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Membrane-based generation of water for injection (WFI)

Production d'eau pour préparations injectables (EPPI) utilisant des membranes

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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*.

This second edition cancels and replaces the first edition (ISO 22519:2019), which has been technically revised.

The main changes are as follows:

— title changed;

— PW systems removed from the Scope;

— document structure revised.

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

The water quality specifications for water for injection (WFI) are given in national and International Standards and are well defined and understood.

The WFI generation systems potentially have to be able to cope with fluctuating feed water quality and be in accordance with the company policy and current good manufacturing practice (cGMP).

Properly engineered, constructed, operated and maintained membrane-based generation systems can have comparable reliability in meeting WFI quality specifications with low operational costs in comparison with thermal-based WFI generation. At the time of publication, all major pharmacopoeia allow non-distillation-based WFI generation, with the exception of the Chinese Pharmacopoeia. The Chinese Pharmacopoeia has initiated revisions to related standards.

This document has been developed to address the lack of an International Standard concerning membrane-based WFI generation.

The aim of this document is to:

— set out clear principles needed for reliable membrane-based generation of WFI;

— improve membrane-based generation of WFI process systems and methods;

— combine relevant standards, guidelines and global expert knowledge into one International Standard;

— consider in-system microbiological aspects of WFI generation;

— standardize expectations for membrane-based WFI generation.

This document provides a global benchmark that can be used by industries that use the WFI generation system.

Membrane-based generation of water for injection (WFI)

1 Scope

This document provides a benchmark for evaluation of the design, operation and performance of water for injection (WFI) generation systems based on membranes.

This document is applicable to the design of new systems.

This document covers the following topics:

— principles of membrane-based WFI generation systems;

— process design, construction, operation and maintenance of membrane-based WFI generation systems;

— controlling membrane-based WFI generation system parameters.

This document does not cover the following topics:

— validation;

— distillation.

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 terms and definitions given in ISO 20670 and the following apply.

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

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

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

3.1 Terms and definitions

3.1.1
pretreatment
equipment and process stages up to and including the first-pass reverse osmosis (RO) pump or other membrane-based primary bioburden reduction step

3.1.2
generation system
equipment and process stages after (downstream) reverse osmosis (RO) stage 1 pump

3.1.3
multimedia filter
MMF
layered filtration media in a pressurized container, used to reduce the level of suspended solids in incoming feed water

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

3.1.4
chlorination
dosage or generation of hypochlorite or chlorine to generate controlled free chlorine levels in the system

3.1.5
activated carbon filter
ACF
activated carbon media for removal of free chlorine, chloramines and total organic carbon (TOC)

Note 1 to entry: The media can be applied as a granular activated carbon (GAC) pressurized container or a cartridge type. The configuration of the activated carbon filter can depend on, for example, the level of feed water impurities and system capacity.

3.1.6
ultraviolet
UV
irradiation of water with light in wavelengths ranging from 180 nm to 350 nm for dechlorination or disinfection purposes at higher wavelengths and total organic carbon (TOC) reduction at lower wavelengths

3.1.7
molecular weight cut-off
MWCO
molecular weight at which 90 % of the macromolecular solute is rejected by the membrane

3.1.8
electrodeionization
EDI
process for ion removal from water utilizing electricity, ion exchange membranes and resin

3.1.9
continuous electrodeionization
CEDI
process for ion removal from water utilizing electricity, ion exchange membranes and resin

3.1.10
polishing UF
polishing ultrafiltration
membrane-based process for reduction of endotoxin, total organic carbon (TOC) and bacteria post-RO or post-electrodeionization (EDI) or continuous electrodeionization (CEDI)

3.2 Abbreviated terms

ACF	activated carbon filter
CEDI	continuous electrodeionization
EDI	electrodeionization
EPDM	ethylene propylene diene (M-group)

HWS	hot water sanitization
MWCO	molecular weight cut-off
MMF	multimedia filter
PTFE	polytetrafluoroethylene
RO	reverse osmosis
SOP	standard operating procedure
SS	stainless steel
TOC	total organic carbon
UF	ultrafiltration
UV	ultraviolet
WFI	water for injection

4 System boundaries

For the purpose of this document, the boundaries for the WFI generation system are as follows:

a) The inlet of potable water to the equipment dedicated to the WFI pretreatment system is the start of the system.

b) A water treatment system that aims to improve the feed water to potable standards is not part of the WFI generation system.

c) The WFI generation system end boundary is at the inlet valve (inclusive) of the WFI storage tank or at the point of use (POU) if a tank is not installed.

d) The WFI storage tank is not included in the WFI generation system boundary.

e) "Industrial" treatment systems upstream of the WFI generation system, including supply to other plant utilities, for example steam boilers, potable water usage and feed to cooling towers, are not included in the WFI generation system.

5 Feed water

Incoming feed water should meet the potable water standards of the World Health Organization (WHO) in Reference [3]. If incoming feed water does not comply with drinking water requirements, additional systems should be installed to improve the feed water parameters before the membrane-based WFI generation system.

6 Process design for membrane-based WFI generation systems

6.1 General

This clause gives guidance on proper design of the water treatment system. A risk assessment should be carried out to improve the final system design by modifying or completing the details in all clauses accordingly, if applicable.

6.2 Design conditions

The WFI generation system design should be stable under common worst-case scenarios:

a) changing seasons;

b) feed water microbial load;

c) fluctuation of feed water quality;

d) other fluctuating environmental conditions.

6.3 Important design factors

For designing a membrane-based WFI generation system, the feed water composition should be taken into account. The following critical parameters may be considered to ensure reliable and effective operation of primary purification unit operations:

a) scale;

b) TOC;

c) silica;

d) iron;

e) manganese;

f) dissolved solids;

g) suspended solids;

h) dechlorination;

i) microbial.

6.4 Examples of possible configurations of water technology stages in WFI generation systems

a) Sanitant: dosing of free chlorine or chlorine dioxide.

b) Initial filtration: MMF, cartridge depth filter, UF, screen filters, disk filters.

c) Membrane anti-scaling: softener, electrical scale control, antiscalant.

d) Sanitant removal stage: activated carbon, UV, sodium bisulfite (SBS) or sodium metabisulfite (SMBS).

e) Production stage: single-pass RO, double-pass RO.

f) CO_2 removal: caustic dosing (upstream final-pass RO) or contact degassing membrane (upstream of final stage).

g) Final stage for further reduction of product conductivity and/or other contaminants (if needed): CEDI/EDI and/or ultrafiltration.

6.5 Primary microbial reduction unit operations

a) A minimum of two membrane barriers for microbiological and endotoxin removal should be implemented in accordance with the options listed or in conjunction with extra process steps:

   — RO-RO;

- RO-UF (polishing UF with endotoxin log reduction or minimum MWCO);
- other validatable membrane-based systems.

b) The following additional processes may be implemented as deemed necessary:

- UV irradiation;
- microbial or absolute retentive filters;
- polishing UF;
- other processes.

c) If only one membrane barrier is used then the following risk assessment and implementation may be drawn up to ensure proper bioburden removal post-membrane:

- institute an independent technological process;
- apply appropriate testing.

6.6 Instrumentation

The minimum instrumentation should be:

a) conductivity instruments after all RO and CEDI/EDI steps;

b) conductivity instruments needed for final product measurement;

c) TOC sample points or TOC online instrumentation for final product monitoring.

7 Sanitization

7.1 General

a) The sanitization performance should be compliant with a contamination control strategy.

b) Sanitization shall be possible throughout the system, from pretreatment to generation included.

c) Sanitization principles and approaches may differ between pretreatment and final treatment systems.

d) Hot water or other proven sanitization is needed for the final membrane barrier.

e) Hot water temperature or sanitant concentration, time and cycle shall be demonstrated to be effective in controlling microbiological growth.

f) If ACF is utilized, it should be thermally sanitized.

7.2 Sanitization types

Sanitization types should be as follows:

a) hot water (preferred);

b) chemical;

c) other equivalent processes.

8 Construction

a) The system shall be hygienically designed and built downstream of final membrane barrier.

b) Consideration should be given to an implementation of hygienic principles in the production system as necessary based on risk assessment.

c) The components in the pretreatment and generation system should be fabricated from:

- SS304/SS316 ("L" for low carbon content needed if components are welded);
- Polyvinylidene fluoride (PVDF) or other non-corroding, resistant against the intended sanitization method, for instance HWS, non-particle shedding and non-leaching materials.

d) Gaskets shall be one of the following:

- EPDM encapsulated with PTFE gaskets;
- full EPDM;
- full PTFE;
- silicone;
- fluoroelastomers;
- combinations of inert, resistant against the intended sanitization method, for instance HWS, non-particle shedding and non-leaching elastomers.

Prior to construction, the system designer should identify certification standards to confirm suitability of components to the operating parameters in the different parts of the system.

9 Demonstrating performance of critical quality attributes

a) Sampling programmes should include in-system and unit operation sampling to verify control of system parameters in the system.

b) The minimum microbial parameters that should be monitored are:

- total microbial count;
- endotoxin;
- objectionable organisms.

c) The minimum chemical parameters that should be monitored are:

- conductivity (online);
- TOC;
- other relevant parameters.

NOTE If an online conductivity instrument or TOC analyser is installed and the online conductivity or TOC analyser has already met regulations for online measurement, there is no need for samples to be taken for off-line conductivity or TOC testing.

10 Sampling

a) Specific sampling locations and appropriate valve type should be provided to demonstrate control and to meet the requirements of Clause 9.