ISO 22519: New Water System Standard

Production of Purified Water and Water for Injection

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The ISO 22519 is the first international standard for water systems. There are large numbers of guidelines and lots of technical literature but a clear-cut standard is missing.
The water qualities for Purified Water (PW) and Water for Injection (WFI) are specified in national and international standards, but before the ISO 22519 there was no standard for the production *system* for PW and WFI.
ISO provides a standardized reference that can be used by industries using PW and/or WFI, national governments, state authorities and regulators to evaluate PW/WFI systems.
This article presents the ISO standard to be published in June 2019 with the following main points:

- Provides auditors with a standard checklist for harmonizing equipment and systems in the water industry
- Sets a benchmark for water system suppliers around the world, to be used as a reference point for their systems
- Scope: system design, materials selection, construction and operation of PW and WFI pretreatment and membrane-based production systems
- Component selection table based on feed water and final product water
- Operation: production, idling when storage tank full, sanitization

1. Introduction

In the pharmaceutical water industry there are lots of guidelines, standards and specifications. All these documents are limited in their aim and scope as they are not intended as standards for Purified Water (PW)/Water for Injection (WFI) production systems.

The ISO 22519 is a standard for PW/WFI production systems with all the information in one place with all the specifications of relevant equipment, materials and operational descriptions.

This ISO standard was developed over a period of two years by technical groups within ISO member bodies. The voting countries were Austria, Bahrain, Canada, China, Egypt, Ethiopia, Finland, France, Hungary, India, Iran, Ireland, Israel, Japan, Kenya, Korea, Mongolia, the Netherlands, Portugal, Rwanda, Spain, the United Kingdom, the United States and Vietnam.

The standard is global and takes different feed water standards as well as the availability of materials into account and is harmonized with all voting member bodies.

2. Existing Documents

Among the more common documents in relation to biopharma water systems referenced are:

- National Pharmacopeias
- ASME BPE-2016 [1]
- ISPE Pharmaceutical Engineering Guide, Volume 4: Water and Steam Systems [2]
- WHO Technical Report Series 970, Annex 2 [3]
- PW United States Pharmacopeia General Chapter <1231> [4]
- VDI 2083 Cleanroom Technology, Quality, Production, and Distribution of Ultrapure Water Pharmacy and Other Life-Science Applications [5]
- ISPE Handbook Production of Water for Injections without Distillation Process [6]

■ 2.1 National Pharmacopeias

These documents define the final specifications of the product water identified as Purified Water and Water for Injection.

These pharmacopeias do not deal with equipment selection and system operation.

■ 2.2 ASME BPE-2016

Standard for design, materials, construction, inspection and testing of vessels, piping, and related acces-

sories such as pumps, valves and fittings – for use in the biopharmaceutical industry. This is not a water system standard and does not deal with water production equipment.

■ 2.3 ISPE Pharmaceutical Engineering Guide, Volume 4: Water and Steam Systems

This guideline reflects ISPE's current thinking and is intended to assist but is neither a standard nor a detailed design guide.

■ 2.4 WHO TRS 970, Annex 2

A guideline providing information about the available specifications for water for pharmaceutical use. This guidance document also has a section about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms. Guidance is given on Good Manufacturing Practices (GMP) regarding the design, installation and operation of pharmaceutical water systems.

All the information given is in the form of "guidance" and not a comprehensive standard.

■ 2.5 PW United States Pharmacopeia General Chapter <1231>

This non-binding information chapter helps users to better understand pharmaceutical water issues and some of the microbiological and chemical concerns unique to water.

It is a background document with basic information on water generation storage and distribution.

■ 2.6 VDI 2083 Cleanroom Technology, Quality, Production, and Distribution of Ultrapure Water Pharmacy and Other Life-Science Applications

A German guideline that summarizes water quality on the basis of the Ph. Eur. It shortly describes the main elements of water treatment and the integration into systems.

Control of microbiological levels is elaborated and sanitization methodologies are discussed. Sampling and instrumentation with monitoring is overviewed.

This document is a guideline without being a standard.

■ 2.7 ISPE Handbook Production of Water for Injections without Distillation Process

This handbook was not available to the author at the time of writing this article but from its "handbook" title it can be assumed that it is not a binding standard.

None of the above-mentioned systems are standards for water systems, all are non-binding guidance for the experienced designer/owner/auditor. There is no easy way to separate the wheat from the chaff and to understand what is more or less relevant to a particular feed water and system. In addition, the systems must meet budgetary constraints and be in accordance with the company policy and cGMP, not an easy combination. The design of an effective and reliable water system is more an art than a science and that is why water systems differ widely. Some systems need constant maintenance and some underperform. Some have excellent microbial levels and some need close supervision.

3. Aim of the Standard

The ISO standard 22519 "Purified Water and Water for Injection Pretreatment and Production Systems" is the first standard in the field. The standard makes it possible for *users* to design water systems that fit specific needs without being experts. The standard has taken into account differing water qualities so the information is not only relevant to European or North American feed water but also to developing countries. The 22519 is an equipment and system standard for design, fabrication, materials, construction and operation of PW/WFI production equipment and systems.

The ISO document provides a standard global benchmark that can be utilized by the *industries* that use PW and/or WFI. The standard can be used to evaluate PW/WFI systems as *auditors, national governments, state ministries and regulatory bodies* have now a standard reference to turn to.

An exhaustive list of production equipment is given with advantages and disadvantages and then put together into a large number of different configurations all based on feed water characteristics.

The standard is presently at the final stages of approval. It is expected to be published in June 2019.

One of the main motivations of the standard is to improve reliability of the water generation process methods and water product while reducing downtime needed for scheduled and non-scheduled maintenance.

For the first time, microbiological aspects of the pretreatment and production, as opposed to microbiological aspects of the product, are considered and firm action/alert levels are given.

Most modern generation systems for PW and WFI are based on Reverse Osmosis (RO) membranes. The standard has been written around the pretreatment for RO and post treatment of the RO water.

4. Scope

The content of the standard include the following subjects:

- Terms and definitions and abbreviated terms
- Design and practices
- Selecting materials, methods and system components
- Sampling
- Instruments
- System design
- Operation
- Maintenance

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- Specific GMP requirements
- Control philosophy
- Alarms
- Recommended documentation

The following issues are not included in the scope of the standard:

- PW and WFI specifications
  The PW and WFI specification of parameters were not included as these are well explained and accepted as set out by the Pharmacopeias.
- Selection of the appropriate compendial water definition, e.g., PW, WFI or other
  The selection of compendial water definition was not included as this is more a product-based decision as opposed to the water system emphasis in the standard.
- Thermal process for production of PW or WFI
  Thermal processes were not included in the standard as these are more expensive to run and operate than membrane-based systems.
  The standard is working towards lower environmental impact and membranes are more sustainable than distillation systems.
- Storage and distribution
  Storage and distributions systems were not included so as to focus only on the production systems. Possibly a future standard will be added.
- Pure steam generation and distribution
  Pure steam systems were not included so as to focus only on the water production systems. Possibly a future standard will be added.
- Laboratory water
  Laboratory water is an important subject but much less critical in patient impact in comparison to PW and WFI.
- Validation
  Validation was not included so as to focus only on water production systems.

In this article, the following highlights will be expanded as representative of the standard:

- Stainless Steel (SS) construction
- Chlorine and Chlorination
- Specific Good Manufacturing Practice (GMP) requirements
- Hot water sanitization
- Continues Bioburden Reduction (CBR) after every stage
- Continuous system recirculation
- Categorization of feed water
- System selection table for components
- Advantages and disadvantages of system components/treatment stages
- Membrane Integrity testing for polishing Ultrafiltration unit

■ 4.1 Stainless Steel construction

In the interest of availability, reliability, cleanability and simplicity, all water production system piping was specified to be Stainless Steel (SS) only. This is understandable as the standard recognizes hot water sanitization as the only effective manner of sanitization. Plastic, heat-resistant piping has been dismissed as a possible construction material. In some places in the world, it is common to install pretreatment and even production systems with heat-resistant polymeric piping but in other areas "no bead" polymeric welds are hard to reliably achieve. So, in the interests of keeping the standard a global standard, the SS piping is given as the only option as it is more commonly available as a heat-resistant material as are qualified contractors for the pipe welding.

■ 4.2 Chlorine and Chlorination

The standard mentions the possible addition of chlorine to the feed water in the system. Chlorine is added to control microorganisms. Chlorination is not a must but should be taken into account if the system does not display reduction of bacteria after every stage, e.g. at the outlet of softeners. Even if chlorine is added, hot water sanitization is still required as chlorine is not always effective against buildup of biofilm.

■ 4.3 Specific Good Manufacturing Practice (GMP) requirements

This paragraph specifies specific GMP requirements as follows:

- Physical breaks shall be provided at all drain lines and these should be at least 50 mm. This simplifies the present GMP requirement.
- Filters should not have bypass piping. This is to discourage permanent bypass of filters due to faulty operational practice.
- There shall be separation between different utility systems to protect against cross contamination, e.g., industrial steam and PW/WFI or compressed air and PW/WFI. Air breaks, non-return valves and cut-off valves may be used.
- A list of recommended system monitoring and recording instruments. Instruments are to be installed to measure relevant parameters, e.g., electrical current in an electrical scale control unit. If such a unit is not installed then this instrument is not mandated.

■ 4.4 Hot water sanitization

The pretreatment and production system must be sanitized at regular intervals. The exact intervals for the sanitization are not specified but could be based on performance. In a perfect world, time is not a problem and the system can be operated until a trend of microbiological growth is detected. On the basis of this trending the timing of the sanitization can be determined. This is what should be performed during the first stage of PQ.

In real life, companies do not have the time and resources to play around with the different parameters, they want the system defined and controlled within constraints from day one. So a weekly sanitization is a good starting point especially as consumption is usually at a low point at least once a week, so the downtime for sanitization is usually not a problem.

As for the sanitization method, chemical sanitization has been dis-

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/100ml)	< 10	< 1	< 1	< 1
7	*E. coli* (cfu/100ml)	< 1	< 1	< 1	< 1
8	Total coliforms, Fungus, (cfu/100ml)	< 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.

qualified by the standard as unreliable. Chemical sanitization is hazardous, environmentally damaging, time consuming, needs operator oversight and is ultimately unreliable. Different types of sanitization chemicals have differing impacts on various biological infestations. The hardest biological growth to deal with is a developed biofilm that is extremely hard to penetrate and remove with chemical agents.

On the other hand, hot water is one of the most reliable and effective sanitization methods. Biofilm in contact with water above 80 °C will be easily penetrated and the bacteria within will perish. True, the hot water will not remove a mature biomechanical scaffolding, but if the sanitization is applied weekly, this mature growth will not form.

As the hot water sanitization cycle does not utilize disinfectants, there is no need to flush chemicals to drain at the end of the sanitization cycle, and there is no need for post sanitization validation for removal of the sanitization factor. Even without human supervision the systems can be relied upon to heat up, hold at high temperatures and then cool down autonomously. Once programed, the heat/cool cycle will proceed weekly or monthly without interference. The sanitization cycle needs to be repeatable both in duration and in temperatures and the standard stipulates that the sanitization parameters in the system must be controlled and recorded.

4.5 Continues Bioburden Reduction (CBR) after every stage

All authorities agree that control of the system's operational parameters needs to be demonstrated. The proof of control is to show improvement of the main characteristics of the water. Translating this into the real world is to show decreasing bacterial levels as the water advances through the system. The principal applies to trending, small excursions are not a problem as long as reduction trends are shown over time.

The bioburden is the most problematic of all the controlled parameters as the biological load can multiply in certain nutrient-rich areas, but it is not the only parameter that should improve.

Active carbon filters are not proscribed by the standard, only that they should be operated in such a manner as to reduce bacterial growth in the media and in downstream filters. This can be achieved by steaming twice weekly with pure steam or if hot water is used, the minimum sanitization temperature shall be 85 °C for one hour at least. The water temperature was stipulated to be relatively high so as to ensure proper penetration through all the media.

The final bacteriological performance of a system is an amalgam of initial design, installation standards, day to day operation and regular maintenance and all of this has been referenced in the standard.

A great deal of effort has gone into recommending different options in selecting the equipment so as to keep system microbial growth to a minimum.

All efforts must be to keep RO permeate microbiological levels below alert/action levels, this cannot be achieved if the pretreatment is allowed to generate uncontrolled amounts of bacteria that will deposit slime on the RO. This biological mud will eventually send permeate microbial levels out of specification.

The recommended standard water quality after every stage can be seen in Table 1.

All pharmacopeias stipulate that the feed water to the PW/WFI production system must meet potable water standards. The ISO standard has stipulated continuous in-system bacterial reduction below these values. The reasoning is, that if undesirables must be absent from the feed water – they must also be absent from inside the system.

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In light of the recent update to the Ph. Eur. allowing membrane production of WFI, this principal is indispensable.

■ 4.6 Continuous system recirculation

If a water system is inoperative for short or long periods of time, there is an inevitable up trend in microbiological levels as nothing is stopping growth. This trend is more pronounced the higher the ambient temperatures, the higher the incoming biological levels and the higher the incoming organic levels.

This standard stipulates that when the PW or WFI tank is full, the production system must persist with the circulation of the water. This circulation in itself will not stop bacterial growth but will allow the system to reduce bacterial levels via cooling/chlorine dosing/ultraviolet (UV)/RO/dilution or with whatever process is used to reduce bacteria. All these processes would stop if the production system is shut down when the PW/WFI storage tank is full.

This principal is complementary to the previous principal of improvement in system parameters.

■ 4.7 Categorization of feed water

This standard has been compiled by teams working in many countries. Every country has its different feed water and there is not one system that can take into account all the different feed water parameters. So as to be able to offer options per type of feed water, four main types have been specified:

1. Typical
2. High bioburden with high organics
3. High hardness
4. High silica/high iron/high manganese

Each category has been characterized by the following parameters:

- TOC
- pH
- Conductivity
- Total hardness
- Microbial total count
- Total Coliforms, *Pseudomonas*, *E. coli*, Fungus
- CO_2 level
- Total silica
- Iron
- Manganese

The user needs to characterize the feed water by chemical analysis and select the closest feed water category. Only on the basis of this classification can a recommendation of the system configuration and equipment be made.

■ 4.8 System selection table for components

Table 2 demonstrates the principle of the full system recommendation table. On the left column are both the feed water category and the product water type.

The other columns are different possible process stages in the water system. The table recommends certain items according to the feed water and product water but even if non-recommended items are selected, the water system will still comply with the standard as this table is in the informative annex of the standard.

An example of the table recommendations: If the feed water is typical, the selection table will recommend single pass RO for PW product and double pass RO for WFI product.

On the other hand, if the feed water is high in bioburden and/or is high in organics, the standard recommends double pass RO for both the PW and WFI systems.

The table also details the type of initial filtration needed (multimedia filter, ultrafiltration, disk filter), the type of scale reduction process (electrical scale reduction, softener, antiscalant) and what sanitant could or should be added and how it should be removed (UV, active carbon, sodium bi sulfate).

If high CO_2 is encountered in the feed then recommendations of the best process for removal are also given.

■ 4.9 Advantages and disadvantages of system components/treatment stages

A large section of the standard is dedicated to an analysis of process equipment.

Advantages and disadvantages are given for every item that is listed:

multimedia filter, pretreatment ultrafiltration, flushed screen/disc filters, chlorination: dosage/electrogeneration, chlorine dioxide, softeners, antiscalant, electric scale control, active carbon filter, sodium meta bi sulfite, NaOH addition, degassing CO_2 contact membrane, UV lamp for dechlorination, single pass RO, double pass RO, continuous electro de-ionization, polishing ultrafiltration.

■ 4.10 Membrane Integrity for polishing Ultrafiltration unit

If a single pass RO is used for WFI production, it is common that a polishing ultrafiltration unit is installed at the last point in the system.

When a membrane is used for a long period of time, the membrane module can be damaged due to chemical or physical deterioration.

This can cause deterioration in membrane separation performance but may not be apparent in monitored water quality. Therefore, it is necessary to regularly test the membrane integrity.

There are both direct integrity monitoring and indirect integrity monitoring techniques. The selection of integrity monitoring method is dependent upon the membrane supplier's recommendation.

5. Conclusions

The ISO 22519 is the first international standard to be written for water system equipment and operation. This standard is to be a yard stick in the hand of inspectors, de-

Table 2

System selection table.

Process:		Sanitant	Initial Filtration	Anti-Scaling	Sanitant Removal	Production	CO_2 Reduction	Polishing
Feed	Final product							
Typical	PW							
	WFI							
High Bioburden and high organics	PW							
	WFI							
High Hardness	PW							
	WFI							
High Silica/High Iron/High Manganese	PW							
	WFI							

Refer to ISO standard 22519 for table contents

signers and users, to enable them to evaluate or design a water system.

The standard is unique in the global scope of the system descriptions that have been selected per incoming water specifications.

Even though the standard recommends certain types of equipment, selection of different types is not in violation of the standard. As long as the principals of stainless steel fabrication, hot water sanitization, reduction trends in water parameters with a special emphasis on bacteria and constant circulation are upheld, the audited system meets the standard.

Systems that keep to the recommendations of the standard need to be designed with principals that will actively reduce the proliferation of biofilm and pathogens and will meet the pharmaceutical market standard of a reliable system capable of controlling bioburden from beginning to end.

Any standard on a subject as wide and complicated as water systems for PW and WFI production cannot hope to contain *all* possible situations and feed water parameters but tools and principals have been set out and expanded so as to allow design and evaluation of as many different feed water values as possible.

The author would like to thank all those who took part in this long, involved and complicated standard. Hopefully, the principals and details recorded in the document will go a long way in improving the performance, reliability and sustainability of all PW and WFI production systems.

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