Welcome

Empowering a healthy tomorrow

USP Standards on Pharmaceutical Waters and Initiatives

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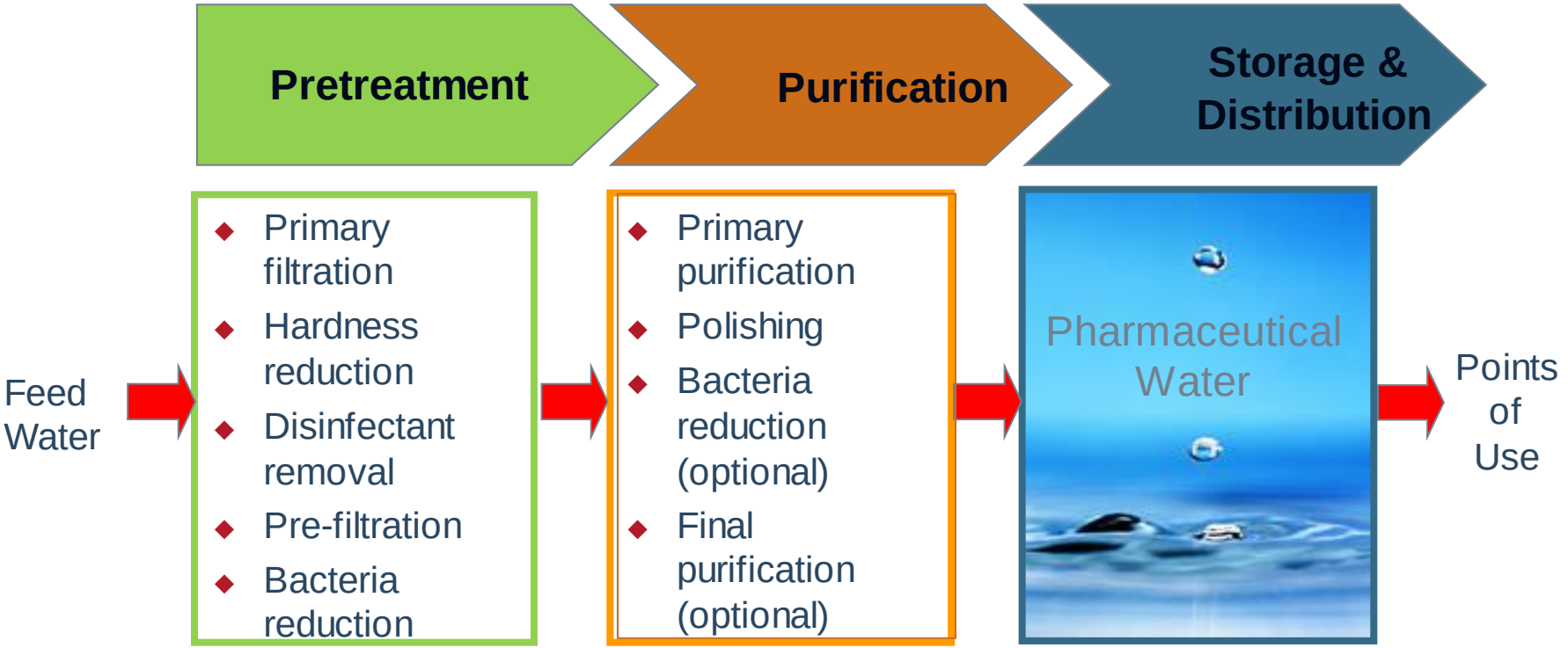
April 15, 2021

Agenda

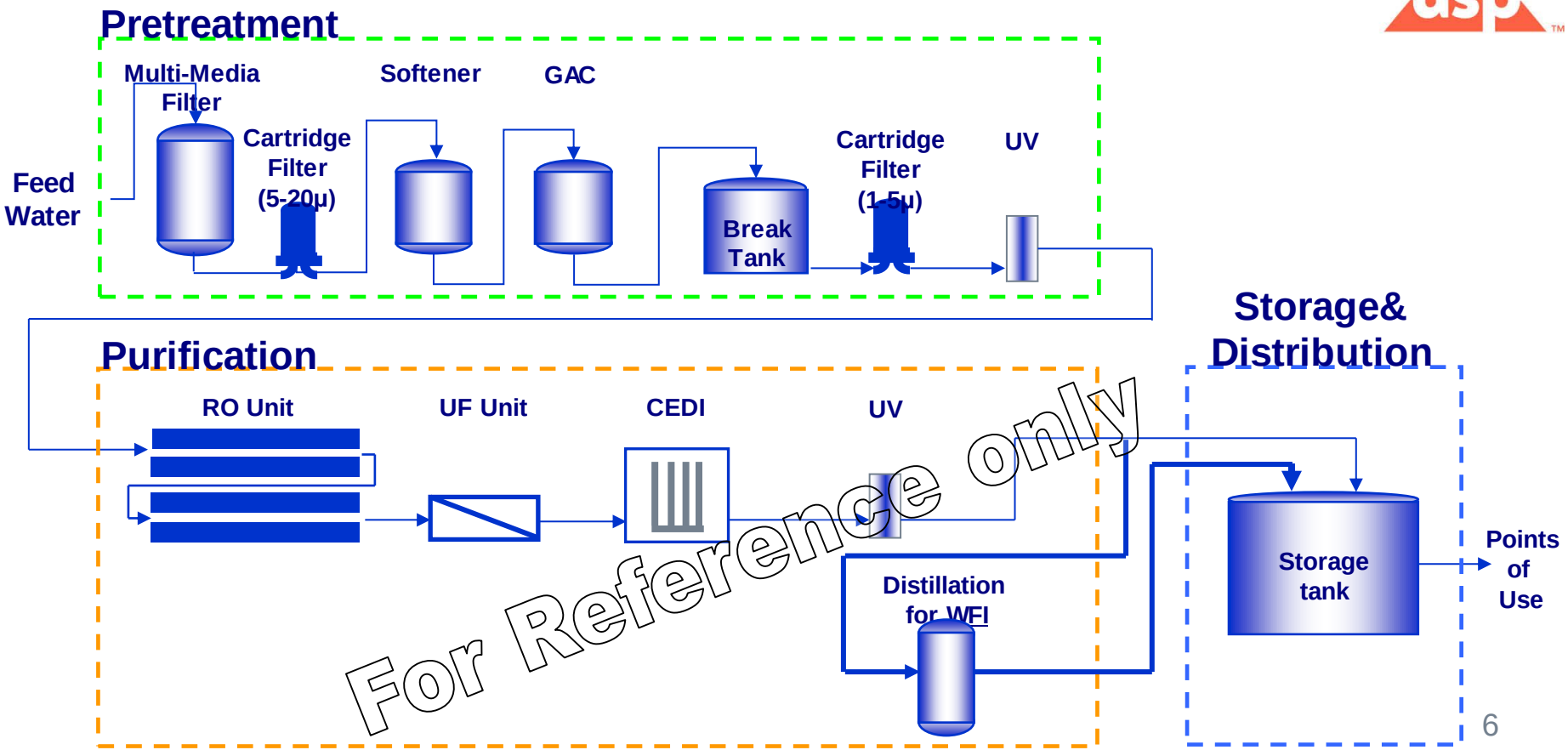
- Overview
- Types of Water, USP-NF
- Chemical and Microbiological Tests
- Recent Changes
- Harmonization

OVERVIEW

Pharmaceutical Water Preparation



Example - Pharmaceutical Water Production



USP Submission of Technical Comments

World Health Organization

Working document QAS/20.842/Rev.1
July 2020

DRAFT WORKING DOCUMENT FOR COMMENTS

Good manufacturing practices: water for pharmaceutical use

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2020
EMA/CHMP/CVMP/QWP/230700/2020
Committee for medicinal products for human use (CHMP)
Committee for medicinal products for veterinary use (CVMP)

Overview of comments received on the draft 'Guideline on the quality of water for pharmaceutical use' (EMA/CHMP/CVMP/QWP/496873/2018)

Characteristics of Impurities in Water

Impurity Types	Characteristics	Types of Tests
Microbiological	living, organic	sterility
Microbiological	dead, organic	BET
Organic	non-ionic	TOC
Inorganic	ionic	conductivity
Particulate	insoluble	filter/particle counter
Dissolved Gases	ionic, non-ionic	usually benign

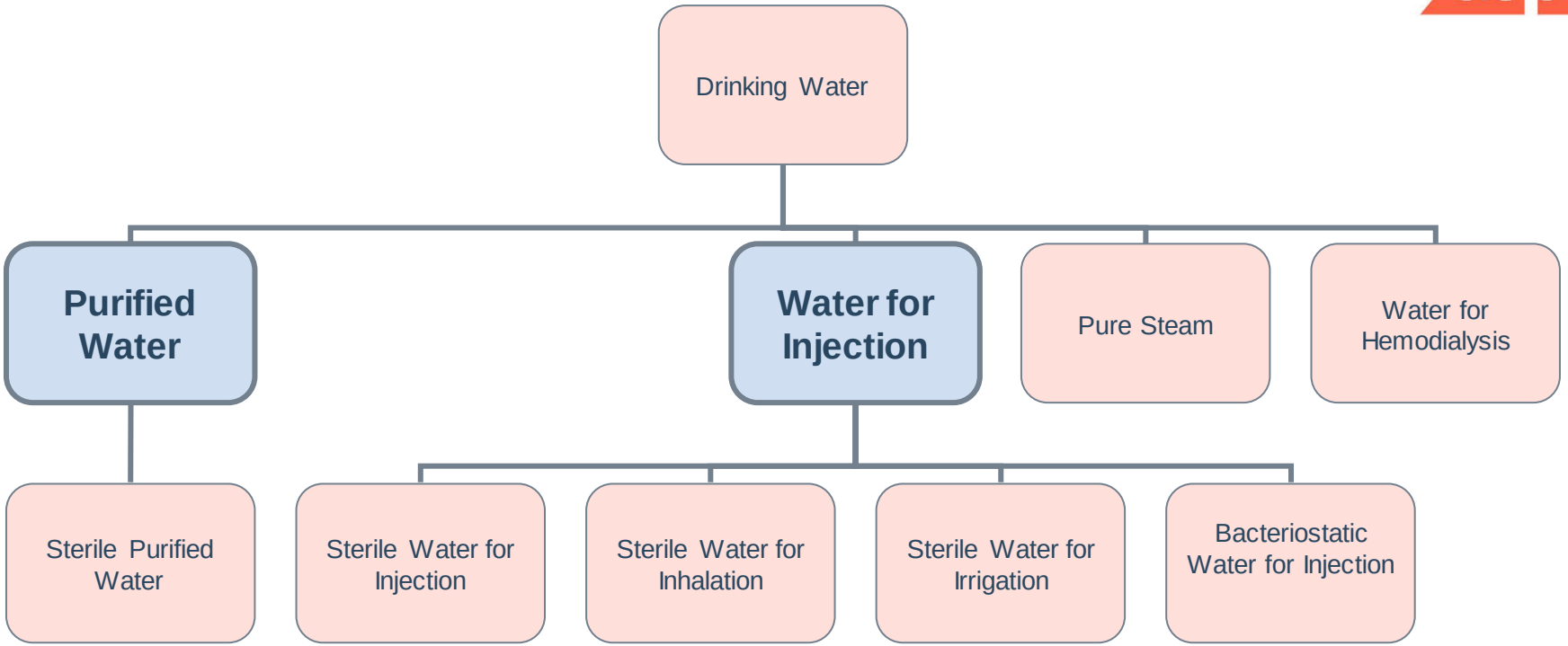
Classes of Contaminants/Removal Methods

Type / Process	Dissolved Ionic Solids	Dissolved Ionic Gases	Dissolved Organics	Particulates	Bacteria	Pyrogens
Filtration micron	P	P	P	E	P	P
Filtration sub-micron	P	P	P	E	E	P
Filtration ultra/nano	P	P	G	E	E	E
Softener	E/G	P	P	P	P	P
Carbon Adsorption	P	P	E/G	P	P	P
Reverse Osmosis	G/E	P	G/E	E	E	E
Deionization	E	E	P	P	P	P
Distillation	E	P/E	G/E	E	E	E
UV Oxidation	P	P	G/E	P	G	P

E = Excellent, capable of complete or near total removal of impurity type
G = Good, capable of removal of large %
P = Poor, little or no removal

TYPES OF WATER, *USP-NF*

USP Pharmaceutical Waters Tree



Bulk Purified Water - Today

Attribute [1]	USP-NF 43, Supp 2	EP 10.5	JP 17, Supp 2 [6]
Production Method	Suitable process	Suitable process	Distillation, ion-exchange, RO, UF, or combination
Source Water	US, EU, Japan, WHO drinking water	Human consumption	JP "Water" specifications
Total Aerobic (cfu/mL) [2]	-	Action Level of 100	-
Conductivity (μS/cm at 25°C) [3]	1.3 (3 stage)	5.1 (1 stage)	1.3 (3 stage)
TOC (mg/L)	0.5	0.5 (optional)	0.5
Bacterial Endotoxins (EU/mL)			
Nitrates (ppm)		0.2	Not detectable
Heavy Metals (ppm)		Risk Assessment [5]	Not detectable
Acidity/Alkalinity			Test with color indicators
Chloride			Not detectable
Sulfate			Not detectable
Nitrite			Not detectable
Ammonium (mg/mL)			0.5
Oxidizable Substances (/100 mL)		<0.1 mL 0.02 M $KMnO_4$ [4]	< 0.10 mL 0.02 $KMnO_4$
Residue on Evaporation (mg)			1.0/100 mL

Note 1: All tests are maximum, unless otherwise stated.

Note 2: Microbiological testing is not considered to be harmonized. The EP test is written into the Production section, and the USP test is contained in a non-compendial general information chapter.

Note 3: Limits are temperature dependent.

Note 4: Alternative to TOC.

Note 5: Not required effective Jan 1, 2009 if WFI conductivity requirements are met

Note 6: Shaded chemical tests were deleted effective in JP16 (4/1/11).

Bulk Water for Injection(s) - Today

Attribute [1]	USP-NF 43, Supp 2	EP 10.5	JP 17, Supp 2 [5]
Production Method	Distillation or suitable process	Distillation OR EQUIVALENT	Distillation, RO with UF, from Purified Water
Source Water	US, EU, Japan, WHO DW	Human consumption	JP "Water" specifications
Total Aerobic (cfu/100 mL) [2]	-	Action Level of 10	-
Conductivity (μS/cm at 25°C) [3]	1.3 (3 stage)	1.3 (3 stage)	1.3 (3 stage)
TOC (mg/L)	0.5	0.5	0.5 (0.3 for control)
Bacterial Endotoxins (EU/mL)	0.25	0.25	0.25
Nitrates (ppm)		0.2	Not detectable
Heavy Metals (ppm) [4]			Not detectable
Acidity/Alkalinity			Test with color indicators
Chloride			Not detectable
Sulfate			Not detectable
Nitrite			Not detectable
Ammonium (mg/mL)			0.5
Oxidizable Substances (/100 mL)			< 0.10 mL 0.02 $KMnO_4$
Residue on Evaporation (mg)			1.0/100 mL

Note 1: All tests are maximum, unless otherwise stated.

Note 2: Microbiological testing is not considered to be harmonized. The EP test is written into the Production section, and the USP test is contained in a non-compendial general information chapter.

Note 3: Limits are temperature dependent.

Note 4: Not required effective Jan 1, 2009.

Note 5: Shaded chemical tests were deleted effective in JP16 (1/1/11).

CHEMICAL AND MICROBIOLOGICAL TESTS

USP-NF: <643> Total Organic Carbon

6. What is the total organic carbon (TOC) limit for Purified Water and Water for Injection?

There is a "target limit response" of 500 µg of Carbon/L. The true limit is the response of the TOC measurement system to a 500 µg Carbon/L (prepared from sucrose) solution, Rs, corrected for the response to reagent water, Rw. This limit is equal to Rs – Rw. The actual number will vary based upon your reference standard solution, your equipment, background carbon, etc. USP Reference Standards are required for use.

FAQs: https://www.usp.org/frequently-asked-questions/water-pharmaceutical-and-analytical-purposes

EP: 2.2.44. Total Organic Carbon in water for pharmaceutical use

the case of a magnetic analyser where the m/z ratio varies exponentially with the value of the magnetic field, there should be as many points as possible.

SIGNAL DETECTION AND DATA PROCESSING

Ions separated by an analyser are converted into electric signals by a detection system such as a photomultiplier or an electron multiplier. These signals are amplified before being re-converted into digital signals for data processing, allowing various functions such as calibration, reconstruction of spectra, automatic quantification, archiving, creation or use of libraries of mass spectra. The various physical parameters required for the functioning of the apparatus as a whole are controlled by computer.

2.2.44. TOTAL ORGANIC CARBON IN WATER FOR PHARMACEUTICAL USE

Total organic carbon (TOC) determination is an indirect measure of organic substances present in water for pharmaceutical use. TOC determination can also be used to monitor the performance of various operations in the preparation of medicines.

A variety of acceptable methods is available for determining TOC. Rather than prescribing a given method to be used, this general chapter describes the procedures used to qualify the chosen method and the interpretation of results in limit tests. A standard solution is analysed at suitable intervals, depending on the frequency of measurements; the solution is prepared with a substance that is expected to be easily oxidisable (for example, sucrose) at a concentration adjusted to give an instrument response corresponding to the TOC limit to be measured. The suitability of the system is determined by analysis of a solution prepared with a substance expected to be oxidisable with difficulty (for example, 1,4-benzoquinone).

The various types of apparatus used to measure TOC in water for pharmaceutical use have in common the objective of completely oxidising the organic molecules in the sample water to produce carbon dioxide followed by measurement of the amount of carbon dioxide produced, the result being used to calculate the carbon concentration in the water.

The apparatus used must discriminate between organic and inorganic carbon, the latter being present as carbonate. The discrimination may be effected either by measuring the inorganic carbon and subtracting it from the total carbon, or by purging inorganic carbon from the sample before oxidation. Purging may also entrain organic molecules, but such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

Apparatus. Use a calibrated instrument installed either on-line or off-line. Verify the system suitability at suitable intervals as described below. The apparatus must have a limit of detection specified by the manufacturer of 0.05 mg or less of carbon per litre.

TOC water. Use highly purified water complying with the following specifications:

- conductivity: not greater than 1.0 $\mu S cm^{-1}$ at 25 °C,
- total organic carbon: not greater than 0.1 mg/l.

Depending on the type of apparatus used, the content of heavy metals and copper may be critical. The manufacturer's instructions should be followed.

Glassware preparation. Use glassware that has been scrupulously cleaned by a method that will remove organic matter. Use *TOC water* for the final rinse of glassware.

Standard solution. Dissolve *sucrose R*, dried at 105 °C for 3 h in *TOC water* to obtain a solution containing 1.19 mg of sucrose per litre (0.50 mg of carbon per litre).

Test solution. Using all due care to avoid contamination, collect water to be tested in an airtight container leaving minimal head-space. Examine the water with minimum delay to reduce contamination from the container and its closure.

System suitability solution. Dissolve *1,4-benzoquinone R* in *TOC water* to obtain a solution having a concentration of 0.75 mg of 1,4-benzoquinone per litre (0.50 mg of carbon per litre).

TOC water control. Use *TOC water* obtained at the same time as that used to prepare the standard solution and the system suitability solution.

Control solutions. In addition to the *TOC water control*, prepare suitable blank solutions or other solutions needed for establishing the baseline or for calibration adjustments following the manufacturer's instructions; run the appropriate blanks to zero the instrument.

System suitability. Run the following solutions and record the responses: *TOC water* (r_w); *standard solution* (r_s); *system suitability solution* (r_{ss}). Calculate the percentage response efficiency using the expression:

$$\frac{r_{ss} - r_w}{r_s - r_w} \times 100$$

The system is suitable if the response efficiency is not less than 85 per cent and not more than 115 per cent of the theoretical response.

Procedure. Run the test solution and record the response (r_u). The test solution complies with the test if r_u is not greater than $r_s - r_w$.

The method can also be applied using on-line instrumentation that has been adequately calibrated and shown to have acceptable system suitability. The location of instrumentation must be chosen to ensure that the responses are representative of the water used.

2.2.45. SUPERCRITICAL FLUID CHROMATOGRAPHY

Supercritical fluid chromatography (SFC) is a method of chromatographic separation in which the mobile phase is a fluid in a supercritical or a subcritical state. The stationary phase, contained in a column, consists of either finely divided solid particles, such as a silica or porous graphite, a chemically modified stationary phase, as used in liquid chromatography, or, for capillary columns, a cross-linked liquid film evenly coated on the walls of the column. SFC is based on mechanisms of adsorption or mass distribution.

APPARATUS

The apparatus usually consists of a cooled pumping system, an injector, a chromatographic column, contained in an oven, a detector, a pressure regulator and a data acquisition device (or an integrator or a chart recorder).

Pumping system

Pumping systems are required to deliver the mobile phase at a constant flow rate. Pressure fluctuations are to be

Test solution. Using all due care to avoid contamination, collect water to be tested in an airtight container leaving minimal head-space. Examine the water with minimum delay to reduce contamination from the container and its closure.

System suitability solution. Dissolve *1,4-benzoquinone R* in *TOC water* to obtain a solution having a concentration of 0.75 mg of 1,4-benzoquinone per litre (0.50 mg of carbon per litre).

TOC water control. Use *TOC water* obtained at the same time as that used to prepare the standard solution and the system suitability solution.

Control solutions. In addition to the *TOC water control*, prepare suitable blank solutions or other solutions needed for establishing the baseline or for calibration adjustments following the manufacturer's instructions; run the appropriate blanks to zero the instrument.

System suitability. Run the following solutions and record the responses: *TOC water* (r_w); *standard solution* (r_s); *system suitability solution* (r_{ss}). Calculate the percentage response efficiency using the expression:

$$\frac{r_{ss} - r_w}{r_s - r_w} \times 100$$

The system is suitable if the response efficiency is not less than 85 per cent and not more than 115 per cent of the theoretical response.

Procedure. Run the test solution and record the response (r_u). The test solution complies with the test if r_u is not greater than $r_s - r_w$.

The method can also be applied using on-line instrumentation that has been adequately calibrated and shown to have acceptable system suitability. The location of instrumentation must be chosen to ensure that the responses are representative of the water used.

EP method is identical to USP method FOR BULK WATERS.

JP: 2.59. *Test for Total Organic Carbon*

General Information section:

G8. Quality Control of Water for Pharmaceutical Use

4.5.2. Monitoring of TOC as the Indicator for Organic Impurities

The acceptance criterion of TOC is specified as "not greater than 0.50 mg/L (500 ppb)" in the monographs of *Purified Water* and *Water for Injection*. However it is recommended for each facility preparing pharmaceutical water to conduct operation control of pharmaceutical water processing system through TOC monitoring on produced water based on its own alert and action levels for TOC determined individually. The following are the recommended action levels for TOC.

- Action Level: ≦ 300 ppb (in-line)
  ≧ 400 ppb (off-line)

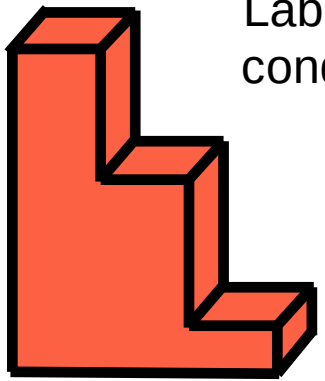
The JP specifies the *Test for Total Organic Carbon* <2.59>, and normally, TOC measurement should be conducted using an apparatus which meets the requirements described in the JP method. However, if a TOC apparatus conforms to the apparatus suitability test requirements described in "*<643> TOTAL ORGANIC CARBON*" of the USP, or those described in the "*Methods of Analysis 2.2.44. TOTAL ORGANIC CARBON IN WATER FOR PHARMACEUTICAL USE*" of the European Pharmacopoeia (EP), the apparatus can be used for the monitoring of pharmaceutical water processing system, if sufficiently pure water not contaminated with ionic organic substances, or organic substances having nitrogen, sulfur, phosphorus or halogen atoms in their structures, is used as the source water supplied to the system.

The JP 2.59. TOC method is different than EP and USP. Or is it?

USP-NF: <645> Water Conductivity

Stage 3 Procedure - Bulk Waters

Measure in-line, non-temperature-compensated conductivity and temperature. Look up conductivity limit for that temperature. If measured uncompensated conductivity is less than conductivity limit, then **Pass - Done**. If not:

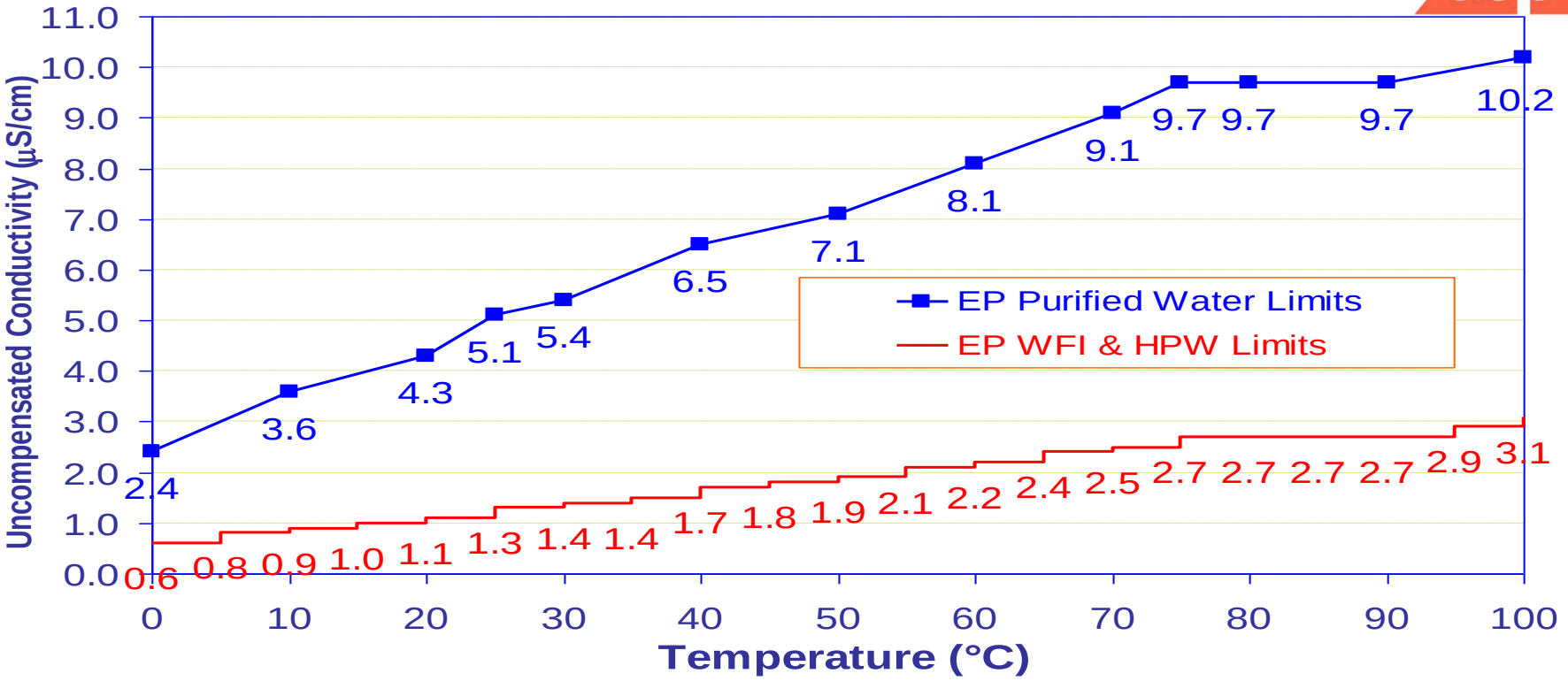


Lab Test : Equilibrate water sample with atmospheric CO_2 : If conductivity is less than 2.1 µS/cm at 25°C, **Pass – Done**. If not:

Lab Test: Saturate previous sample with KCl : Measure pH. Look up conductivity limit for that pH. If measured conductivity (from Stage 2) is < conductivity limit, **Pass – Done**. If not:

Fail

EP: 2.2.38. Conductivity



JP: 2.51. *Conductivity Measurement*

Water for injection monograph

Conductivity ⟨*2.51*⟩ When the test is performed according to the following method, the conductivity (25°C) is not more than 2.1 $\mu S \cdot cm^{-1}$.

Transfer a suitable amount of Water for Injection to a beaker, and stir the water specimen. Adjust the temperature to 25 ± 1°C, and begin agitating the water specimen vigorously, while observing its conductivity periodically. When the change in conductivity becomes not greater than 0.1 $\mu S \cdot cm^{-1}$ per 5 minutes, adopt the observed value as the conductivity of the water specimen.

The JP 2.51. conductivity method is different than EP and USP. Or is it?

JP: 2.51. Conductivity Measurement

General Information section:

G8. Quality Control of Water for Pharmaceutical Use

4.5.1.1. Monitoring of Conductivity by applying the *Conductivity Measurements* <2.51> of the JP

When the monitoring of the conductivity of *Purified Water* and *Water for Injection* is performed at the standard temperature (20°C), measure the conductivity after confirming that the measure temperature is within a range of 20 ± 1°C. In this case, the recommended allowable conductivity (action level) for *Purified Water* and *Water for Injection* is as follows.

- Action Level 1.1 $\mu S \cdot cm^{-1}$ (20°C)

Since the above allowable conductivity is established for in-line monitoring, an alternative action level may be used for the monitoring based on offline batch testing.

4.5.1.2. Monitoring of Conductivity by applying the <645> *WATER CONDUCTIVITY* of the USP with some modification

Usually, it is somewhat difficult to control the temperature exactly in in-line conductivity monitoring. Therefore, the following approach can be applied for the monitoring at temperatures other than the standard temperature (20°C) of the JP. This approach is based on the Stages 1 and 2 of the three-stage approach described in "<645> *WATER CONDUCTIVITY*" of the USP and in the monographs being associated with water for pharmaceutical use ("Purified Water", "Highly Purified Water" and "Water for Injections") of the European Pharmacopoeia (EP).

You can follow USP <645> method to meet conductivity process monitoring requirements in JP

USP-NF: Microbial Requirements in <1231> *Water for Pharmaceutical Purposes*

1. Why are there no microbial requirements included in the monographs for Purified Water and Water for Injection?

Because of the various uses of these waters, microbial requirements are not included in these monographs since this would unnecessarily burden some users with meaningless and/or inconsequential or inappropriate requirements, e.g. water used for many laboratory analyses. Microbial guidelines are provided under the informational chapter *Water for Pharmaceutical Purposes <1231>* where it states that the user should establish in-house specifications or fitness for use microbial levels above which the water is unsuitable for use.

2. What is the purpose of microbial Alert and Action Levels for Purified Water and Water for Injection?

Alert and Action Levels are process control terms and should be established at levels indicative of the water system trending outside of its normal microbial control range. These levels should be established at levels no higher than, and preferably lower than, those listed in *Water for Pharmaceutical Purposes <1231>* based on the normal microbial performance trends in your water system. The purpose of Alert and Action Levels is to trigger additional, non-routine, rather than routine microbial control measures. These additional control measures should prevent objectionable levels and types of microorganisms from being present in the water, based on for the water's use.

FAQs: https://www.usp.org/frequently-asked-questions/water-pharmaceutical-and-analytical-purposes

RECENT CHANGES

Sterile packaged waters: TOC measurement

- Stakeholder Roundtable conducted at USP on June 6, 2019
  - Participants included 6 manufacturers, 1 consultant, PDA, USP
  - Presentations by USP Water EP, 2 stakeholders

- Publication in *PF* 45(6) [Nov-Dec, 2019]
  - Replace *Oxidizable Substances* test with a "meaningful" attribute to limit organic impurities
  - Incorporating outcomes from roundtable into drafts of <643> and SWFI
  - Proposed multilevel specification based on container volume
  - Based on a survey of the industry's current capability for sterile products, stakeholder comments, and roundtable
  - Multi-staged limit requiring additional work to identify and quantify individual organic species and to cite safety documentation, if needed

Specification Schema

- Multi-level specification with characterization option based on process capability:

- Stage 1: If TOC level is NMT Limit 1, it complies. If it does not, go to Stage 2
  - ≤ 5 mL container volume 32.0 mg C / L
  - ≤ 100 mL 24.0 mg C / L
  - > 100 mL 8.0 mg C / L

- Stage 2: If TOC level is greater than Limit 2 (150%), it does not comply
  - ≤ 5 mL container volume 48.0 mg C / L
  - ≤ 100 mL 36.0 mg C / L
  - > 100 mL 12.0 mg C / L

- Stage 3: If Limit 1 is exceeded but it is NMT Limit 2, identify and quantify each individual organic impurity exceeding a concentration of ≥ 0.20 mg C / L (as per ICH M7)

Container Nominal Volume (mL)	Limit 1* (mg C / L)	Limit 2* (mg C / L)
≤ 5	32.0	48.0
> 5 and ≤ 100	24.0	36.0
> 100	8.0	12.0

Timeline

- USP Next Steps
  - Changes posted on November 1, 2020 in *USP 2021, Issue 1*
  - Official status on May 1, 2021

- Pharmacopeial Discussion Group (PDG) Next Steps
  - Need to address disconnect between PDG topic (SWFI) and non-PDG topic (GC)

<1231> *Water for Pharmaceutical Purpose* - Ballot for *USP-NF 2021, Issue 3*

- Introduction
- Source Water
- Waters Used for Pharmaceutical Manufacturing and Testing
- Validation and Qualification of Water Purification, Storage, and Distribution Systems
- Design and Operation of Purified Water and Water for Injection Systems
- Sampling
- Chemical Evaluations
- Microbiological Evaluations
- Use of Alert and Action Levels and Specifications

Revisions under discussion

- Proposed additions and changes to <1231> *Water for Pharmaceutical Purposes*
  - Nitrosamines in pharmaceutical waters
  - Guidelines for hot water as sanitizing
  - Rapid microbiological methods
  - Validation of novel technologies for purification
  - New technologies for instrumentation and purification
  - Biotech water
  - Standardization of analytical waters
  - … and many more
- New general chapter <1232> *Instrumentation for Analysis of High Purity Pharmaceutical Waters*
- <1230> *Water for Hemodialysis Applications*

HARMONIZATION

USP-NF: Sterile Water for Injection (SWFI)

- PDG:
  - USP Stage 1 draft for SWFI (E62), version 2 distributed in July 2020
  - Comments received from EP on November 30, 2020
  - Comments received from JP on December 14, 2020

- Next Steps:
  - USP responses in process and targeting March 2021

Harmonization: Conductivity Methods and Limits

Parameter	USP	EP	JP	CP
Conductivity test required	yes	yes	yes	2010
Eliminate chemistry tests	yes	no [1]	yes	no [3]
Purified Water 3-stage test	yes	no	yes	
Purified Water test limits [2]	1.3 µS/cm	5.1 µS/cm	1.3 µS/cm	?
WFI 3-stage test	yes	yes	yes	yes
WFI limits [2]	1.3 µS/cm	1.3 µS/cm	1.3 µS/cm	1.3 µS/cm
Instrument requirements	yes	yes	yes	
Sensor accuracy	±2%	±2%	yes	
Sensor calibration method	not specific	not specific	yes	
Calibration solutions	user selected	user selected	yes	
Calibration Method	works	works	yes	
Compensation	none	none	yes	
Method tested	yes	yes	yes	yes

[1] Heavy metals and nitrates tested required for EP; aluminum test required for dialysis solutions
[2] at 25°
[3] retained ammonia and heavy metals tests

USP Proposal for Harmonization of *Purified Water*, *Water for Injection*, *Pure Steam*

- Scope:
  - Support the PDG project for Early Engagement of Industry by performing a pilot for harmonization
  - The three proposed monographs are among the most used in numerous aspects of the industry. Harmonization would be most impactful on all stakeholders by defining common quality elements (e.g., description, starting material, methods of manufacturing, quality attributes, test methods, specifications, packaging)
- Next Steps:
  - USP to introduce the proposal to PDG in March 2021 meeting

Thank You

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