**User Requirement Specification (URS)**

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# Purpose

This user requirement Specification (URS) describes the user requirements for affected media for [location e.g. building] and includes the functional, operational and data requirements for the systems.

# Area of application

This URS specifies the requirements for the media concerned [e.g. (compressed air, oxygen and purified Water )] for [location e.g. building] at [customer name, address] .

# Terms and abbreviations

## Definitions

**Water qualities**

|  |  |
| --- | --- |
| **Name / Abbreviation** | **use** |
| City water / SW | Manufactured by EW, used for emergency shower |
| Softened water / EW | Production PW, use for dishwasher |
| Purified Water / PW | Buffer and media preparation, rinsing of glassware,  Cooling of exhaust air in the fermenter, steam generation in the autoclave |
| Water for Injection / WFI | Final formulation of the final product |

## 

## Abbreviations

|  |  |
| --- | --- |
| **Expression /** **abbreviation** | **Explanation** |
| DQ | Design qualification |
| FMEA | Failure Mode Effects Analysis​ |
| GMP | Good Manufacturing Practice |
|  |  |
|  |  |

# User Requirements​

Qualification is carried out using a risk-based approach. The qualification procedure and regulatory classification are finally described in the system-specific Qualification Master Plan (QMP) . Based on a GMP relevance analysis (Doc ID GMP-I\_GRA\_GEB\_O2; Oxygen, GMP-I\_GRA\_GEB\_PW; Purified Water and GMP-I\_GRA\_GEB\_DL; compressed air) the media systems were classified as GMP-relevant.

The URS is classified according to its relevance (GxP or safety/economic efficiency) and criticality (necessary/optional).

GxP-relevant points must be considered in the qualification process; safety/economically relevant points must be considered by the engineering/operator. Requirements classified as "necessary" must be implemented; for points classified as "optional," implementation may be waived.

In the "URS#" column of this URS, direct requirements are assigned a number. This number consists of the chapter number of the URS and a sequential number.

## 4.1 Technical standards

The design and implementation of the affected media (generation, storage and distribution) must comply with the relevant local, regional and national regulations (European Union, USA) and correspond to the state of the art.

## Requirements

### 4.2.1 General requirements

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.1-1 | The supplied and installed components must be clearly and permanently marked to clearly identify the medium, flow direction and gradient. | GxP, necessary |
| **Maintenance/Repair** | | |
| 4.2.1-2 | The systems must be serviceable. In particular, the accessibility of system components requiring maintenance must be ensured (if possible from outside the RR). | GxP, necessary |
| 4 .2.1-3 | PW:   * Regular disinfection / sanitization of the system (UV) (e.g. monthly sanitization by 80°C treatment for at least 30 minutes)   Before release:   * Chemical testing * Microbiological results within specification | GxP, necessary |
| **calibration** | | |
| 4.2.1-4 | Only calibrated sensors shall be supplied, allowing easy recalibration. | GxP, necessary |

### Environmental conditions/interfaces

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.2-1 | Construction site of building GMP-I is the factory premises of company, location, street | GxP, necessary |
| 4.2.2-2 | Specification regarding quality ( Ph.Eur ):   * Microbiological * particles * Chemical | GxP, necessary |
| 4.2.2-3 | Use of filters for compressed air before and after drying | GxP, necessary |
| 4.2.2-4 | Manual sampling points must be available after filters in the compressed air in the system | GxP, necessary |
| 4.2.2-5 | Production of PW quality is done via equipment | GxP, necessary |
| 4.2.2-6 | Relevant interfaces are listed in Appendix A1:  GMP- I\_Media\_URS A1 Media connections described | GxP, necessary |

#### Media supply

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.2.1 | All necessary connections for the media supply must be provided | GxP, necessary |
| **Water** | | |
| 4.2.2.1-3 | Initial water quality according to definitions (Chapter 3.1)   * WFI is intended as an option for a qualitative upgrade of the PW system. | GxP, necessary |
| 4.2.2.1-4 | * Connection for heat exchanger (heating PW for sanitization ) * Electricity * Cooling circuit, flow temperature 6 °C, return 12 °C * Connection to process air (fittings) * Oil-free process air: pressure 6.0 bar * Connection to power supply * Normal network: 3 x 230 V/400 V, 50 Hz * Wastewater connection * Processes of the PW generator and the pump | operation, necessary |

### 4.2.3 Structural requirements

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.3-1 | Low dead space design: Dead spaces must be avoided | GxP, necessary |
| 4.2.3-2 | Unless otherwise specified, pipelines must be designed according to the 3-D rule | GxP, necessary |
| 4.2.3-3 | Residual emptying possible (pipelines must have a gradient of at least 1%, ideally 2%, towards the consumer)  no gradient in DL and O 2 | GxP, necessary |
| 4.2.3-4 | All cables must be laid in the cleanroom wall elements (cavity of the walls).  Alternatively, point media columns are permitted. In the technical room, the cables can be laid as an open installation, | GxP, necessary |
| 4.2.3-5 | Manually detachable connections (e.g. Triclamp connections) on pressurized lines must be designed as safety TriClamps | GxP, necessary |
| 4.2.3-6 | The generating plant(s) is to be designed as a pre-assembled compact plant including storage tank, ready for connection and pre-qualified with its own control system in a frame as a package unit | GxP, necessary |
| 4.2.3-7 | All lines (PW/O 2 /DL) made of stainless steel (material 1.4404 (316L) or 1.4435 according to DIN 11866 Series B DF Class 2.) | GxP, necessary |
| 4.2.3-8​ | Sampling points: All sampling points must be freely accessible | GxP, necessary |
| **welding** | | |
| 4.2.3-9 | The manufacturer’s pipe markings must be retained (even for shorter pipe sections after welding) | GxP, necessary |
| 4.2.3-10 | Weld seams must be pickled to remove any tarnish or scale on the outside. Weld seams must be subjected to a penetration test wherever possible. This must be documented.  Not applicable for oxygen distribution | GxP, necessary |
| 4.2.3-11 | Areas not accessible for penetration testing must be 100% inspected endoscopically  Penetration testing of welds is not required for mechanical welding processes. | GxP, necessary |
| 4.2.3-12 | Preferably orbital welding | GxP, necessary |
| 4.2.3-13 | Distribution: for each medium according to the appendix media connections ( PW: ring line, avoid branch lines at taps, O 2 : branch line, DL: branch line) | GxP, necessary |
| **Valves and detachable connections** | | |
| 4.2.3-14 | Shut-off valves: Diaphragm valves (2/2-way) or ball valves  Extraction valves: ~~T-~~ diaphragm valves | GxP, necessary |
| 4.2.3-15 | Detachable connections: If clamp connections are required, clamp connections according to DIN 32676 must be used | GxP, necessary |

#### 4.2.3.1 Drawings and plans

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.3.1-1 | Creation and delivery of P&I flow diagrams (PDF and DWG format)  Uniform component marking in P&ID | GxP, necessary |
| 4.2.3.1-2 | Isometries of the piping ( as built ) with position of the numbered welds  In the compressed air system, pipes are pressed. | GxP, necessary |
| 4 .2.3.1-3 | P&I must be marked with medium, flow direction, gradient (no gradient for DL and O 2 ), diameter  Also tank and container details, as well as valves, filters, extraction points, waste water pipes | GxP, necessary |

#### 4.2.3.2 Material/Surfaces

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.3.2-1 | Hygienic Design:   * Smooth, free of cracks, dense * Gaps, sharp edges and dead spaces must be avoided * easy to clean | GxP, necessary |
| 4.2.3.2-2 | Product contact areas:  Metal. Material 1.4404 (316L) or 1.4435 according to DIN 11866 Series B DF Class 2. 1.4571 may also be used for sensors. | GxP, necessary |
| 4.2.3.2-3 | Non-metallic parts in contact with the product (e.g., membranes) must be made of GMP-compliant, plasticizer-free plastic. The non-metallic material of the PW piping system must withstand a temperature of at least 80°C. | GxP, necessary |
| 4.2.3.2-4 | Non-product contact areas: Material 1.4301 or better. | GxP, necessary |
| 4.2.3.2-5 | Surface finish in contact with the product:  Ra≤0.8 µm, electropolished | GxP, necessary |
| 4.2.3.2-6 | Internal surfaces of the pipes should  be oil/grease free.  The pipes should  be tested for leaks (test pressure ≥1.5 x operating pressure). | GxP, necessary |
| 4.2.3.2-7 | Filter:  maximum pore size 0.22 µm | GxP, necessary |
| 4.2.3.2-8 | Lubricant:   * must be at least food grade (proof of conformity according to NSF-H1) * TSE certified (free from materials of animal origin) | GxP, necessary |
| 4.2.3.2-9 | Initial cleaning and passivation of water pipes | GxP, necessary |

#### 4.2.3.3 Performance data

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| **Purified Water** | | |
| 4.2.3.3 | The system must meet the specifications for PW generation and distribution. | GxP, necessary |
| **compressed air** | | |
| 4.2.3.3-9 | Compressed air ( ISO 8573-1 Class 1.2.1 to be monitored):   * Operating pressure: ≥6.0 bar (g) | GxP, necessary |
| **oxygen** | | |
| 4.2.3.3-10 | Oxygen (to be monitored):   * Operating pressure: ≥9.0 bar (g) | GxP, necessary |
| 4.2.3.3-11 | Product description/declaration: “Oxygen KW-free”  Specification:   * Purity: ≥ 99.6% * H 2 O: ≤ 5 ppm * HC: ≤ 0.1 ppm * CO2 : ≤ 1 ppm * N 2 + Ar: ≤ 4000 ppm   (Information is to be understood as ideal volume fractions (=molar fractions)) | GxP, necessary |

### Safety requirements

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.4-1 | Piping systems must be able to be safely depressurized. | GxP, necessary |
| 4.2.4-2 | After the main power is shut down or in the event of a main power failure, the affected system or subsystem must return to a safe state. When power is restored, the system must not restart automatically.  There must be no hazards from affected systems/partial systems | Security, necessary |
| 4.2.4-3 | Systems must be designed in accordance with Machinery Directive 2006/42/EC. | Security, necessary |
| 4.2.4-4 | Vessels and pipes covered by the Pressure Equipment Directive must be designed in accordance with 2014/68/EU. | Security, necessary |
| 4.2.4-5 | All electrical equipment must be designed in accordance with the Low Voltage Directive 2006/95/EC. | Security, necessary |
| 4.2.4-6 | Noise pollution: The generating plant has a maximum sound pressure of 80 dB(A). | Security, necessary |
| 4.2.4-7 | All electrical and EMSR components used must correspond to the respective environmental requirements in terms of their protection class, so that safe system operation is guaranteed. | Security, necessary |
| **oxygen** | | |
| 4.2.4-8 | Shut-off valve must be present with BMZ (emergency stop in case of fire alarm) | GxP, necessary |

### Process requirements

|  |  |  |
| --- | --- | --- |
| **URS#** | **Description** | **Classification** |
| 4.2.5-1 | Constant volume flow at tapping points | GxP, necessary |
| 4.2.5-2 | The same quality must be available at every sampling point at all times | GxP, necessary |
| 4.2.5-3 | For PW, the following process conditions must be considered. The pressure at the final consumer must be set at 3 bar. | GxP, necessary |

### Functional requirements

|  |  |  |
| --- | --- | --- |
| **URS#** | **Description** | **Classification** |
| 4.2.6-1 | Calibration of the sensors must be present | GxP, necessary |
| 4.2.6-2 | Monitoring of critical parameters: triggering alarms  Normal state: no alarm  . Overshoot/undershoot: alarm (acoustic or visual) | GxP, necessary |
| 4.2.6-3 | Operating mode: Fully automatic, continuous operation should be ensured | GxP, necessary |
| 4.2.6-4 | The PW system must be sanitizable ( e.g. 30 min / 80°C cycles with tolerance) | GxP, necessary |

### Monitoring

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.7-1 | Monitoring of previously defined critical parameters | GxP, necessary |
| 4 .2.7-2 | The system must be able to trigger alarms in case of violation of GMP-relevant limits | GxP, necessary |
| 4.2.7-3 | An overview of maintenance and fault messages in the system must be presented, this includes in particular alarm messages | GxP, necessary |
| 4.2.7-4 | Documents and data must be easily accessible to users | GxP, necessary |
| 4.2.7-5 | Data (monitoring) is recorded and archived | GxP, necessary |
| 4.2.7-6 | Data must be protected from manipulation by unauthorized persons (within the organization as well as during transmission) | GxP, necessary |
| 4.2.7-7 | Data must be made readable/durable for the entire retention period | GxP, necessary |
| 4.2.7-8 | PW monitoring   * Continuous monitoring of conductivity in the flow and return lines * Continuous monitoring of TOC in the return line | GxP, necessary |
| 4.2.7-9 | * PW storage temperature: 20°C ± 2°C * Conductivity: see URS# 4.2.3.3-3 * Sanitizing temperature : ≥ 80°C * Flow velocity: 2-4 m/s | GxP, necessary |

#### Requirements for security and access and authorization controls

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.7.1 | Multiple security levels and audit trail must be implemented | GxP, necessary |
| 4.2.7.1-1 | The system must be protected either by physical access control or by changing passwords | GxP, necessary |
| 4.2.7.1-2 | The system must provide several levels of security depending on the user's responsibilities | GxP, necessary |
| 4.2.7.1-3 | The system must generate an audit trail | GxP, necessary |
| 4.2.7.1-4 | Fail-safe operation including data storage via UPS (uninterruptible power supply) | GxP, necessary |

#### Backup and recovery requirements

|  |  |  |
| --- | --- | --- |
| **URS#** | **Description** | **Classification** |
| 4.2.7.2-1 | enable backup and recovery functionality­ | GxP, necessary |

#### Data Integrity Requirements

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.7.3-1 | The system generates electronic records as defined in 21 CFR 11, EU GMP Annex 11 or other regulations | GxP, necessary |
| 4.2.7.3-2 | Electronic data is archived on an internal server | GxP, necessary |

#### Hardware requirements

|  |  |  |
| --- | --- | --- |
| **URS#** | **Description** | **Classification** |
| 4.2.7.4-1 | Standard hardware components from well-known manufacturers must be used | GxP, necessary |

#### Software requirements

|  |  |  |
| --- | --- | --- |
| **URS#** | **Description** | **Classification** |
| 4.2.7.5-1 | Standard software components from well-known manufacturers must be used (e.g. Microsoft Windows, Microsoft SQL database) in accordance with GAMP requirements | GxP, necessary |
| 4.2.7.5-2 | Security patches and updates are installed by the maintenance technician during inspection/maintenance according to previously agreed rules | GxP, necessary |

### Documentation and training requirements

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.8 | The documentation must be prepared in German and must include all relevant lists and electrical documentation. | GxP, necessary |
| 4.2.8-1 | The complete documentation must be in German | GxP, necessary |
| 4.2.8-2 | The documentation must be delivered in one copy in paper form (filed in DIN A4 folders including table of contents) and on a data storage device (USB stick) | GxP, necessary |
| 4.2.8-3 | Uniform labeling of all components and parts in all documents | GxP, necessary |
| 4 .2.8-4 | Version control of all manufacturer documents must be ensured by means of a change history | GxP, necessary |
| 4.2.8-5 | All documents must be finalized by the time of acceptance (SAT) | GxP, necessary |
| 4.2.8-6 | EC declaration of conformity for all components of the scope of delivery | GxP, necessary |
| 4.2.8-7 | CE marking | GxP, necessary |
| 4.2.8-8 | Initial calibration of the sensors | GxP, necessary |
| 4.2.8-9 | Functional description | GxP, necessary |
| 4.2.8-10 | Recommendations/instructions including manufacturer's schedules regarding maintenance/servicing | GxP, necessary |
| 4.2.8-11 | Test certificates of the welders and testing personnel employed | GxP, necessary |
| 4.2.8-12 | Endoscopic inspection of all hand welds  Not applicable for oxygen distribution | GxP, necessary |

#### Lists

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.8.1-1 | Spare parts list with storage recommendations | GxP, necessary |
| 4.2.8.1-2 | Wear parts list  Except DL distribution | GxP, necessary |
| 4.2.8.1-3 | Warning and alarm list (list and explanation of all alarm functions and error messages depending on the operating status including the system's response) | GxP, necessary |
| 4.2.8.1-4 | Parameter list | GxP, necessary |
| 4.2.8.1-5 | Component list | GxP, necessary |
| 4.2.8.1-6 | Measuring device list | GxP, necessary |
| 4.2.8.1-7 | A measuring point plan must be created | GxP, necessary |
| 4.2.8.1-8 | A calibration specification list for relevant measuring points with description and acceptance criteria must be created | GxP, necessary |
| 4.2.8.1-9 | A maintenance schedule must be created | GxP, necessary |

#### Electrical documentation

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.8.2-1 | A cable list must be created | GxP, necessary |
| 4.2.8.2-2 | A circuit diagram must be available in “ as-built ” version | GxP, necessary |
| 4.2.8.2-3 | Certificate of compliance with safety regulations (CE conformity for control cabinet) | GxP, necessary |

#### Operator documentation

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.8.3-1 | Logbooks must be available or created if necessary | GxP, necessary |
| 4.2.8.3-2 | Technical data sheets or manuals must be provided (including sensors) | GxP, necessary |
| 4.2.8.3-3 | Instructions for the operation/safeguarding/maintenance of media (maintenance, servicing, calibration, operation) and clean room conditions (monitoring) | GxP, necessary |

#### Material quality

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.8.4-1 | For materials that come into contact with the product, at least tool certificates 2.2 are required | GxP, necessary |
| 4.2.8.4-2 | Declarations of Conformity according to 21 CFR 177 | GxP, necessary |
| 4.2.8.4-3 | Certificates surface roughness | GxP, necessary |
| 4.2.8.4-4 | Welding report, welding protocol | GxP, necessary |
| 4.2.8.4-5 | Final assembly test report/acceptance test certificate | GxP, necessary |
| 4.2.8.4-6 | Carrying out a pressure test | GxP, necessary |
| 4.2.8.4-7 | Filter certificate (separation efficiency and suitability) | GxP, necessary |

#### Training requirement

| **URS#** | **Description** | **Classification** |
| --- | --- | --- |
| 4.2.8.5-1 | Initial operator training must be provided | GxP, necessary |

# Cited or relevant documents

GMP-I\_GRA\_GEB\_O2 GMP Relevance Analysis Oxygen

GMP-I\_GRA\_GEB\_DL GMP Relevance Analysis Compressed Air

GMP-I\_GRA\_GEB\_PW GMP relevance analysis PW

21 CFR Title 21 of Code of Federal Regulations

AMWHV Medicinal Products and Active Substances Manufacturing Ordinance

EU-GMP Part II Basic requirements for active substances used as

and Annices starting materials

# Attachments

GMP- I\_Media\_URS A1 Media connections

GMP- I\_Medien\_URS A2 Block flow diagram PW generation and distribution