hardware and software such that flow rates, volumes, and measurements for both systems are monitored and controlled.	Y	
FNC-06	The CVI System outlet shall integrate various downstream surge vessels and/or hold tank configurations as required. The outlet configuration shall not impact the desired viral inactivation time period.	Y	
FNC-07	The system will be able to operate for a period of 28 days (24/7) without interruption at maximum flowrate and volumes.	N	2
FNC-08	The CVI system shall not reduce the overall incoming process volume by more than 2.0%.	N	2, 3
FNC-09	System shall possess a viral inactivation incubation chamber allowing for a minimum 30 minutes residence time.	Y	
FNC-10	The system will operate under low pressure with a maximum allowable pressure of 3 bar.	N	1
FNC-11	Process control strategies shall be in place to limit the system under the maximum allowable pressure.	N	1
FNC-12	System shall be within all listed accuracies for all listed processing ranges.	Y	
FNC-13	Flow, pH, temperature, and pressure measurement sensors will be provided on both upstream and downstream streams of the CVI system.	Y	
FNC-14	System shall utilize a single use flow meter.	Y	
FNC-15	The CVI System shall provide volume measurements of acidic solution and basic solution additions well as the final process stream volume within ± 5%.	N	2, 3
FNC-16	System shall possess volumetric readings of each component of system of actual volume	Y	
FNC-17	The CVI system shall be capable of treating an input process flow rates as low as 3.7 L/hr (500L Bioreactor) to 58 L/hr (4000 L	Y	

	Bioreactor) from chromatography eluate surge tank to CVI system.		
FNC-18	The CVI system acid addition shall be capable of delivering flow rate as low as 0.46 L/hr (500 L Bioreactor) to 7.5 L/hr	Y	
FNC-19	The CVI system Tris Base addition shall be capable of delivering flow rate as low as 0.54 L/hr (500 L Bioreactor) to 8.3 L/hr	Y	
FNC-20	The CVI system shall be capable of a minimum output flow rate range of 4.7 L/hr (500 L Bioreactor) to 74 L/hr (4000 L Bioreactor) following the base addition neutralization through to the downstream system.	Y	
FNC-21	Flow rate of the system, as well as acid and base additions shall be automatically controlled within acceptance criteria of +/- 2%	Y	
FNC-22	Agitation of the surge system shall have a minimum power input of 14W/L over the total volume ranges and flow rates stated. Mixer shall be automated to control speed of impeller, varying RPM to keep power input constant at different volumes.	Y	
FNC-23	The system's mixing chamber fill volume shall be adjustable through the control system, reducing hold-up and thus yield loss	N	2, 3
FNC-24	Upstream of inactivation vessel hold tank the inline static mixer shall provide uniform blending of monoclonal antibody feed stream with buffer components and acidification pH adjustment solutions. The monoclonal antibody concentration is 8.00 to 12.00 mg/mL.	Y	
FNC-25	Inline static mixer shall provide thorough mixing while maintaining a narrow distribution of residence time	N	2, 3
FNC-26	The CVI System pH monitoring shall provide accurate measurements of the pH within +/- 0.1 pH units over a period of 28 days.	N	2, 3
FNC-27	All pH probes shall have a response less than residence time between the sensor and any diversion valve prior to the next step.	Y	
FNC-28	pH probes of system will be able to operate in the range of pH 2.0 to 10.0	Y	
FNC-29	pH probes shall experience minimum drift and will operate in a range of ± 0.1 pH units in a time period of 24 hours.	Y	

FNC-30	pH sensor/transmitter can be calibrated while system is operating without impacting system performance.	N	2, 3
FNC-31	System shall be able to perform reverse titration in the event over titration occurs at either acid or base addition steps.	N	2, 3
FNC-32	The CVI System should be provided with a process interlock to divert the product stream to waste if the measured pH should deviate outside of the acceptable criteria.	Y	
FNC-33	The CVI System will measure temperature but not control temperature.	Y	
FNC-34	System temperature shall not be impacted by external components such that the ambient temperatures around the product flow path does not exceed the external room condition set points.	N	2, 3
FNC-35	In the event of a temperature excursion outside of allowable range (typically 15°C to 30°C), system shall alarm and send product to drain.	Y	
FNC-36	System shall have a conductivity probe following base addition and aggregate removal	Y	
FNC-37	Conductivity meter/probe of system shall have an accuracy of ± 0.1 mS/cm	Y	
FNC-38	The CVI System shall remove air bubbles from its outlet stream, monitor that air bubbles have been removed and alarm if bubbles are detected	Y	
FNC-39	All parts with contact to process fluid, media or clean gasses shall be made from corrosion resistant (inert) materials which require material certificates: - In the case of metal : DIN EN 10204 material certificates 3.1 or 2.2 (in case of 2.2 including spot checks for incoming material) - In the case of polymers/plastics: Conformity with the FDA Regulations 21 CFR 170-199.NNNN, Regulation (EC) No. 2023/2006, USP Class VI, animal origin free (AOF) compliance according to EMA 410/01.	Y	
FNC-40	All non-metallic, non-polymeric material parts (e.g. glass, cermaics etc.) with contact to process fluid, media or clean gasses shall meet the pharmaceutical standards according to current ASME BPE.	Y	
FNC-41	System reusable parts shall be easily cleanable and resistant to cleaning agents in event of contamination, i.e., 316L stainless steel with pharmaceutical grade finish .	Y	

FNC-42	CVI System inlet from acidic addition shall be compatible with 1M HCl and 1M acetic acid.	Y	
FNC-43	CVI System inlet for Tris Base addition shall be compatible with 1M NaOH and 1.2M Tris Base	Y	
FNC-44	HCl hold container must be of sufficient volume to contain 0.15 to 0.25 ratio to that of total feed stream volume	N	2, 3
FNC-45	Tris Base holding container must be of sufficient volume to contain 1.5 to 2.0 that of the total CVI System volume to include the initial feed stream plus the addition of HCl	N	2, 3
FNC-46	The CVI system's inlet and outlet stream flows shall be actively controlled.	Y	
FNC-47	Single use components which comprise the system must assemble and operate so that sterility is maintained over the 28 day processing period.	Y	
FNC-48	Single use components of system shall be connected in an aseptic manner to make a close fluid flow path.	Y	
FNC-49	All single use containers shall allow for filtered venting during filling and filtered breathing during draining.	N	1, 3
FNC-50	All flow path connectors shall be single use pre-sterilized consumable, with multi-use pumps and multi-use valves.	Y	
FNC-51	The system flow path design and valve control shall enable transfers from both the Upstream operation to the CVI System, and then to the Hold tank(s).	Y	
FNC-52	All single use components, connectors, and any other components of system that must be user installed prior to use will be designed in a manner only allowing the correct flow orientation.	N	3
FNC-53	Fixed and multi-use components shall meet the performance requirements over the entire defined range. Removable and consumable parts may be sized accordingly for the specific targeted flow rate. The system shall be able to use flow paths of different sizes/diameters to meet all requirements over the flow ranges specified.	N	5
FNC-54	Valves and actuators shall be selected and installed to not allow for any back mixing of inactivated to non-inactivated material.	Y	
FNC-55	The system shall have sampling ports to allow for sampling at defined positions in the process.	Y	

FNC-56	Sampling lines of system shall be sterile and designed to not allow potential contamination through the introduction of outside contaminants.	Y	
FNC-57	Sampling lines of system shall be of sufficient diameter and length to allow for the sampling minimum of 5.0 mL	Y	
FNC-58	Sample lines of system shall have ability to be connected and configured to an automated sampling instrument	N	2, 3
FNC-59	System shall possess a filtration device(s) downstream of 1.2M Tris base neutralization to remove aggregates. The connection of the filter assembly shall be aseptic.	Y	
FNC-60	Filtration unit downstream of neutralization shall operate for a minimum period of 28 days to accommodate perfusion bioreactor process.	N	2
FNC-61	System shall allow for the change out of filtration devices downstream of 1.2M Tris Base without interruption of continuous process	N	2, 3
FNC-62	System shall be able to operate properly at room temperature within a range of 15°C to 30°C	Y	
FNC-63	System must be able to operate in room humidity range of 20% to 60%	Y	
FNC-64	System shall allow for further customization and installation of additional valves and/or actuators	N	2, 3
FNC-65	CVI System control software must allow user to select either manual or automatic-sequence operation.	N	2, 3
FNC-66	System shall possess a touch screen user interface to allow for monitoring, viewing isolation of individual steps in process, execution of step control or pausing/aborting process.	N	2, 3
FNC-67	System shall possess a visible system to allow operator to clearly visualize the status of an operation such as equipment run conditions, critical alarm conditions and process interlock activation.	N	3
FNC-68	All peripherals for system such as touch screen, mouse, and keyboard shall be placed ergonomically	N	1
FNC-69	System shall possess process analytical capability to monitor aggregate levels in real time (Optional)	N	2

FNC-70	System must be designed to ensure operator safety and not possess any sharp corners and/or edges.	N	1
FNC-71	The system shall have secondary containment measures for fluid systems where the bulk chemicals are stored and introduced to the system. This includes where intermediate product may have pH below 3 or above 11.	N	1

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 must be able to connect to the following utilities: Instrument air (0 to 7 barg)	N	3
UTL-02	The gas inlets of the system shall be equipped with pneumatic quick connects.	N	3
UTL-03	Flowpath to system inputs and from system outputs shall be (multi-use) hoses for the following fluids: -Instrument air	N	3
UTL-04	The system must be operable with the user donning one to two pairs of latex/neoprene safety gloves .	N	3

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
ASME	American Society of Mechanical Engineers
ASTM	American Standard for Testing and Materials
BPE	Bioprocessing Equipment
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CVI	Continuous Viral Inactivation
DIN	German Institute for Standardization (Deutsches Institut fuer Normung)
EMA	European Medicines Agency
EN	European Standard (Europaeische Norm)
FDA	Food and Drug Association
ICH	International Council for Harmonization
RPM	Revolutions per minute
USP	United States Pharmacopeia

CA : Critical Aspects: Functions, features, abilities and performance or characteristics necessary for the manufacturing process and systems to ensure product quality and patient safety. ASTM E2500-13[5]

CPP: Critical Process Parameter: A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored to ensure the process produces the desired quality. ICH Q8 [4]

CQA: Critical Quality Attribute: A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality. ICH Q8 [4]

Model Virus: Typically refers to a non-pathogenic or engineered virus that is used in laboratory setting to study and understand various aspects of viral biology, replication or as a platform for developing and testing antiviral drugs or vaccines. Model viruses can be used during the qualification steps for new equipment.

7 Attachments and References

a. Attachments

#	Title	Doc. No.

b. References

#	Title	Doc. No.
1		
2		