ISO 22519 Clear, Pioneering, Advanced

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Introduction

The ISO standard 22519, standard for “Purified water and water for injection pretreatment and production systems” has the following main requirements:

1. Stainless steel (SS) construction
2. Hot water sanitization
3. Continues Bioburden Reduction after every stage
4. Continuous system recirculation

In addition it has the main following features:

1. Detailed categorization of feed water
2. System selection table for components
3. Advantages and disadvantages of system components/treatment stages

The standard was published June 2019 and is now active.

For the first time users can specify water systems that fit specific needs without being experts in the water system field.

Anyone looking for a benchmark can refer to the standard and it can be used as a point of reference and as a standard for design and operation of their systems.

In the market are many guidelines and plenty of literature but before ISO 22519 a cut and dried standard for producing PW and WFI was not in place.

ISO standard was formulated to meet this lack.

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

The article “ISO 22519: A Flawed and Counterproductive Standard” (“the article”) was published in the PDA letter in the September issue.

The article is worded more as a protest petition than a researched and scientifically based critique besides having slanted and inaccurate content.

The Petitioners, that penned the article, would like to preserve the industry preference for outdated and unreliable systems.

The ISO sounds the death knell for the “cheap and dirty” softener and carbon filter based on plastic fabrication. Systems that are contaminated by the feed water as soon as they are commissioned and cannot be cleaned or sanitized

in any effective way. These systems were the cutting edge of technology 40 years ago but now should be taken out of service.

The critique shows a how industrial inertia, antiquated knowledge, narrow engineering view and insular outlook are trying to keep the industry at the present point of stagnation.

The petition co-signees are ignorant of the ISO organization and its processes and a large part of the arguments, stated as demands, are aimed at the ISO mode of operation as an organization and not at the standard.

Most of the criticisms presented can be divided in to the following categories:

1. Ignorance of ISO Modus Operandi
2. Misinterpretation of the standard
3. Adhering to present type of systems with no aspirations for improvement
4. Low sensitivity to quality and reliability issues in water systems
5. Not reading all of the standard
6. Unfamiliarity as to contemporary technologies
7. Not being up to date on present industry thinking
8. Not internally consistent

1 Ignorance of ISO Modus Operandi

1.1 Member Bodies Compose and Vote on ISO Standards

The Petitioners call for repeal of the ISO standard, the ISO doesn't work like that.

ISO standards are based on the *Member Bodies* to compose and vote on the draft standards. *Member Bodies* are national bodies considered the most representative standards body in each country. The standards are accepted and passed on to the next stage of the approval process or fail to pass based on a ballot. Comments are implemented in the next draft, a conference is convened and another vote taken. After the draft is voted in it is published.

The next step is a revision and only then changes can be made.

There is no option for repealing of a published standard.

Changes can be made only if *Member Bodies* take part in a revision but the Petitioners state that there was "no public review process".

Again, this is not how the ISO standard works. As explained, the public have no part in the standards and only *Member Bodies* can comment and vote.

Every *Member Body* has a mirror committee organized around the national standards institution of each country.

The Petitioners statement that the input for the standard was "extremely limited" is baseless in addition to being factually untrue.

The standard passed through all the mandated stages with hundreds of comments and changes.

The stages were as follows:

Stage	Version	Description	Started	Status
10.00	1	Proposal for new project registered	2017-02-21	CLOSED
10.20	1	**New project ballot initiated**	2017-02-22	CLOSED
10.60	1	Close of voting	2017-05-19	CLOSED
10.99	1	New project approved	2017-06-01	CLOSED
30.00	1	Committee draft (CD) registered	2018-01-29	CLOSED
30.20	1	**CD study/ballot initiated**	2018-01-29	CLOSED
30.60	1	Close of voting/comment period	2018-03-23	CLOSED
30.99	1	CD approved for registration as DIS	2018-05-31	CLOSED
40.00	1	DIS registered	2018-06-13	CLOSED
40.20	1	**DIS ballot initiated**	2018-08-15	CLOSED
40.60	1	Close of voting	2018-11-08	CLOSED
40.99	1	Full report circulated: DIS approved for registration as FDIS	2019-01-22	CLOSED
50.00	1	Final text received or FDIS registered for formal approval	2019-02-05	CLOSED
50.20	1	**Proof sent to Secretariat or FDIS ballot initiated: 2 months**	2019-03-08	CLOSED
50.60	1	Close of voting -- Proof returned by Secretariat	2019-05-04	CLOSED
60.00	1	International Standard under publication	2019-05-04	CLOSED
60.60	1	International Standard published	2019-05-29	CURRENT

The ISO standard 22519 passed four ballots, in bold above. Member bodies commenting and voting: Austria, Bahrain, Canada, China, Egypt, Ethiopia, Finland, France, India, Iran, Ireland, Israel, Japan, Kenya, Korea, Mongolia, Netherlands, Portugal, Rwanda, Spain, United States, Vietnam.

The different comments were discussed in three international conferences.

This three year effort international project had extensive input from 22 countries.

2 Misinterpretation of the Standard

2.1 Cation exchange softening

The original article in the PDA Letter [1] and the standard both send the reader to Table 1.

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)	<1	<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 ºC according to USP.					

This table states that the conductivity is "like feed water" and the total microbial count should be less than 500 cfu/ml. Slight changes of conductivity in the feed water are well within the general category of "like feed water". With this in mind, it is now easy to accept the slight rise in conductivity due to softening/sodium bisulphite addition or caustic addition.

The summery of this table for RO feed water is as follows:

Conductivity: "like feed water"

Bacterial total count: <500 cfu/ml

Cation exchange softening has the following characteristics:

- The conductivity will rise slightly from the inlet of the softener to the outlet of the softener.
- There will be increase of bacteria from the inlet of the softener to the outlet of the softener.

If there is a slight conductivity rise after a softener, this is not a noncompliance issue as long as the conductivity is "like feed water".

If there is a slight microbiological rise after a softener or a carbon filter, this is not a noncompliance issue as long as the total count is below 500 cfu/ml like the common standard for potable water.

Systems that do not meet these modest criteria do not meet the ISO standard.

The standard is taking a stand against softeners that are biological fermenters and cultivate mats and clumps of bacteria on the organic carbon based resins.

2.2 Electric Scale Control

In section 5 of the ISO 22519 there is a full review of contemporary technologies on the global market.

The table in section 5.2: "Advantages and disadvantages of system components/treatments stages", presents the technologies in a succinct, clear and realistic manner. All the facts in the table are unembellished, precise and correct.

Table, partial from ISO 22519 section 5.2:

System components/treatment stages	Advantages	Disadvantages
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;

2.3 Stainless Steel Construction of the Pretreatment and Production

The ISO requires that the piping in the pretreatment of PW and WFI be fully *fabricated* of Stainless Steel but not that the system needs to be sanitary.

The pretreatment is not a storage system for PW or WFI but an intermediate stage between potable water to the final product. The ISO allows use of flanges and non-sanitary valves as long as they are fabricated of Stainless Steel.

The usual practice is to use the more cost effective Tri Clamps that are smaller and lighter than flanges.

The ISO has not stated that the piping should be fully sanitary.

The Petitioners read into the ISO standard requirements that do not exist.

2.4 Sampling valves

The Petitioners are not familiar with the terminology of the standard as they state that these valves cannot be installed on short outlet tees. The “Zero dead leg” sample valves are those valves that do not have a dead leg. They are commonly used, can be specified with Tri Clamp connections and can be purchased economically.

A *non-zero dead leg valve* can be any type of valve, including those with large dead legs on the inlet and including ball valves that trap water in the valve body. This type of valve commonly will give false positives as the sample will include large amounts of bacteria growing on the inside of the valve and the valve connection.

2.5 Instrumentation

The standard lists the minimum instrumentation for a water system and presents a table that summarizes the parameters needed for measuring, alarming, storing and graphing from online instruments

The Petitioners declare that as the table states that ESC amps should be measured then the ESC should be installed.

With this logic, the meaning of “put a hat on in the sun” is “it’s daytime”.

This is not a logical conclusion and has been clearly stated otherwise [2].

3 Adhering to Present Type of Systems with No Ambition to Improve

3.1 Not replacing softeners

Softeners are a proven technology but have their drawbacks. The softeners can be used but are not the optimum choice.

The softener resin is organic and operates with slow water flow for proper ion exchange. In the softener media bed the proliferation of unwanted biological growth is almost inevitable. Control of this biofilm is possible but only by considerable investment in routine maintenance. The needed maintenance can range from backwash and regeneration to sanitizations and rebeddings.

In addition softeners effluent contaminate the environment with high levels of chloride from post regeneration rinses, this pollution is not sustainable in a shrinking globe suffering from water shortage and degradation of arable land.

That softeners are “proven technology” is not a criticism of the ISO standard as this technology is acceptable but sets modest quality goals.

3.2 Pretreatment Operating Temperatures

The ISO has set a cap on pretreatment operating temperatures, this was criticized by the Petitioners.

It is well known that temperatures 30-35ºC are ideal for growth of bacteria as this is a common range of incubation temperatures for a Microbial Enumeration Test [3].

It is also written in the ISPE Baseline, paragraph 13.4.1.4 [4]

“Effect of Water Temperature on Biofilm Control:

Rapidly recirculating water systems, whose circulating temperatures are not appropriately moderated by cooling heat exchangers, **could reach the range of 30°C to 35°C, an ideal growth temperature for many water system bacteria**.” (Bold for emphasis)

Also the same has been stated in the WHO “Production of Purified Water” [5]:

“The following should be considered: control of temperature in the system by heat exchanger or plant room cooling to **reduce the risk of microbial growth (guidance value < 25 °C).”**

The ISO has a cap on the operating temperature in the system of 25ºC in line with ISPE and WHO so as to discourage microbial growth. This is so even in warm climates where raw water temperatures are higher than this, the system will be cooled to below 25ºC.

The ISO states that cooling systems are to be provided, this is also per ISPE baseline and per WHO.

4 Low Sensitivity to Quality and Reliability Issues in Water Systems

4.1 Sampling

The ISO is fully in line with USP approach and no extra sampling is needed.

The Petitioners quote the USP<1231> to resist setting specific water quality limits in the pretreatment.

As stated in the USP <1231> 4.1.Validation Requirement: “A typical water system validation program involves an **initial increased frequency of monitoring** of the treatment system process parameters and sampling and testing of major process points to demonstrate the ability to produce the acceptable water and to characterize the operation of the system. **This is followed by a life cycle approach of validation maintenance and monitoring**.”(Bold added for emphasis)

The USP<1231> adds: “A validation program qualifies and documents the design, installation, **operation, and performance** of the system.” (Bold for emphasis)

Furthermore, the USP <1231> states in paragraph 4.2.5 PQ:” **However, chemical purification can be compromised by poor microbial control** and, to a lesser degree, vice versa.” (Bold for emphasis)

If we look at further statements of the USP <1231> 5.3.4 Sanitization Procedures: “The routine frequency of sanitization **should be supported by the results of system microbial monitoring**.” (Bold for emphasis)

The sampling of pretreatment and production systems is well defined and entrenched in the industry as can be seen from the USP General Chapter, the ISO sets very modest limits to define what is “in a state of microbial control”.

The logic behind the ISO setting limits is that if the pretreatment is allowed to generate uncontrolled amounts of bacteria that slime deposit on the RO will eventually send permeate microbial levels out of specification.

4.2 Online TOC

The online TOC has been mandated by the ISO as in line with the latest in water systems thinking as stated in [6] “Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies.”

This Q&A document deals with membrane production of WFI but the ISO has adopted this view also for PW production for better control.

4.3 Reliability and Quality Issues

The Petitioners quote the USP<1231> that “Quality deviations in the early portions of the purification process can affect unit operation efficiency but **usually** do not impact the finished water quality or acceptable use.”(Bold added for emphasis)

Is this how we want to run our pharmaceutical water system? On the assumption that if we allow deviation in the pretreatment quality parameters then the finished water quality is **USUALLY** unaffected?!

This is the reason that the ISO was composed, to give clear quality targets.

5 Not Reading All of the Standard

5.1 ISO and National Pharmacopoeias complement each other

The ISO states in the introduction: “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.” (Bold for emphasis)

In addition, in paragraph 4.2.5 the ISO states: **PW/WFI quality shall be according to the last revision of the local/national/relevant Pharmacopoeia**”. (Bold for emphasis)

So the final quality of water is always according to the relevant Pharmacopoeia.

After this clear statement, it is hard to understand the Petitioner's claim that the ISO contradicts the USP.

There are no contradictions as the standard has stated that the recommended water quality levels given are for pretreatment and production stages, the final quality is per the relevant Pharmacopoeia.

It is pioneering, that finally, a standard has stated that SYSTEM microbial parameters must not exceed the potable water limits, after entering the boundaries of the PW/WFI pretreatment and production.

The situation, before ISO 22519, was not clear if growing coliforms, fungus, *Pseudomonas* and other undesirables in the PW/WFI pretreatment/production system disqualified it. After the ISO 22519, the situation is well defined, the water in system must have a quality no worse than the potable water feeding it.

The logic in this statement is unassailable, as if it is important that the incoming water from the municipality has potable water specifications why should these specifications be relaxed inside the water system?

Why did we have to make sure that undesirables were absent in the first place if we are allowed to let them grow in the system?!

5.2 Activated Carbon Sanitization

The standard states in paragraph 9.3.4: "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." (Bold for emphasis)

The Petitioners state that Active Carbon can be sanitized, per the ISO, only with steam.

This is untrue as can be seen above.

In paragraph ISO 22519, 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."

This means that industrial steam must not be used in contact with the carbon, only pure steam.

Perhaps this is the basis for the miscomprehension.

6 Unfamiliarity as to Contemporary Technologies

The Electrical Scale Control is based on electrolysis and is very well entrenched in the international market, both industrial and pharma.

ESC installations have been in operation for decades and there are worldwide "ESC" unit manufactures on the market in Germany, Singapore, Denmark, India and Israel.

The theory and practice is well covered in articles published in Germany, US, France, many in peer reviewed magazines. This includes the ISPE Pharmaceutical Engineering, Pharmind, La Vague, Pharma and Food, Technopharm and more.

There is EMA official recognition of the technology as viable pretreatment as in "EMA Guideline for WFI Production" [6].

The above facts prove error of the Petitioners statements that the Electrical Scale Control (ESC) is only available from a single proprietary manufacture, is patented and trademarked.

Processes that are based on electrolysis are nearly impossible to patent. There seems to be an unawareness by the Petitioners as to what is patented and what is in the realm of public knowledge.

There is no trademark on “Electrical Scale Control” or on “ESC”.

7 Not Being Up To Date on Present Industry Thinking

Hot water is one of the most reliable and effective of sanitization methods. Proper contact with water above 80°C will easily penetrate biofilm and kill the bacteria within. In addition, the hot water sanitization cycle doesn’t utilize disinfectants so there is no need to flush chemicals to drain at the end of the sanitization cycle. The systems can be relied upon to heat up, hold at high temperatures and then cool down autonomously without human supervision. In this way the sanitization cycle is repeatable both in the heat/cool cycle but also, once programed, will weekly or monthly go through the routine without interference.

The ISO standard is in line with the USP General Chapter USP<1231> 5.3.1: “Thermal sanitization:

Frequent use of thermal sanitization at appropriate temperatures should eliminate the need for other sanitization methods.” (Bold for emphasis)

This is the basis of the ISO.

This line is logical as chemical sanitization has basic problems of biofilm penetration.

The Petitioners disagree with this statement and differ with the USP General Chapter USP<1231> and ISO standard 22519.

8 Not Internally Consistent

The ISO minimum acceptable ID polish for Surface finish has been set at Ra<0.6 micron.

This is in line with the BPE and ISPE recommendations.

As in the ASME BPE, SD-4.1.2.2 [7]: “When compendial water systems are constructed of 316L stainless steel or other alloy steels, **the surface finish should be less than or equal to 25 in. Ra or 0.6 m** (see Part SF) and may be internally electropolished.” (Bold for emphasis)

In the ISPE Base Line [4] Para 8.4.4: “The benefits of any specified finish should be weighed against the application and the risks associated with using a lower finish. Though the value of high quality finishes is undecided, **finishes in the range of 25 microinch (0.6 micrometer) Ra are most common**.” (Bold for emphasis)

The Petitioners recommend the ASME BPE on the section for Sanitary Design but do not accept it in the section for Surface Finish.

In the interest of reliability, cleanability and simplicity, piping was specified to be 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 discounted as a construction material as high quality heat resistant polymeric piping with “no bead” welds is hard to reliably achieve. In the interests of keeping the standard simple and fool proof, the SS piping is given as the only option.

ISO is Clear, Pioneering and Advanced

It is **CLEAR** in all its statements, parameters are stated, tables with names of equipment and typical configurations with unambiguous list of criteria and instructions.

The standard is **PIONEERING** in that it gives specific quality standards in the pretreatment and production stages. it 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, designers and users, to enable them to evaluate or design a water system.

It is **ADVANCED** in that it encompasses new technologies as well as old and has a unique global scope per incoming water specifications.

Conclusions

Quite a few of the Petitioners were invited to take part in the standard, a number of them tried without success to join.

The Author is sure that if they would have been able to contribute they would have had a positive input on the standard. The Author is also sure that had the Petitioners managed to join the ISO effort, their reaction to its publication would have been different.

The article is a hasty, knee jerk reaction to a new, pioneering and advanced standard.

The Petitioners, in their rush to publish their opinion on the standard, published a muddled list of factual mistakes, wild claims, inaccuracies and false statements based on misunderstandings. The article is un-researched, based on spotty reading of the standard and based only on the mistaken judgment of the writers.

The industry has been stagnant for decades, every guideline has been loose and general in its requisites. So many open issues so that bottom line you can nearly do what you like. Now there is a ruler, a way to measure if the system is compliant to a standard or not.

For the first time, microbiological aspects of the pretreatment and production for PW and WFI systems are considered and firm action-alert levels are given.

Systems that keep to the recommendations of the standard will minimize proliferation of biofilm, quality and reliability will be improved and will meet the pharmaceutical market demands of a well-designed system capable of controlling bioburden from beginning to end.

References:

[1] “New ISO Standard Available for Water Systems”, PDA Letter, Volume LV, Issue 6, June 2019, Shlomo Sackstein

[2] Pharmind, Wissenschaft und Technik, ISO 22519: New Water System Standard, Shlomo Sackstein, Pharm. Ind. 81, Nr 6, 843-850 (2019)

[3] PW United States Pharmacopeia General Chapter <1231>, USP 42-NF 37, 2019

[4] ISPE Baseline Guide, Volume 4: Water and Steam Systems, Second Edition, 2012

[5] WHO, Water for Pharmaceutical use TRS 970, Annex 2, 2012

[6] EMA/INS/GMP/443117/2017, GMP/GDP Inspectors Working Group, Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies, 1 August 2017

[7] ASME BPE 2014, Bioprocessing Equipment