User Requirement Specification (URS) for General Equipment

VERSION 1

December 31, 2023

Revision History

Revision Number	Date	Description of Changes
0	August 1, 2023	First Draft
0.1	Sept 22, 2023	Flexibility Team Input
1.0	Dec 31, 2023	Final

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1 Purpose and Scope

The purpose of this User Requirements Specification (URS) is to specify general equipment requirements for unit operations 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 attributes 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.

A unit operation will be referred to as "System" in this document. The system will be used in a continuous purification process for the manufacture of biopharmaceutical products (e.g. monoclonal antibody production). The system will be used for a 500Liter, 2,000-Liter, and 4,000-Liter perfusion process over a range of titers. The system will operate continuously for twenty-eight (28) days. 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)

This document describes general requirements, including cleaning, automation, metrology, electrical, health/safety/environment requirements that is typically expected. Refer to unit operation specific URS for specific process requirements.

2 Area of Application

This URS applies to the following systems:

Item	Description	Tag Number
1	Any Unit Operation	NA

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

A vendor agnostic manufacturing of pharmaceuticals (mAb) under cGMP conditions with a scale of a 500Liter, 2,000-Liter, and 4,000-Liter perfusion process over a range of titers. See process equipment specific URS for detailed description of unit operation.

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

ID	Requirement	Product Quality Critical (Yes/No)	Comments
GEN-01	Equipment shall have suitable mobility to move around the facility. The frame shall be stable in operation and have non-marking lockable wheels. The frame and equipment shall not cause damage to the flooring in the manufacturing area during routine use.	N	1, 3
GEN-02	Instrument air service pneumatic tubing and/or piping lengths between system internal components (valves, instruments, and filters) shall be as short as possible.	N	3
GEN-03	The system shall be designed for easy access to all relevant components during production for sampling, tube welding, calibration and maintenance.	N	2, 3
GEN-04	Measures shall be taken to prevent overpressurization to avoid bursting.	N	1
GEN-05	Operation of system (Connection and disconnection of components and tubing) shall occur under closed conditions.	Y	
GEN-06	Internal Metallic parts / surfaces in contact with clean gases shall meet Material AISI 316L or equivalent or better.	Y	

GEN-07	All parts in contact with 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 EMEA 410/01.	Y	
GEN-08	The system design shall comply to the current ASME BPE pharmaceutical standards.	Y	
GEN-09	External metallic parts/surfaces shall be compatible (chemically resistant, nonpermeable) with cleaning and sanitization agents specified (e.g. sporicidal agents, peracetic acid, 70% IPA).	Y	
GEN-10	Lubricants (including oil and grease) in contact with Process Fluid, Media or Clean Gasses: Food grade with FDA compliance to 21 CFR part 178, certified to USDA H1 or equivalent, animal origin free (AOF) compliance according to EMEA 410/01.	Y	
GEN-11	The system shall be delivered clean and free of residue. (Suppliers shall be required to submit cleaning procedure documentation.,	Y	
GEN-12	Metallic parts / surfaces with no product contact, but visible in production area shall be mechanically polished or glass bead blasted.	Y	
GEN-13	Welding seams shall be ground flush with base material and smooth.	N	3
GEN-14	All instrument air service pneumatic tubing shall be made from PTFE.	N	3
GEN-17	System shall have a Human Machine Interface (HMI), that is cleanable and capable of being operated with a gloved hand.	N	4
GEN-22	System shall allow use of single-use components from other vendors if required (e.g. in a force majeure situation) with any additional components fully compatible with proposed process design.	N	3

GEN-23	The single-use flow path assembly shall be supplied with sufficient packaging to protect the outer packaging from puncture by components with sharp edges.	N	3
GEN-24	The single-use flow path assembly shall be supplied double-bagged.	N	3
GEN-25	All product contact components of the system shall be single use. Single-use assemblies shall be supplied gamma-irradiated (25-50 kGy)or approved equivalent) and ready to use without prior sterilization.	Y	
GEN-27	Single-use assembly shall be able to be assembled with minimal connections and complexity. Genderless connections are preferred.	N	3
GEN-28	Single-use assembly shall have an accompanying extractables and leachables documentation Package and shall meet current BPOG protocol and USP 665 and 1665	Y	

GEN-29	Sensors and probes shall be disposable (where possible) and supplied integral to the single-use assemblies or capable for aseptic connection. Sensor tolerances and robustness to be defined in Unit Op specific URS.	N	3
GEN-30	Single-use assemblies shall be supplied and manufactured in a facility which has been assessed for provision of GMP consumables.	Y	
GEN-31	Single-use assembly shall have a shelf life which does not exceed its components. Post-sterilization room temperature shelf life must be > 1 year.	Y	
GEN-32	Manufacturing of the single-use assemblies shall take place in a minimum Iso 8 clean room.	Y	
GEN-33	All single-use flow path assemblies shall comply with USP 665 and 1665.	Y	
GEN-34	All single-use flow path assemblies shall be ADCF-free and BSE-TSE free (animal origin free (AOF) compliance according to EMEA 410/01).	Y	
GEN-36	The system shall be compatible with Data Historian or PI software (or equivalent, as proposed by supplier).	Y	3
GEN-38	Single-use assembly shall be able to be recycled or a disposal mechanism provided that limits impact to the environment.	N	3
GEN-39	The set up of system should be possible within one shift.	N	2
GEN-40	Single use assemblies and connections (including welding) shall be designed to ensure no breach of sterility during routine operation and assembly.		

5.3 Functional Requirements

See unit operation specific URS for detailed functional requirements.

5.4 Cleaning, Sanitization and STERILIZATION Requirements

ID	Requirement	Product Quality Critical (Yes/No)	Comments / Questions
CLN-01	The system shall be designed such a way (minimum ledges, non-shedding, sealed, crevice free) that it can be easily and efficiently cleaned.	Y	
CLN-02	The system product contact flow path must allow for sterilization by gamma irradiation (min 25 kGy) or x-ray prior to use.	Y	

CLN-03	The system product contact surfaces shall be compatible with 1.0N NaOH		

5.5 Utility Requirements

See unit operation specific URS for detailed Utility Requirements.

5.6 Automation Requirements

ID	Requirement	Product Quality Critical (Yes/No)	Questions / Comments
AUT-01	The volumetric flow rate of the system is to be continuously adjustable within pre-defined limits during operation based on a target flow rate input from a supervisory control (SCADA) system.	**Y**	
AUT-02	The system shall monitor and alarm faults with the following: 1. Network communications 2. Process status 3. Field instrumentation 4. PID control loops 5. Alarms - (Arrival, Acknowledgement & Departing) 6. Process pause and stop 7. E-stop activated 8. Loss of instrument air	Y	
AUT-03	The system shall be in full compliance with FDA Regulation 21CFR Part 11, pertaining to Electronic Records and Electronic Signatures, in relation to access control, data integrity, audit trail.	Y	
AUT-04	The system shall generate the following electronic records: reports, parameters (including recipes), process trends, alarms, warnings, messages.	N	3
AUT-05	The system shall display the following: process equipment status, device status (valves, motors, PID loops), instrumentation (digital and analog), trending (real-time and historical), alarms (process and system), warnings (process and system), messages (process and system), operator prompts (when manual operations or interventions are required).	N	3

AUT-06	The system shall control the following: Process (step sequencing with prompts for manual intervention when required) and Devices (automatic and manual operation).	Y	
AUT-07	The following modes of operation shall be provided: 1. Automatic Mode - The system is acquiring data, handling alarms and performing Audit Trail management. The system is actively controlling the process in this mode by running the relevant process sequences, monitoring and controlling all equipment. 2. Semi Automatic Mode - The system is acquiring data, handling alarms and performing Audit Trail management. Sequence step transitions are manually validated in this mode. The system is monitoring and controlling all equipment? 3. Maintenance Mode - The system is acquiring data, handling alarms and performing Audit Trail management. The HMI is used to manually control the individual actuators. This operation mode requires Engineer access privileges.	Y	
AUT-08	It shall be possible to operate all valves, motors and PID loops, including Modulating Valves and Variable Speed Drives, in manual maintenance mode from the HMI.	N	3
AUT-09	Safety and equipment protection logic shall be processed continuously, where applicable.	N	1
AUT-10	The system shall fail safe in the event of a failure or critical alarm.	N	1
AUT-11	The vendor shall specify in the Design Specification, actions to be taken on failure of following: Power outage (and subsequent restoration of power), loss of communication, valve error (failed to open, failed to close), motor error (failed to run, failed to stop), analogue input (under range & over range).	N	3
AUT-12	Alarms shall have a configurable parameter that defines the type of alarm as absolute alarm or deviation alarm.	Y	
AUT-13	Alarms shall have a configurable parameter that defines alarm set points for the following monitoring levels: low-low, low, high, and high-high.	Y	
AUT-14	Alarms shall have a configurable parameter that defines alarm deadband to configure an alarm to turn on at one value and clear at another.	Y	
AUT-15	Alarm messages, acknowledgements and other events shall be able to be included in reports.	Y	

AUT-16	Alarm information provided in reports shall include Date, Time, Alarm Text and Alarm Acknowledgement with Username (or User ID).	Y	
AUT-17	System screen updates and control actions shall be updated within two seconds.	N	3
AUT-18	Original time stamping of raw data shall be used for system reports.	Y	
AUT-19	Server and PC clocks shall be synchronized with one master clock (NTP time server) automatically at 15 minute intervals.	Y	
AUT-20	The System shall be capable of being configured for Daylight Savings Time.	Y	
AUT-21	Data logging intervals shall be configurable.	N	3
AUT-22	All automatic valves shall fail closed except those which are specified as fail open.	N	1
AUT-23	System shall have a Human Machine Interface (HMI), that is cleanable and capable of being operated with a gloved hand.	N	4
AUT-24	The system shall have the capability to issue an alarm warning system to operators if alert or action limits are breached on key operating parameters and when other equipment-related issues are encountered during processing.	Y	
AUT-25	Any instruments that monitor critical operation parameters shall have pre-defined process tolerances.	Y	
AUT-26	The system shall have a mechanism for automatic Pause / Stop of the process if parameters are breached.	Y	
AUT-27	Vendor shall provide a control system to monitor and/or control the system.		
AUT-28	All data generated by equipment shall be capable of being communicated to other systems via Ethernet.	Y	

5.7 Metrology Requirements

ID	Requirement	Product Quality Critical (Yes/No)	Comments / Questions
MET-01	All process measurement devices shall be calibratable.	Y	

MET-02	Cable-lengths and installation of measuring instruments shall ensure easy calibration (cable loops and easy removal) to allow calibration at floor level.	N	3
MET-03	All instruments shall be delivered calibrated (dated no more than three months before installation date).		
MET-04	All transmitters shall be calibrated to NIST traceable standards. Where possible a three-point calibration shall be performed: 0%, 50%, and 100% of the scale.		
MET-05	Instrument cabling and transmitters shall be designed to ensure minimal impact on signal robustness and accuracy.		

5.8 Electrical Requirements

ID	Requirement	Product Quality Critical (Yes/No)	Comments / Questions
ELC-01	The power supply (high voltage: pumps, motors, etc.) shall be completely separated from measuring and control technology (low voltage), to exclude disturbance of measurement signals.	N	3
ELC-02	System shall be compatible with site electrical utilities (120V single phase or 480V three phase). If not, transformer shall be provided.	N	3
ELC-03	The equipment shall be furnished with all wiring, controls, motor starters, motor control devices and circuits, etc. for operation of the complete system, pre-wired to a single connection point on each skid and shall comply with NFPA 70 "National Electrical Code" and International Electrical Code.	N	
ELC-04	A fused and lockable disconnect switch shall be included on each skid to cut power to the entire skid. This disconnect shall be included in the enclosure that accepts the single connection for external power.	N	
ELC-05	Panel enclosures shall be NEMA 4X.	N	
ELC-06	All engineered wiring systems and their components shall be UL listed or recognized	N	

	and labeled as such or shall be certified by an approved electrical inspection facility.		

5.9 Health, Safety, and Environment

ID	Requirement	Product Quality Critical (Yes/No)	Comments / Questions
EHS-01	Compliance with local HSE legislation is required.	N	1
EHS-02	Compliance of the product with the relevant directives - standards shall be confirmed by the CE marking and the declaration of conformity (EC declaration of conformity). With these the manufacturer confirms that the product complies with all European directives and standards that address the areas concerning the product.	N	1
EHS-04	Equipment shall be stable during operation.	N	1
EHS-05	Equipment shall pose no risk to manufacturing operator's health and safety.	N	1
EHS-06	The equipment shall comply with PUWER, Health & Safety at Work Act, Safety of Machinery EN60204.	N	1
EHS-07	The equipment and system shall have no sharp edges that may cause damage to facility during transfer or increased risk of injury to operators.	N	1
EHS-08	The system shall have an emergency stop that stops the operation in a safe manner and is accessible to operators	N	1
EHS-11	Safety and equipment protection logic shall be processed continuously, where applicable.	N	1
EHS-16	Surfaces that may be contacted by personnel shall be insulated so the external temperature cannot exceed 50°C and be below 0°C.	N	1
EHS-17	The noise level during production, with all system parts activated and at maximum capacity, may not exceed 80dB(a) at the normal operator point.	N	1
EHS-18	Rotating or moving equipment shall be designed with appropriate personnel protection.	N	1

EHS-19	The operation shall be designed to avoid the need for heavy lifting.	N	1
EHS-20	The system shall be designed and constructed to meet the local seismic requirement of the project site.		

5.10 Maintenance requirements

ID	Requirement	Product Quality Critical (Yes/No)	Comments
MNT-01	All major components shall be tagged and fully traceable to the P&ID.	Y	=
MNT-02	Recommended preventive maintenance and calibration shall be identified in the technical documentation, with their suggested frequency.	N	3
MNT-03	Support frames shall be made of 304, 316, or 316L stainless steel and have adjustable feet.	N	3
MNT-04	Equipment shall be able to be removed from the clean area / be accessible for maintenance.	N	3

5.11 Flexibility

Flexibility requirements shall be applied at the unit operation level to ensure unit operation systems can be interchanged for equivalent while maintaining system performance.

ID	Requirement	Product Quality Critical (Yes/No)	Comments
FLX-01	Key system components can be exchanged for equivalent (defined in unit op specific URS) without requiring customization.	N	2, 3
FLX-02	System performance characterization shall be defined to ensure system equivalence and conformance to industry standard.	Y	

FLX-03	System connections (physical, data, power, *etc*.) designed with appropriate Standards to enable exchange without requiring customization.	N	2, 3
FLX-04	System shall accept smart components (Self-Monitoring, Analysis and Reporting Technology) Example: pumps, probes, instrumentation.	N	3
FLX-05	System capabilities can be changed by adding or removing components (hardware or consumable) without requiring customization and aligning with FLX-02, FLX-03 and FLX-04	N	2, 3
FLX-06	System POL designed to automatically connect and configure new components with added system capabilities using DNP protocol and NAMUR MTP.	N	3
FLX-07	Scalability needs are accommodated by interchangeable component design (reference FLX-04). E.g., to meet a wide range of flows required in specific equipment URS, different ID single-use flow path can be utilized.	N	2, 3
FLX-08	Autonomous system and component tests facilitate verification of correct configuration and performance in a cGMP validated state based on the process requirements for use case. Example: System MTP file contains system capability and is recognized by POL and compared against pre-defined process requirements.	N	3
FLX-09	System capable of verification (as per FLX-08) upon reconfiguration (new use case).	N	3
FLX-10	Product contact systems shall be capable of operating in environments as high as grade C and as low as CNC	N	3
FLX-11	System is capable of completing automated system verification upon moving to a new location (see FLX-08).	N	3

5.12 Scope of required documentation

Standard technical documentation shall be provided in paper or electronic form.

ID	Requirement	Product Quality Critical (Yes/No)	Questions / Comments
DOC-01	The standard scope of technical documentation should include: 1. P&ID diagram 2. Layout installation drawings including: (a) general arrangement drawing, (b) 3D model drawing. 3. Technical documentation and Bill of Material of all built-in elements, components, instruments and equipment. 4. Certificates and declarations of built-in materials and equipment parts 5. Wiring diagram 6. Power panel general assembly drawing 7. Electrical and pneumatic connections 8. Instrument datasheets 9. Software and hardware documentation for PLC: (a) Software Functional Specification (FS), (b) Hardware design specification (HDS). PLC programming for complete operation of equipment. 10. Spare parts list 11. EC Declarations and certificates to all applicable EC directives (PED, Machinery Directive, EMC, etc.) 12. Factory Calibration Certificate (original; NIST traceable) 13. Utility Summary 14. Gas / process contact material certifications.	N	3
DOC-02	The following instruction manuals are to be included: 1. Installation of Equipment 2. Routine Operation of the Equipment 3. Maintenance of the Equipment 4. Calibration Procedures for Measuring Instruments	N	3
DOC-03	The following quality and validation documents should be available (possibly at additional charge to customer)- 1. Functional Requirement Specification (FRS) 2. Software Design Specification (SDS) 3. Design Qualification (DQ) 4. Factory Acceptance Test (FAT) 5. Site Acceptance Test (SAT) 6. Installation Qualification (IQ) 7. Operational Qualification (OQ)	Y	
DOC-04	Vendor shall provide extractable test report consistent with BPOG extractable protocol.	Y	

DOC-05	Documentation package should be submitted as: 1. one (1) set of documentation as hardcopy, At a minimum, a table of contents, tabs separating each section with the section title appearing on each tab, and page numbers corresponding to the page numbers defined within the table of contents are required. 2. one (1) copy of other documents in PDF format on a suitable medium (e.g. CD/DVD/US)	N	2
DOC-06	The FS should include the following information, as a minimum: control system hardware and software standards; system architecture; alarm list; I/O list; sequence of operations including all safety interlocks.		
DOC-07	The Detailed Design Spec (DDS) should include the following information, in addition to the final version of all documents included in the FS, as a minimum: I/O list, Alarm list, Interlock list, final hardware drawings, including bill of materials; detail wiring diagrams; operations and maintenance manuals for all components		

6 Abbreviations & Acronyms

Abbreviation / Acronym	Description
URS	User Requirement Specifications
cGMP	Current Good Manufacturing Practices
GMP	Good Manufacturing Practices
POL	Process Orchestration Layer
DNP	Discover/Negotiate/Pair technology
MTP	Modular Type Package
PEA	Process Equipment Assembly (currently as per VDI/VDE/NAMUR 2658, Sheet 1)

7 Attachments and References

a. Attachments

#	Title	Doc. No.

b. References

#	Title	Doc. No.
	ASME BioProcessing Equipment Standard	
	21 CFR part 178, certified to USDA H1 or equivalent, animal origin free (AOF) compliance according to EMEA 410/01.	