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Purified water and water for injection pretreatment and production systems

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

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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).

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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.