INTERNATIONAL STANDARD

ISO 22519

First edition
2019-06

Purified water and water for injection pretreatment and production systems

Systèmes de prétraitement et de production d'eau purifiée et d'eau d'injection

Reference number
ISO 22519:2019(E)

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 282, *Water reuse*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

A large variety of water systems exists today in the Biopharma market; often these water systems are of differing levels of efficiency and have different maintenance needs. Water quality for Purified Water (PW) and Water for Injection (WFI) is specified in national and international standards, but a standardized system for producing PW and WFI is not in place.

This document provides a standard benchmark that can be used by the industries that use PW and/or WFI, national governments, state authorities and regulatory bodies to evaluate PW/WFI systems.

This document

— allows users to specify water systems that fit specific needs without being experts in the water system field;

— allows users to decide whether the offered systems are safe, efficient and sustainable;

— enables national governments, state authorities and regulatory bodies to perform professional audits;

— provides auditors a standard check list to harmonize equipment and systems in the water industry;

— sets a high benchmark for suppliers of water systems all over the world, to be used as a point of reference for their systems and;

— will improve reliability of the water generation process methods and water product while reducing downtime needed for scheduled and non-scheduled maintenance.

This document also defines technical terms related to PW and WFI generation.

See Annex A, "examples of PW production systems".

See Annex B, "examples of feed water categories".

See Annex C, "system selection table".

See Annex D, "configuration of typical integrity test for polishing UF".

Purified water and water for injection pretreatment and production systems

1 Scope

This document specifies design, materials selection, construction and operation of Purified Water (PW) and Water for Injection (WFI) pretreatment and membrane-based production systems.

As many different types of feed water are possible, different components and configurations are presented. A decision matrix is provided to give guidance for the different types of feed water.

This document excludes

— selection of the appropriate compendial water definition per system: e.g. PW, WFI or other;

— thermal process for generation of PW/WFI;

— loops, storage and distribution;

— pure steam generation and distribution;

— laboratory water systems and

— validation.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 20670, *Water reuse — Vocabulary*

3 Terms, definitions and abbreviated terms

For the purposes of this document, the following terms and definitions given in ISO 20670 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1 Terms and definitions

3.1.1
pretreatment
equipment and process stages before (upstream) high pressure RO pump

3.1.2
production system
equipment and process stages after (downstream) high pressure RO pump

Note 1 to entry: If there is a tank, before the high pressure RO pump, then the tank can be included in the production system.

3.1.3
pretreatment ultra filtration
pretreatment UF
membrane based process for removal of suspended solids, bacteria and TOC upstream of RO

Note 1 to entry: Usually operated with a reject stream and cleaned with a back wash.

3.1.4
MMF
multi media filter
layered filtration media in a pressurized container, used to reduce the level of suspended solids (turbidity) in incoming feed water

Note 1 to entry: Media layers can consist of anthracite, sand and garnet.

3.1.5
flushed screen/disc filter
FS/DF
filter based on a static screen with a water flush of the cake that builds up on the screen

3.1.6
chlorination
dosage/generation of Hypochlorite/Chlorine to generate controlled free chlorine levels in the system

3.1.7
softener
pressurized container of softening resin for replacement of hardness ions, calcium, magnesium, barium and strontium, with the sodium ion

3.1.8
antiscalant
AS
chemical scale inhibitor or sequestering agent that minimize the potential for scale precipitation on the reject surface of a RO membrane

3.1.9
electric scale control
ESC
electrolytic scale inhibitor that minimizes the potential for scale precipitation on the reject surface of a RO membrane

3.1.10
activated carbon filter
ACF
granular activated carbon (GAC) pressurized container of activated carbon media for removal of free chlorine, chloramines and Total Organic Carbon (TOC)

3.1.11
degassing CO_2 contact membrane
degasser
microporous hollow fiber membrane that brings into direct contact a liquid and strip gas and/or vacuum

Note 1 to entry: The dissolved gas in the liquid will pass though the membrane and into the strip gas and/or vacuum on the other side of the membrane.

3.1.12
ultra violet (UV) lamp
irradiation of water with UV light in wavelengths ranging from 180 nm to 350 nm

3.1.13
microfiltration
MF
pressure driven separation process designed to remove particles and macromolecules. MF is usually installed as part of the pre-treatment for other downstream process

Note 1 to entry: The nominal filtration sizes are 0,05 micron to 2 micron.

3.1.14
single pass reverse osmosis
SPRO
single pass membrane based process to separate dissolved ions and suspended solids

3.1.15
double pass reverse osmosis
DPRO
double pass membrane-based process to separate dissolved ions and suspended solids

3.1.16
continuous electro de-ionization
CDI/EDI/CEDI
process for ion removal from water utilizing: electricity, ion exchange membranes and resin

3.1.17
polishing ultra filtration
polishing UF
membrane based process using molecular weight cut off 6 000 or smaller for reduction of endotoxin, TOC and bacteria post RO or post CDI/EDI/CEDI

3.1.18
anion and cation de-ionizers
separate pressurized containers of anion ion exchange resin and cation ion exchange resin, for removal of both cations and anions

Note 1 to entry: Resins are regenerated on site or off site.

3.1.19
single use mixed bed polisher
pressurized containers of mixed anion and cation ion exchange resin for removal of both cations and anions

Note 1 to entry: Resins are regenerated off site.

3.2 Abbreviated terms

ACF	activated carbon filter
AS	antiscalant
BW	butt welding
CD	chlorine dioxide
CFU	colony forming units
CIP	cleaning in place
CIT	conductivity indicator and transmitter
CLIT	chlorine indicator and transmitter

DPRO	double pass RO
EP	European Pharmacopeia
EPDM	ethylene propylene diene monomer
ESC	electric scale control
FAT	factory acceptance test
FIT	flow indicator and transmitter
FRP/PE	fibre reinforced plastic (on) polyethylene
FS/DF	filter screen/disk filter
GAC	granular activated carbon
GMP	good manufacturing practice
HOD	hydro optical dechlorination
HP	high pressure
HSDS	Human Services Data Specification
HWS	hot water sanitization
ID	inside diameter
IQ	Installation Qualification
ISPE	International Society for Pharmaceutical Engineering
JP	Japanese Pharmacopeia
L/D	ratio between piping/tubing length/diameter
LT	level transmitter
MF	microfiltration
MMF	multimedia filter
MP	mechanical polish
NA	non applicable
NaOH	sodium hydroxide
NFPA	National Fire Protection Association
NR	not recommended
OSHA	Occupational Safety and Health Administration
ORP	oxidation reduction potential
OQ	Operational Qualification
P	possible

PEEK	polyether ether ketone
PFA	perfluoralkoxy alkanes
PI	pressure indicator
PIT	pressure indicator and transmitter
POU	point of use
PPP	PW/WFI pretreatment and production
PQ	Performance Qualification
PS	pure steam
PTFE	polytetrafluoroethylene
PVC	polyvinyl chloride
PW	Purified Water
QIT	quantity indicator and transmitter
R	recommended
RO	reverse osmosis
SBS	sodium bi sulfite
S&D	Storage and Distribution
SOP	standard operating procedure
SPRO	single pass reverse osmosis (RO)
SS	stainless steel
TC	Tri Clamp
TDS	total dissolved solids
TIG/GTAW	Tungsten Inert Gas/Gas Tungsten Arc Welding
TT	temperature indicator
TOC	total organic carbon
UF	ultrafiltration
URS	User Requirements Specifications
USP	US Pharmacopeia
WFI	Water for Injection

4 Design and practices

4.1 Setting system boundaries

4.1.1 A PW/WFI Pretreatment and Production system starts at the valve (inclusive) before the first supplied water filter component/MMF.

4.1.2 A PW/WFI Pretreatment and Production system end boundary is at the inlet valve (inclusive) of the PW/WFI storage tank or at the POU if a tank is not installed.

4.1.3 The PW/WFI storage tank should not be included in the PW/WFI Pretreatment and Production.

4.1.4 "Industrial" treatment systems upstream to the PW/WFI Pretreatment and Production, including supply to other plant utilities e.g. steam boilers, potable water usage, feed to cooling towers etc. should not be included in the PW/WFI Pretreatment and Production.

4.2 General system requirements

4.2.1 A "build clean" concept shall be employed during the installation of PW/WFI Pretreatment and Production systems: supply of piping/tubing and equipment in clean condition and installation methods that prevent ingress of contaminants.

4.2.2 Incoming feed water shall meet local standards or WHO standards for potable water. If this is not the case, additional systems shall be installed to improve the water feed parameters before the PW/WFI Pretreatment and Production.

4.2.3 The PW/WFI Pretreatment and Production water quality shall show improvement in all quality parameters as the water advances through the system.

4.2.4 The following parameters shall be steadily reduced at each stage in the system:

— microbial total count;

— conductivity and;

— TOC.

4.2.5 PW/WFI quality shall be according to the last revision of the local/national/relevant Pharmacopoeia. Table 1 provides recommended water quality.

Table 1 — Recommended water quality

#	Parameter	RO feed	After RO	PW	WFI
1	Hardness (PPM $CaCO_3$)	≤ feed water	< 1	< 1	< 1
2	TOC (ppb)	≤ feed water	< 500	< 500 (online)	< 500 (online)
3	Endotoxin (EU/ml)	NA	NA	NA	< 0,25
4	Microbial total count (cfu/ml)	< 500	< 200	< 100	< 10 cfu/100 ml
5	Free Chlorine (ppm)	< 0,05	< 0,05	< 0,05	< 0,05
6	*Pseudomonas* (cfu/100 ml)	< 1	< 1	< 1	< 1
Conductivity shall be measured uncompensated at 25 °C according to USP.					

Table 1 *(continued)*

#	Parameter	RO feed	After RO	PW	WFI
7	*E. coli* (cfu/100 ml)	< 1	< 1	< 1	< 1
8	Total coliforms, Fungus, (cfu/100 ml)	< 1	< 1	< 1	< 1
9	Conductivity (µS/cm)	Like feed water	< 10	< 1,3 (online)	< 1,3 (online)
Conductivity shall be measured uncompensated at 25 °C according to USP.					

4.2.6 A sampling programme with acceptance criteria shall be in place to gather, analyse and document this water quality improvement.

4.2.7 During production, the PW/WFI Pretreatment and Production shall control the maximum water temperature in the system. During production, the maximum temperature of the warmest point in the system shall be no more than 25 °C (guidance value).

4.2.8 All parts of the PW/WFI Pretreatment and Production shall be hot water sanitized, from the feed water inlet valve to the PW/WFI fill valve. During sanitization, the PW/WFI Pretreatment and Production shall control the water temperature in the system. During sanitization, the all the points of the system should be at a minimum of 80 °C (guidance value).

4.2.9 The PW/WFI Pretreatment and Production system shall be designed, controlled, regulated, operated and maintained to ensure that the final water quality reliably meets final water quality standard set in 4.2.5. This performance shall be stable under all conditions including common worst-case scenarios, changing seasons or other fluctuating environmental conditions.

4.3 User Requirements Specifications (URS) scope

The scope of the User Requirements Specifications shall include the following;

— selection of water compendial standard based on products supplied;

— specification of the final water standard parameters;

— safety and Good Manufacturing Practice requirements for the system;

— list of main components;

— preliminary sizing of production flow rate;

— number of production units;

— functional requirements;

— materials of construction;

— equipment surface finish;

— biological control concept;

— high level control: interlocks, alarms and warnings;

— documentation required (see Clause 14);

— validation as required by respective authorities and;

— Performance Qualification (PQ) monitoring parameters.

The scope of the User Requirements Specifications shall include analysis of incoming water over all yearly seasons, both chemical and microbiological.

4.4 Detailed system capacity calculation

4.4.1 Data and/or estimates of current and future PW/WFI use shall be used to size the flow rate of the PW/WFI Pretreatment and Production System.

4.4.2 The flow rate shall be analysed in conjunction with the worst-case consumption scenario, taking into account PW/WFI storage tank size.

4.4.3 A full tabulation of all users, present and future, shall be compiled, listing the quantity of PW/WFI required, per day, per hour over a week period. The draw off flow shall be calculated, from the Storage and Distribution (S&D), per hour of the day and plot the storage tank levels for a full week. In some cases listing of required PW/WFI and take off flow calculations for a period that exceeds one week may be necessary. In such cases the evaluation period shall be extended accordingly.

4.4.4 Once this information has been summarized, the sizing for the PW/WFI Pretreatment and Production and PW/WFI storage tank may be determined.

5 Selecting materials, methods and system components

5.1 Recommended system components/treatment stages

5.1.1 Pretreatment, ultra filtration and microfiltration– membrane based process for removal of suspended solids, bacteria and TOC upstream of RO.

NOTE Pretreatment UF is usually operated with a reject stream and cleaned with a back wash.

5.1.2 MMF – removal of coarse particulates pre RO in the range of 30 micron – 50 micron cleaned by back flush of water to drain.

5.1.3 Flushed Screen/Disc Filters (FS/DF) – removal of coarse particulates upstream of RO in the range of 30 micron – 50 micron.

5.1.4 Chlorination – dosage and/or generation of hypochlorite and/or chlorine to generate free chlorine levels in system with a range of 0,2 ppm – 0,5 ppm (with suitable contact time) for control of incoming and system bacteria levels.

5.1.5 Chlorine dioxide (CD) – generation and dosage of chlorine dioxide to a range of 0,1 ppm – 0,4 ppm (with suitable contact time) for control of incoming and system bacteria levels.

5.1.6 Softeners – for replacement of magnesium-calcium, barium and strontium with sodium to reduce scale precipitation on the RO membranes with a recommended downstream 10 micron – 20 micron resin trap.

5.1.7 Antiscalant (AS) – addition of chemicals to RO feed water to defer hardness precipitation on the RO membranes.

5.1.8 Electric scale control (ESC) – resin free electrolytic precipitation of scale to stop hardness precipitation on the RO membranes. Also used for heavy metal oxidation and removal. Non sacrificial anode and cathode.

5.1.9 Active carbon filter (ACF)/Granular Active Carbon (GAC) – removal of oxidizers, chlorine/chloramine, TOC, upstream of RO membranes.

5.1.10 Sodium Bi Sulfite (SBS) – (or other sulfite based) chemical addition pre RO for reduction of oxidizers, chlorine/chloramine.

5.1.11 Sodium Hydroxide (NaOH) - addition of chemical for pH control upstream of RO membranes to control CO_2 in RO permeate.

5.1.12 Degassing CO_2 contact membrane (degasser) – water contact membrane for reduction of CO_2 gas in water upstream of RO and CDI/EDI/CEDI. Fabricate degasser housing from SS 316L and the membrane will resist hot water sanitization so the degasser will be able to undergo hot water sanitization. Clean, dry, oil free compressed air will sweep through a filter and into the membrane housing for CO_2 removal. Optionally if appropriate compressed air is not available, air can be drawn through the housing by a vacuum pump. The outside air shall be filtered before being drawn through the housing.

5.1.13 Ultra Violet (UV) Lamp – irradiation of the water for dechlorination of chlorine/chloramine, upstream of RO membranes. A UV lamp may also be used for microbial load reduction. The feed water is de-chlorinated by exposure to ultraviolet irradiation by degrading the free chlorine into an Oxygen molecule (O_2) and a Chloride ion. The unit sizing should reduce a minimum of 0,5 ppm free chlorine to safe levels of < 0,02 ppm. The unit can include a UV-MPL (medium pressure lamp) – with wide emission spectrum. The unit housing may be fabricated from SS 316 and the internal parts from SS 316 or high-grade Quartz." Design the UV for hot water sanitization.

5.1.14 Single Pass Reverse Osmosis (SPRO) – membrane based process for reduction of: ions, TOC, bacteria and endotoxin. Always operated with a reject stream.

5.1.15 Double Pass Reverse Osmosis (DPRO) – membrane based process for reduction of: ions, TOC, bacteria and endotoxin. The first pass permeate is the feed to the second pass. Always operated with a reject stream.

5.1.16 Continuous Electro De-Ionization (CDI/EDI/CEDI) – for reduction of water ion levels downstream of RO using electrically regenerated resin.

5.1.17 Polishing Ultra filtration - Is a membrane based process using molecular weight cut off 6 000 or smaller for reduction of endotoxin, TOC and bacteria or post CDI/EDI/CEDI.

5.2 Advantages and disadvantages of system components/treatment stages

System components/ treatment stages	Advantages	Disadvantages
MMF	— cost effective for a large range of flow rates; — simple and reliable; — operates with a wide range of free chlorine levels and; — back washing enables self-cleaning without replacement of media.	— filtration range limited to 10–50 micron nominal; — regular replacement of the media needed and; — will always grow microbiological contamination if feed is over the minimum temperature.
Pretreatment ultra filtration	— cost effective for a high flow rates; — very effective removal of organics, viruses, particulates; — operates with a wide range of free chlorine levels and; — back washing enables self-cleaning without replacement of media.	— need to operate with a reject stream; — regular back washing of membrane needed and; — can have higher investment than MMF on lower flow rates.
Flushed Screen/Disc Filters	— cost effective for a large range of flow rates; — simple and reliable; — no media to be replaced or to get contaminated; — operates with a wide range of free chlorine levels and; — back flushing enables self-cleaning.	— is not always effective in high load feed waters as filtration range limited to 30–100 micron nominal.
Chlorination: dosage/electro-generation	— keeps pretreatment clear of most bacteria; — maintains a residual throughout the system and; — easy to control and easy to test free chlorine levels.	— can be hard to control if side stream through chlorine analyser not stable and; — incomplete removal can damage RO membranes and CEDI.
Chlorine dioxide	— very effective against biofilm; — maintains a residual throughout the system and; — easy to control and easy to test chlorine dioxide levels.	— hazardous to generate and handle; — short shelf life and; — incomplete removal can damage RO membranes and CEDI.

System components/ treatment stages	Advantages	Disadvantages
Softeners	— simplicity and; — low cost.	— salt handling and usage, need constant makeup; — waste of water for regenerations and rinses; — disposal of spent brine solution; — sends high chloride effluent to drain; — not environmentally friendly; — in certain areas, brine discharge to sewer systems may be restricted or banned; — collects organic and inorganic particles and contamination; — will grow microbial colonies when the feed water is above a certain minimum temperature even if exposed to chlorine; — multifunctional valve with low reliability.
Anti scalant	— low investment cost and; — low operational cost.	— antiscalant effectiveness fluctuates widely as a function of incoming water quality; — RO permeate needs to be chemical free and show full removal of antiscalant chemicals; — need for constant fresh antiscalant makeup; — antiscalant can be media growth medium for bacteria and; — high incidence of unplanned cleaning due to scaling and fouling.
Electric scale control	— media free operation without resins; — chemical free operation; — generates free chlorine from incoming feed water chlorides; — actively reduces microbiological contamination; — stainless steel construction allows full hot water sanitization; — low power usage — no moving parts, simple operation and; — very low maintenance.	— investment costs can be more than softeners and anti scalant; — need to circulate constantly and; — scale needs to be removed at regular intervals by manual or automatic means;

System components/ treatment stages	Advantages	Disadvantages
Active carbon filter	— effective for organics reduction and; — reliable removal of free chlorine and chloramines;	— rapid and unavoidable bacterial build up; — regular sanitizations needed and; — shedding of carbon fines that foul downstream equipment and; — medium to high capital cost for thermally sanitized units and; — water waste due to back flushing and forward rinses.
Sodium meta bi sulfite	— low cost;	— low reliability, when the pump stops then water production stops; — unreliable Oxidation-Reduction Potential (ORP) instrumentation for system control; — risk of catastrophic failure of RO membranes and CDI/EDI/CEDI hydraulic stack due to break though of free chlorine or chloramines and; — need for constant fresh solvent makeup because of short shelf life.
Sodium Hydroxide dosage	— low cost and; — effective for reducing large levels of incoming CO_2;	— hard to control accurately; — pH instrumentation complicated and high maintenance; — needs regular makeup of solutions and; — hazardous to handle.
Degassing CO_2 contact membrane	— simple, no moving parts; — low maintenance and; — effective for reducing small to medium levels of incoming CO_2;	— high investment costs; — high operational costs (compressed air) and; — can be overwhelmed by high levels of incoming CO_2.
Ultra Violet (UV) Lamp for dechlorination	— media free operation without resins; — chemical free operation; — removes free chlorine from incoming feed water; — actively reduces microbiological contamination; — allows full hot water sanitization; — no moving parts, simple operation and; — very low maintenance.	— high investment costs and; — not highly effective in removal of chloramine;

System components/ treatment stages	Advantages	Disadvantages
Single Pass Reverse Osmosis	— effectively removes most feed water contamination; — allows full hot water sanitization; — well known and; — relatively low maintenance.	— sensitive to low levels of free chlorine; — susceptible to fouling, biofilm growth and scaling; — hot water sanitizable system are of medium to high investment and; — always need a reject stream to drain.
Double Pass Reverse Osmosis	— very effectively removes most feed water contamination; — more reliable permeate conductivity than single pass reverse osmosis; — allows full hot water sanitization; — well known and; — relatively low maintenance.	— sensitive to low levels of free chlorine; — susceptible to fouling, biofilm growth and scaling; — are larger and more complicated than single pass RO; — hot water sanitizable system need high investment and; — always need a reject stream to drain.
Continuous Electro De-Ionization	— very effectively reduces RO permeate conductivity; — allows full hot water sanitization; — no regeneration chemicals; — well known and; — relatively low maintenance.	— very sensitive to low levels of free chlorine even downstream to RO; — susceptible to fouling, biofilm and scaling and; — are expensive to replace;

System components/ treatment stages	Advantages	Disadvantages
Polishing Ultra filtration	— very effectively reduces RO permeate bacteria and endotoxin levels; — allows full hot water sanitization and; — simple dead end operation without reject stream.	— medium capital cost and; — needs regular integrity testing.
Anion and Cation de-ionizers	— low conductivity product.	— high cost of operations on high Total Dissolved Solid (TDS) feed water; — regeneration on site uses large amounts of: water, base and acid solutions; — ion exchange resin can become the source of organic contamination; — changing product water quality, the water after a regeneration will be different than just before a regeneration; — liable to produce high TOC product water and; — down time of system for regenerations.
Single use mixed bed polisher	— low capital cost.	— polisher replacement necessitates opening the piping system downstream of RO and can introduce contaminants into product water and; — high operational costs.

5.3 Materials of construction — General

5.3.1 All components in the PW/WFI Pretreatment and Production system shall be manufactured from Stainless Steel (SS) 316/316L. All PW/WFI contact parts to be fabricated from SS 316L, including: piping/tubing, tanks, pumps, heat exchangers, valves, instruments and other accessories.

5.3.2 Additional materials that shall be used are as following:

— EPDM;

— PTFE-Polytetrafluoroethylene (PTFE);

— fluoroelastomers (FKM PEEK);

— PFA;

— high grade (low impurity) fused quartz and;

— other non-corroding, hot water sanitization (HWS) resistant, non-particle shedding and non-leaching materials.

5.3.3 For materials of construction, exposure to hot water sanitization at 80 °C – 90 °C shall be taken into account.

5.3.4 Elastomers and plastics shall be compatible with national regulations.

5.4 Stainless steel (SS) piping — General

5.4.1 SS piping/tubing in contact with free chlorine and/or low conductivity water shall be SS 316/316L

5.4.2 SS tubing shall have dimensions as per national standards.

5.4.3 Tubing may be seamless or welded with seam.

5.4.4 Material used for piping and fittings shall meet the pressure requirements for the system and specifically for the high pressure RO feed and concentrate.

5.4.5 Welding shall be performed with TIG/GTAW 99,97 % or better, argon shield gas shall be used.

5.4.6 The dimensions of the physical air break shall be at least 50 mm from the bottom of piping/tubing to the highest point on the drain. Piping/tubing shall have identification labels within line of sight of access areas. The content of the piping and direction of flow shall be clearly indicated.

5.4.7 Gaskets shall be one of the following:

— EPDM encapsulated with PTFE gaskets;

— full EPDM;

— full PTFE-Polytetrafluoroethylene (PTFE);

— silicon;

— fluoroelastomers and;

— combinations of inert, Hot Water Sanitization (HWS) resistant, non-particle shedding and non-leaching elastomers.

5.4.8 Dead legs:

— Dead Legs shall be measured by the term L/D, where L is the leg extension from the inside diameter wall normal to the flow pattern or direction and D is the inside diameter of the extension or leg of a tubing fitting or the nominal dimension of a valve or instrument and;

— Dead legs should be avoided where ever possible, otherwise L/D ratio should be 3:1 or less.

5.5 Non-final product water piping/tubing in the PW/WFI pretreatment and production

5.5.1 Only butt welding for piping/tubing welding shall be used.

5.5.2 Butt-welding may be manual or by orbital welding machine. Inspection with borescope and passivation is not required.

5.5.3 Piping/tubing standards shall be 3A/food grade with flange or Tri Clamp (TC) connections.

5.5.4 Piping/tubing internal finish may be polished or standard mill surface finish.

5.5.5 Valves installed may be of the following types: ball, angle, diaphragm, needle and butterfly.

5.5.6 Threaded connections shall not be used.

5.6 Piping/tubing in contact with PW/WFI product

5.6.1 Minimum acceptable ID polish shall be Ra ≤ 0,6 micron.

5.6.2 Butt-welding shall be by orbital welding machine where ever possible, a minimum of 70 % of automatic welds shall be inspected and 100 % of manual welds with borescope shall be inspected.

5.6.3 Welding shall be performed with TIG/GTAW, 99,997 % argon shield gas shall be used.

5.6.4 Test coupons shall be performed every start of work per day and per piping/tubing diameter.

5.6.5 Weld logs shall record all the piping/tubing welds in the system.

5.6.6 Weld logs shall contain the following minimum information:

— date of weld;

— welder name;

— supervisor/inspector;

— weld identification number and description;

— description of items being welded;

— items diameter and;

— heat numbers of the items being welded.

5.6.7 Passivation shall be performed during commissioning/start up.

5.6.8 Only certified welders shall be used.

5.6.9 Piping/tubing connections shall be Tri Clamp (TC) or other sanitary style connection.

5.6.10 Threaded or flanged connections shall not be used.

5.6.11 Drainage slopes shall apply to the following:

— a 1 % minimum drainage slopes shall be designed where ever possible and;

— the slope direction shall be towards the piping low point, which shall be drainable.

5.6.12 Installed valves shall be one of the following types: diaphragm or other aseptic design with barrier between valve mechanism side and PW/WFI side.

6 Sampling

6.1 Sampling principles

6.1.1 There shall be provision for sampling the water upstream and downstream of all components that could affect the microbial or chemical quality of the water.

6.1.2 Zero dead leg sample valves shall be used throughout the system, both on non PW/WFI piping/tubing and on product water piping/tubing.

6.1.3 The sample valves shall be installed on short outlet tees so as not to contaminate samples by bioburden growing in the fitting.

6.1.4 Every process relevant component in the water system shall have a sample valve before and after the component, e.g. heat exchanger, filter, pump etc.

6.1.5 The sample valves shall be above a tundish drain that will allow full drainage of the sample valve flow before taking the sample.

6.1.6 There shall be sufficient clearance between the sample valve and the tundish to allow insertion of all the standard sample bottles.

6.2 Minimum sampling point and locations

- before and after MMF;
- at supplied water tank inlet;
- after circulation pump;
- after hardness reduction stage;
- at the cartridge filters inlet and outlet;
- after heat exchangers;
- after dechlorination stage;
- after each RO housing and at their joint stream and;
- at RO reject lines and;
- CDI/EDI/CEDI feed, product and reject.

6.3 Sampling conductivity

If an online conductivity instrument is installed and the online conductivity has already met national regulations, there is no need for samples to be taken for off line conductivity testing.

7 Instruments

7.1 Minimum instrumentation for installation

7.1.1 Pressure indicators (PI):

- local pressure display shall be installed at inlets and outlets of major components;
- pressure Indicators (PI) shall be installed at pump outlet, before and after filtration elements and;
- only directly mounted membrane type connections shall be used.

7.1.2 Pressure indicator transmitter (PIT):

- for monitoring the system pressure in various points.

7.1.3 Conductivity iindicator transmitter (CIT):

— for monitoring the non-compensated conductivity and;

— CIT shall be used at: RO feed, RO permeate/product streams, inter-stage for Double Pass Reverse Osmosis (DPRO), CDI/EDI/CEDI product.

7.1.4 Flow indicator transmitter (FIT):

— for monitoring the flow rate and;

— flow indicator transmitter (FIT) shall be used at: permeate/product/reject streams.

7.1.5 Quantity indicator transmitter (QIT):

— for monitoring the total volume entering the system.

7.1.6 Free chlorine indicator and transmitter (CLIT):

— for monitoring the free chlorine level before and after the chlorine removal stage.

7.1.7 Temperature transmitter (TT):

— for monitoring water temperature and;

— temperature transmitter (TT) shall be used at: inlet and outlet of heat exchangers, feed water, PW/WFI product water and RO reject.

7.1.8 Level transmitter (LT):

— for monitoring the supplied water storage tank level.

7.2 Parameters for measuring, alarming, storing and graphing from online instruments

Table 2 lists the parameters that shall be measured, alarmed, stored and graphed.

Table 2 — Parameters for measuring, alarming, storing and graphing from online instruments

Level of criticality	Water inlet	Pre-treatment	RO feed	RO reject	RO permeate	CEDI permeate
Shall	—	Chlorine Temperature ESC amps UV Dosage	Chlorine Conductivity	Flow Temperature Pressure	Conductivity Temperature Flow % Rejection	Conductivity Temperature Flow
Should	Chlorine	—	Flow Pressure	—	Pressure	Pressure
May	Temperature Flow/Quantity Pressure	Flow Pressure	pH	Conductivity	—	TOC
Conductivity shall be measured uncompensated at 25 °C.						

8 System design

8.1 Specification of feed water

Examples of feed water categories are in Table B.1.

8.2 System selection table based on feed water quality

8.2.1 Table C.1 can be used for system selection and guideline.

8.2.2 See Annex A for system examples.

9 Operation

9.1 Production

9.1.1 The PW/WFI Pretreatment and Production system shall operate/circulate constantly 24/7, no stoppage of the pump or flow.

9.1.2 The constant operation/circulation shall keep the water moving without stagnation.

9.1.3 There is no objective criterion of minimum flow or minimum speed. Minimum flow or turbulent flow may be defined per system.

9.1.4 Savings may be realized by throttling of the concentrate and lowering speed of pumps when storage tank full.

9.1.5 A system with electric scale control (ESC) and UV dechlorination shall continuously reduce bacteria while operating.

9.1.6 Areas of the system that do not have constant flow, as in CIP return lines and bypasses, shall be gravity drained between uses. Every time the system has not been in operation for a certain period of time a subsequent start up should be carried out according to a Standard Operating Procedure (SOP).

9.2 Recirculation when storage tank full

9.2.1 When the PW/WFI storage tank is full, the PW/WFI Pretreatment and Production shall shunt the product water back to the raw/ supplied water inlet of the PW/WFI Pretreatment and Production.

9.2.2 The production system shall not operate Start/Stop when the storage tank is full. The production system should continue to operate continuously.

9.3 Sanitization

9.3.1 Hot water sanitization shall be the method for keeping the systems clean of microbial contamination.

9.3.2 To prevent build-up of scale on the heating surfaces, water used shall be soft (less than 20 ppm as $CaCO_3$).

9.3.3 Appropriate temperature, time and cycle shall be determined, for example: A periodic heat sanitization shall be performed so that the lowest temperature in the system is 80 °C for at least 30 min

9.3.4 All equipment units in the PW/WFI Pretreatment and Production shall be compatible with hot water sanitization (HWS). This includes the electric scale control (ESC), UV, filters, RO, CDI/EDI/CEDI and UF units - For example, all shall be able to withstand the minimum sanitization temperature at 80 °C for one hour. If Activated Carbon Filter (ACF) is used it shall be sanitized at least twice a week with steam. If hot water is used, the minimum sanitization temperature shall be 85 °C for one hour at least.

9.3.5 Activated Carbon Filter (ACF) sanitization shall include all downstream filter elements.

9.3.6 Activated Carbon Filter (ACF) steam sanitization shall be performed with Pure steam (PS) only; industrial steam for direct Activated Carbon Filter (ACF) contact sanitization shall not be used.

9.4 Chlorine and chlorination

9.4.1 The feed water may be chlorinated in accordance with the feed water quality and per system configuration.

9.4.2 A pretreatment including an electric scale control (ESC) and UV dechlorination combination will not need any chlorination, as continuous operation will continuously reduce the bacterial load.

9.4.3 Residual chlorine shall be left in the system for maximum process steps.

9.4.4 Chlorine shall be removed at the last possible point before the RO while leaving upstream equipment chlorinated.

10 Maintenance

10.1 Standard Operating Procedure (SOP´s)

10.1.1 Maintenance Standard Operational Procedures (SOP's) shall be composed during the system commissioning for implementation during the first stage of Performance Qualification (PQ).

10.1.2 Standard Operational Procedures (SOP's) shall include:

— procedures for operating the system;

— list of scheduled preventive maintenance per: day, week, month, quarter, year etc.;

— monitoring table for recording critical quality parameters and operating conditions;

— calibration schedule of instruments;

— schedule for periodic sanitization;

— control of changes to the mechanical system and to operating system;

— sanitization procedure;

— filter replacement procedure and;

— filter replacement schedule.

10.1.3 The Standard Operating Procedures (SOP's) shall be regularly reviewed periodically, when equipment is replaced, or when the system is otherwise updated.

10.1.4 Any maintenance Standard Operating Procedure (SOP) shall include a daily check list of the system that will include at a minimum:

— screen alarm log check;

— visual inspection of system for faults: e.g. Leaks, vibrations;

— check of free chlorine or chlorine dioxide (CD) levels at critical sample points and;

— other critical parameters like pressure, flow that are not saved to a history file on the screen alarm log check.

10.2 Filter replacement

10.2.1 Filter replacement shall always be accompanied by an inspection of the cartridge surface to detect changes in system operation. For pretreatment filters that shall be based on differential pressure, time or other relevant parameter, Standard Operating Procedures (SOP) shall be provided.

10.2.2 Any out of the ordinary discoloration, buckling, surface crushing or sagging shall be reported and investigated.

10.3 Chlorine instrumentation

10.3.1 A chlorine meter measuring zero chlorine usually needs maintenance every 2-3 months. The exact Standard Operating Procedure (SOP) shall be written up on the basis of manufacturer's instructions.

10.3.2 If Oxidation-Reduction Potential (ORP) instrumentation is installed, usually in conjunction with SBS dosage, the instrument shall be cleaned and checked every month.

10.4 Carbon dioxide

10.4.1 A degasification step shall be installed when incoming CO_2 can pass 10 ppm level.

10.4.2 Either NaOH dosing or contact membranes may be used.

10.4.3 If contact membranes are considered, clean, dry, oil free air shall be used as the sweep gas. Oil or other contaminants in the sweep air can clog the membrane and render it useless.

10.4.4 If incoming CO_2 levels can pass 40 ppm then two membranes in series shall be installed.

10.4.5 NaOH dosing shall be realized after the first stage RO; the dosing shall be controlled with online pH monitoring.

10.5 Membrane Integrity for polishing UF

10.5.1 Membrane integrity tests for polishing UF shall be performed to identify membrane modules with breaches.

10.5.2 The selection of integrity monitoring method is dependent upon membrane supplier or water systems supplier's recommendation.

10.5.3 Polishing UF shall pass the integrity tests on a regular basis, per recommendation of suppliers/manufactures but not less than twice a year.

10.5.4 Membrane replacement shall be performed on the basis of the integrity tests results.

See Annex D for configuration of typical integrity test

11 Specific Good Manufacturing Practice (GMP) requirements

11.1 General

11.1.1 This clause describes specific Good Manufacturing Practice requirements such as for monitoring and testing that shall be met to demonstrate that the system is operating within the predetermined acceptance criteria and the system is maintained in a state of control.

11.1.2 Physical breaks shall be provided at all drain lines.

11.1.3 Physical breaks shall be at least 50 mm.

11.1.4 There shall be no piping bypass on filters.

11.1.5 There shall be separation between systems to protect against cross contamination, e.g. industrial steam and PW/WFI. Air breaks, non-return valves and cut-off valves may be used.

11.1.6 System monitoring and recording shall be established as following.

— Alert limits shall be established for all system operating parameters that will be used on a regular basis to ensure that the system is operating properly;

— Action limits shall be established based on maximum operating parameters to ensure system and associated equipment or products are not compromised;

— Testing at sample points to the established standards shall be completed as part of the ongoing monitoring of the water system and;

— The testing shall confirm that the water specifications are met and the integrity of the distribution system is maintained.

11.2 Safety considerations

11.2.1 As chlorine dioxide (CD) is a dangerous substance in high concentration, whereby fumes are liable to explode and are toxic. Only custom made equipment from respectable suppliers shall be used to generate small amounts of CD for immediate dosage and use in system.

11.2.2 Hot water sanitization (HWS): suitable barriers and/or signage shall be used for personnel protection from hot surfaces during sanitization.

11.2.3 Suitable signage of chemicals and hot surfaces shall be used.

11.3 Commissioning and qualification requirements

11.3.1 Pressure testing.

11.3.2 Piping/tubing and equipment flushing.

11.3.3 Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) protocols.

12 Control philosophy

12.1 Minimum control loops needed for installation

— water tank level control;

— water tank temperature control;

— Electric scale control (ESC) operation;

— Hydro optical dechlorination (HOD) operation;

— RO-CEDI skid operation;

— pressure control of RO feed water;

— pressure control of HP RO pump and;

— Temperature and during the sanitization from the supplied water inlet to the CDI/EDI/CEDI outlet.

12.2 Automation

An automated process monitoring and process control system shall be implemented in the water system Computer (PC) or control panel.

13 Alarms

13.1 Required alarms

Table 3 — Required alarms

Parameter	Alarm	Action	Alarm display
Chlorine level after chlorine destruction stage	> alarm set-point	The supply valve to the RO unit shall close and open drain valve	Y
Conductivity level at CEDI outlet	> alarm set-point	Recirculate to Supplied Water Tank	Y

13.2 Recommended alarms

Table 4 — Recommended alarms

Parameter	Alarm	Action	Alarm display
Tank low levels	> alarm set-point	Alarm and/or pump stop	Y
Temperature levels high	> alarm set-point	Alarm and/or cooling	Y
Temperature levels low	< alarm set-point	Alarm and/or heating	Y
Conductivity levels high	> alarm set-point	Alarm and/or fill stop	Y
Flow rates high	> alarm set-point	Alarm	Y
Flow rates low	< alarm set-point	Alarm and/or system stop	Y
Pressure levels high	> alarm set-point	Alarm and/or pump stop	Y
Pressure levels low	< alarm set-point	Alarm and/or system stop	Y

14 Recommended engineering documentation

14.1 General user guide

The minimum documents to be included in the user guide shall be as follows:

— Piping and Instrumentation Diagram (P&ID);

— updated consumer table including all design parameters;

— start up and tuning (water flow quantities, correct instrument readings etc.);

— operation instructions (including system operation parameters);

— maintenance instructions;

— components list - equipment and devices;

— "To scale" Piping layout drawings and;

— equipment layout.

14.2 Instrumentation documentation

The minimum instrumentation documents to be included in the user guide shall be as follows:

— instrument list;

— data sheets;

— operating and calibrating instructions;

— "as made" instrumentation wiring diagrams;

— calibration certificates with traceability of the calibrating instrument to international standards and;

— original manufacturer catalogue.

14.3 General piping/tubing

The minimum general piping/tubing documents to be included in the user guide shall be as follows:

— piping/tubing isometrics;

— technical specifications (piping/tubing material, wall thickness; pressure rating etc.);

— material certificate;

— pressure test reports;

— welder qualification certificates;

— welding log and;

— cleaning report (water flush; to clean from construction debris).

14.4 PW/WFI product piping/tubing

The minimum PW/WFI piping/tubing documents to be included in the user guide shall be as follows:

— surface finish certificate;

— weld inspection certification;

— piping/tubing passivation protocol/report and;

— video of borescope inspection.

14.5 Tanks

The minimum tank documents to be included in the user guide shall be as follows:

— technical specifications (tank material, wall thickness, pressure rating etc.);

— material certificates and;

— manufacturer's drawing.

14.6 Pumps

The minimum pump documents to be included in the user guide shall be as follows:

— technical specifications (material, graphs, rating etc.);

— original manufacturer catalogue;

— material certification and;

— manufacturer's drawing.

14.7 Insulation

The minimum insulation documents to be included in the user guide shall be as follows:

— spec for insulation, without asbestos and without chloride.

14.8 Signs

The minimum signs to be posted on and around the system shall be as follows:

— All equipment shall be marked. This includes instruments, manual valves, pneumatic valves and any other equipment supplied.

— All electrical and instrument wires shall be marked according to client standard.

— Piping shall be marked with the relevant fluid and the flow direction.

14.9 Software

The minimum software documents to be included in the user guide shall be as follows:

— detailed schedule of system operation- Functional Design Specification (FDS);

— software component data sheet;

— list of messages and warnings;

— software code;

— graph list and printout;

— synoptic screen list and printout;

— functional screen list and printout and;

— software documentation – software documentation and human services data specification (HSDS).

14.10 Electrical documentation

The minimum electrical documents to be included in the user guide shall be as follows:

— list of all relevant electric components;

— “as made” electrical wiring diagrams;

— grounding reports;

— electrical cupboard layout and;

— electrical cupboard specification.

14.11 Factory acceptance test (FAT) protocol

The minimum FAT documents to be included in the user guide shall be as follows:

— pretreatment skid (protocol and report);

— RO-CEDI skid (protocol and report) and;

— tank (protocol and report).

14.12 IQ/OQ protocol

This protocol is a minimum requirement for validation of the systems.

14.13 Spare parts list

The minimum spare parts lists to be included in the user guide shall be as follows:

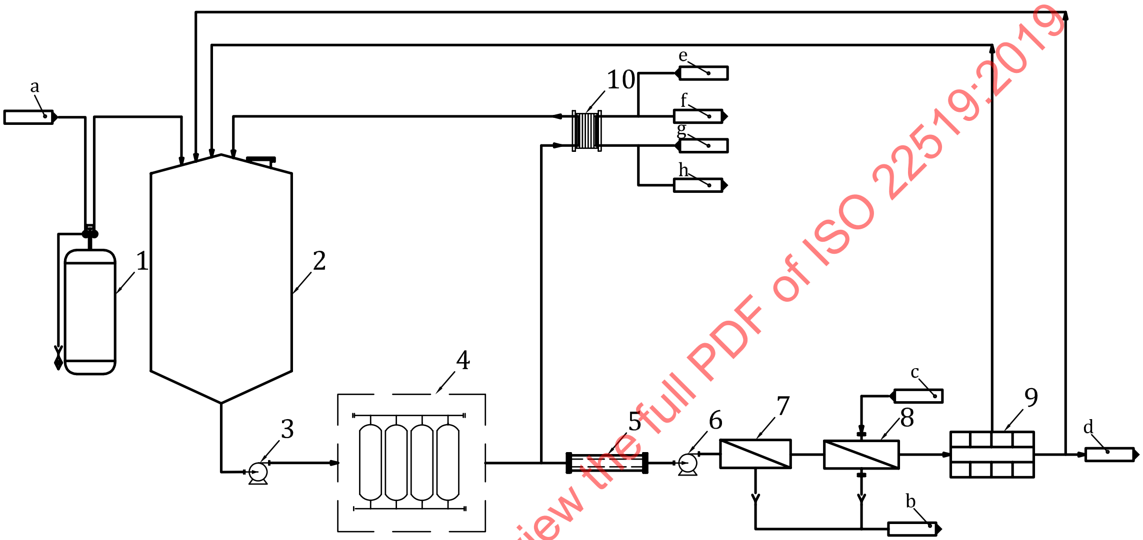
— critical spare parts list and;

— general spare parts list.

Annex A
(informative)

Examples of PW production systems

A.1 Typical water feed PW production



Key

1	MMF/Filtration	a	Supplied water
2	break tank	b	Drain
3	circulation pump	c	Compressed air
4	ESC	d	To storage tank
5	HOD (UV)	e	Steam
6	HP RO Pump	f	Chilled water
7	RO	g	Chilled water
8	CO_2 Degasser	h	Condensate
9	CEDI		
10	heat exchanger		

Figure A.1 — Example of typical water feed PW production