University of Ljubljana
Faculty of Pharmacy

WATER FOR PHARMACEUTICAL USE

assist. prof. dr. Špela Zupančič, M. Pharm.
spela.zupancic@ffa.uni-lj.si

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Module 1: Pharmacy

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WATER – THE NECESSITY OF LIFE

- Forms salvia (digestion)
- Keeps mucosal membranes moist (eyes, nose, mouth)
- Enables the growth and proliferation of human cells
- Eliminates the body waste through urine and bowls
- Lubricates the joints and sinews
- The needed component to produce hormones and neurotransmitters
- Regulates temperature sweating and respiration
- It acts as a shock absorber for the brain and spinal cord
- Participate in conversion of food into available components through digestion
- Participate in the delivery of oxygen and nutrients all over the body

WATER

demineralised water

tap water

distilled water

water for injections

dionised water

drinking water

purified water

feed water

source water

mineral water

potable water

water for the production of extracts

WATER FOR PHARMACEUTICAL USE

Water can be used:

- for cleaning agent for rinsing vessels, equipment, primary packaging material
- during synthesis of active ingredient
- during production of final product
- as an excipient
- for reconstitution of the product

We can choose between:

- Potable water
- Water for preparation of extracts
- Purified water
- Water for injections

WATER FOR PHARMACEUTICAL USE

Water can be used:

- during synthesis of active ingredient
- during production of final product
- as an excipient
- for
- for

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- Water for injections
- Water for preparation of extracts
- Purified water

AIM

Why is water so special?
How to prepare water with defined quality?
What is the difference between these waters?
Which water to use for specific pharmaceutical use?

CONTENT

1 Physiochemical properties of water

2 Potable water

3 Water contaminants

4 Water purification methods

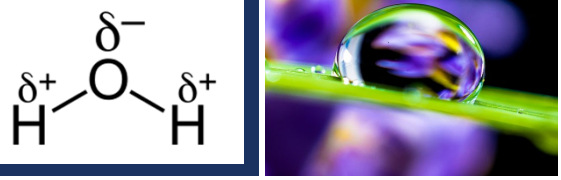
5 Pharmaceutical water systems

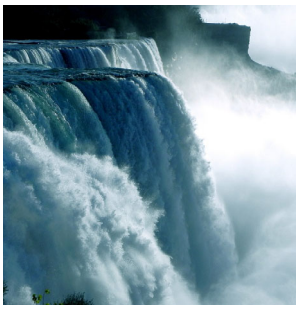
6 Waters in the pharmacopoeias

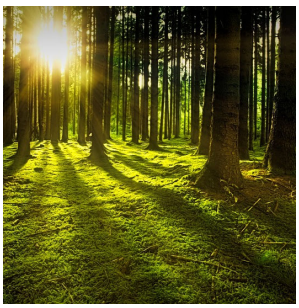
7 Which water to use for preparation of (radio)pharmaceuticals?

WATER PHYSICO-CHEMICAL CHARACTERISTICS

- one of the smallest by volume (0.03 nm^3) and the lightest molecules
- water has over 70 anomalies in physico-chemical characteristics
- **polarity and H-bonds -** unique chemical properties





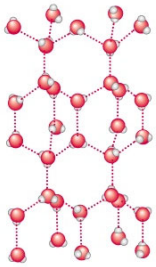


WATER PHYSICO-CHEMICAL CHARACTERISTICS

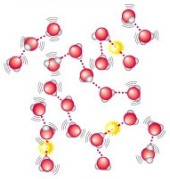
WATER
PHYSICO-CHEMICAL CHARACTERISTICS

- water molecules form an infinite **hydrogen-bonded** network with localized and structured clustering
- formation and breaking of H-bonds is a dynamic process that takes about 0.1 ps (10^{-13} s)

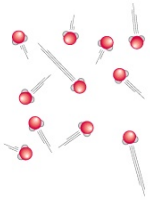
(*a*) **Solid water (ice)**



(*b*) **Liquid water**



(*c*) **Gaseous water (steam)**

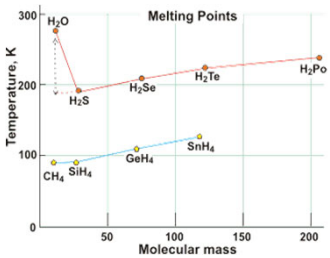


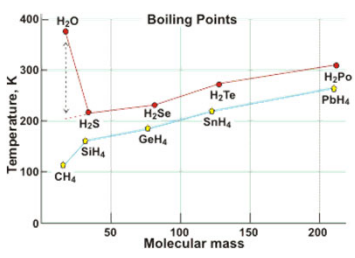
In solid form, each water molecule forms 4 H bonds (tetrahedrally arranged), average lifetime: (10^{-5} s)

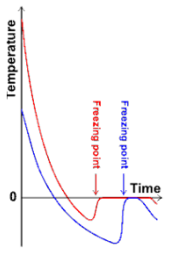
In liquid water (near 0 °C), each water molecule form on average 3.4 H-bonds, average lifetime: ($1 - 20\times10^{-12}$ s)

WATER
PHYSICO-CHEMICAL CHARACTERISTICS

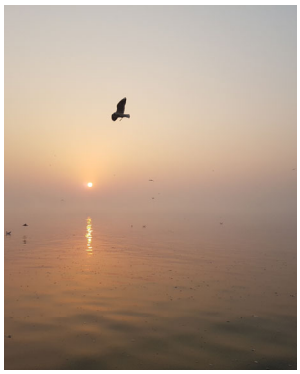
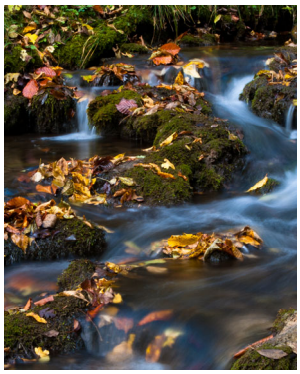
* the anomalous properties are those where the behavior of liquid water is quite different from what is found with other liquids
  - unusually high melting point and boiling point
  - the Mpemba effect – hot water may freeze faster than cold water!







http://www1.lsbu.ac.uk/water/water_anomalies.html

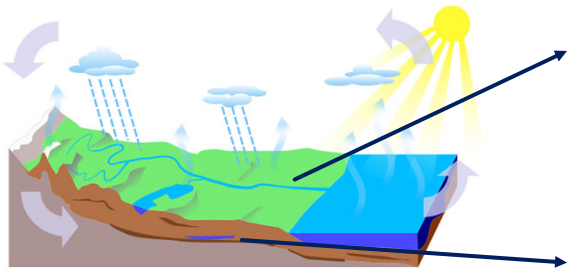

WATER SOURCES FOR POTABLE WATER

- Natural surface waters (e.g. rivers and reservoars)
- Deep bed well waters
- Sea waters

„Our planet consists mostly of oceans and seas but only small percent of water -0,007% is drinkable."
3x Environment

WATER SOURCES

- there is no pure water in nature due to water's unique chemical properties
- the type and concentration depend on geological, meteorological, and biospherical influences



SURFACE WATER
higher in biological material
higher in particulates
lower in dissolved ions

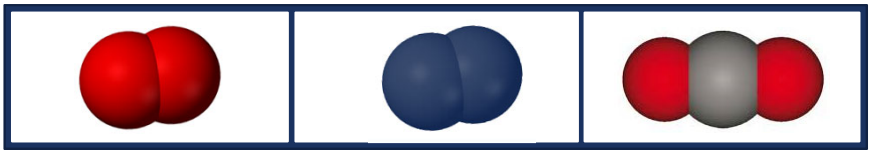
GROUND WATER
higher in dissolved ions
lower in particulates
lower in biological material

Surface waters: sea water (aqua marina), river water (aqua fluvialis)
Ground waters: mineral waters, spring waters (aqua mineralae), groundwater (aqua fontis, aqua fontana)

WATER CONTAMINANTS

- gases
- inorganic compounds
- organic compounds
- particles / colloids
- microorganisms
- microplastics

GASES



oxygen (O_2) nitrogen (N_2) carbon dioxide

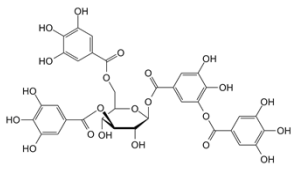
- gases are usually removed by degasification:
  - heating,
  - membrane degasification,
  - pressure reduction, …

INORGANIC COMPOUNDS

- the exact types of compounds depend on the **chemical composition of surrounding rocks**
- the most common are **Mg^2**, **Ca^2** and **Fe^2** salts
- as counterions, the **bicarbonate** and **carbonate** are prevalent
- cations: Na^+, Ca^{2+}, Fe^{2+}, Mg^{2+}, Al^{3+}
- anions: Cl^-, HCO_3^-, SO_4^{2-}, CO_3^{2-}, ClO^-, PO_4^{3-}
- **more problematic ions**: Pb^+, Cu^{2+}, Mn^{2+}, NO_3^-, SiO_4^{4-}, $Si_2O_7^{6-}$, hydrogen sulfide (in areas of thermal activity)

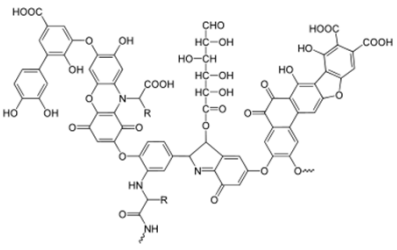
ORGANIC IMPURITIES - naturally occurring

tannins



phenols

humic acids



lignin

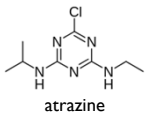
folic acid

pyrogens

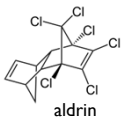
ORGANIC IMPURITIES - artificial

chlorinated solvents (CH_2Cl_2, $CHCl_3$, CCl_4) - byproducts of chlorination

herbicides, insecticides

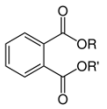


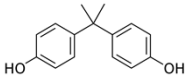
atrazine



aldrin

phthalates

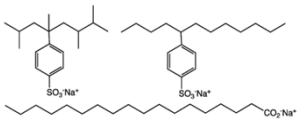




bisphenol A (BPA)

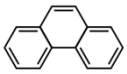
endocrine disrupting compounds (EDCs)

detergent residues



antibiotics

other hydrocarbon trace pollutants, e.g. PAH


phenantrene

COLLOIDS AND PARTICLES

COLLOIDS

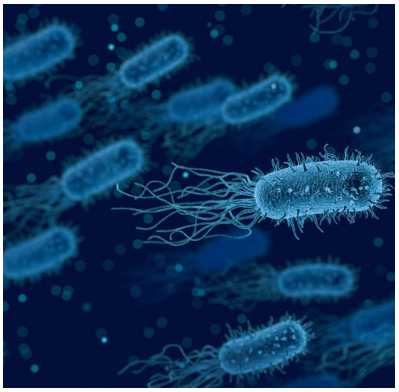
- Size: < 1 μm
- inorganic or organic particles
- form a stable nanosuspension that does not precipitate

- removed in the pretreatment phase by **sand filtration** or by **coagulation** (addition of $FeSO_4$)

PARTICLES

- Size: > 1 μm
- e.g. silt, clay, soil
- removed in the pretreatment phase by **sedimentation**

MICROORGANISMS



- one of the major obstacles to successful treatment of water
- particularly troublesome because of fast growth (even in nutrient-depleted conditions)
- **protozoa**
  - *Giardia lamblia*
  - *Cryptosporidium*
- **bacteria**
  - Gram negative (*Escherichia coli, Pseudomonas, Shigella, Campylobacter,…*)

➡ microbial byproducts and cellular fragments (such as LPS and nucleases) are more problematic

PYROGENS

Lipopolysaccharides (LPS)

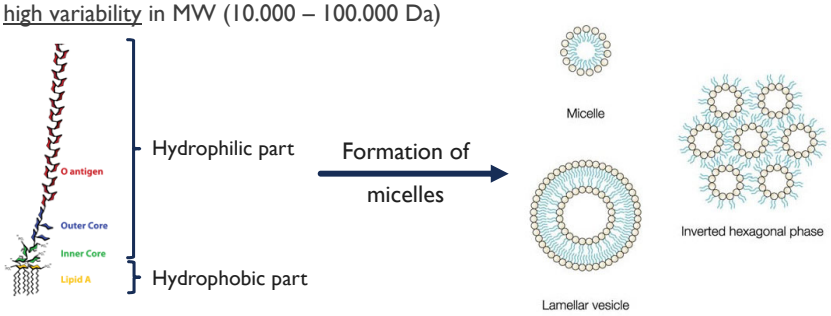
- an integral part of the outer membrane of Gram negative bacteria
- are released upon bacterial cell lysis
- categorized as endotoxins and have pyrogenic activity

→ **can cause fewer when released into the bloodstream**

PYROGENS

Lipopolysaccharides (LPS)

- thermally stable and insensitive to pH changes
- high variability in MW (10.000 – 100.000 Da)



- endotoxin levels measured in ‚endotoxin units' (EU) or IU
- **difficult to remove**

MICROPLASTICS

- 51 trillion microplastic particles in the seas
- plastic fragments < 5 mm
- **Primary** microplastics – directly released in the environment as small particles.
- **Secondary** microplastics – originate from degradation of larger plastic objects.
- found in food and drinks, including beer, honey and tap water
- accumulated in the bodies and tissues of many organisms
- lead to infertility of some animals
- animal death by malnutrition
- lack of study about the toxicity to human

Water sources for potable water

Water purification methods

Potable water

Water purification methods

- Water for preparation of extracts
- Purified water
- Water for injections

POTABLE WATER

DRINKING WATER, TAP WATER (*Aqua potabile*)

- the quality of potable water is determined by:
  - the **WHO** (*Guidelines for drinking-water quality, 4th edition, incorporating the 1st addendum, 2017*),
  - **ISO** (*ISO 24510, ISO 24511 and ISO 24512, Activities relating to drinking water and wastewater services*) drinking-water guidelines, and
- other relevant directives include:
  - **in EU, the European Drinking Water Directive (2020/2184)**
  - in US, The National Primary Drinking Water Regulations (NPDWR)
- in modern **pharmacopoeias there are no monographs for potable water**
- potable water is the raw material that is used to produce water for pharmaceutical use → regular testing needed to confirm the quality

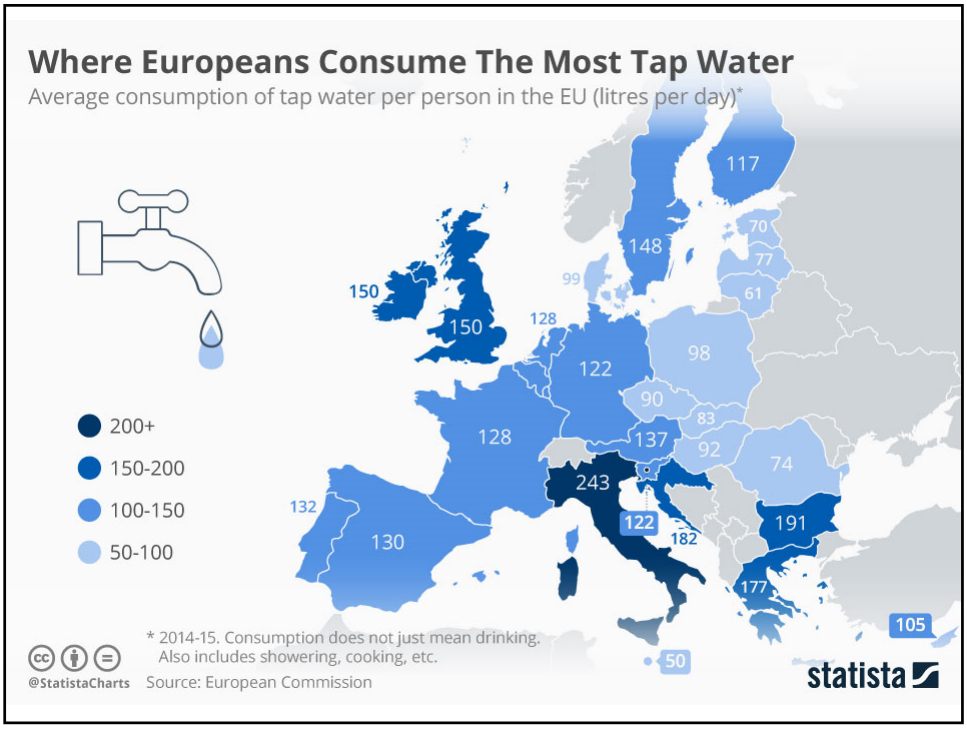
POTABLE WATER

European Drinking Water Directive (2020/2184)

- *1. This Directive concerns the quality of water intended for human consumption for all in the Union.*
- *2. The objectives of this Directive are to protect human health from the adverse effects of any contamination of water intended for human consumption by ensuring that it is wholesome and clean, and to improve access to water intended for human consumption.*

Need to monitor and regularly test:

- **microbiological** parameters
- **chemical** parameters
- **indicator** parameters



Water sources for potable water

Water purification methods → Potable water

Water purification methods

- Water for preparation of extracts
- Purified water
- Water for injections

WATER PURIFICATION METHODS

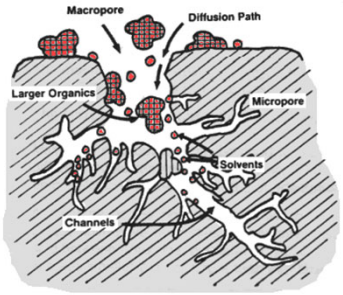
- the nature, type, and concentration of impurities define the selection of a water purification technique!
- there is no single process that can remove all contaminants in water
- to produce the level required a combination of processes is needed
- the method of choice is not defined in the Ph. Eur.

METHODS:

- distillation
- deionization
- electrodeionization
- reverse osmosis
- ultrafiltration
- microfiltration
- adsorption (activated carbon)
- UV technology

ADSORPTION (ACTIVATED CARBON)

- high surface area of particles: 500 – 1500 m^2/g
- adsorbs many organic compounds, mostly used for excess chlorine removal
- the efficiency is based on flow regulation



ADVANTAGES

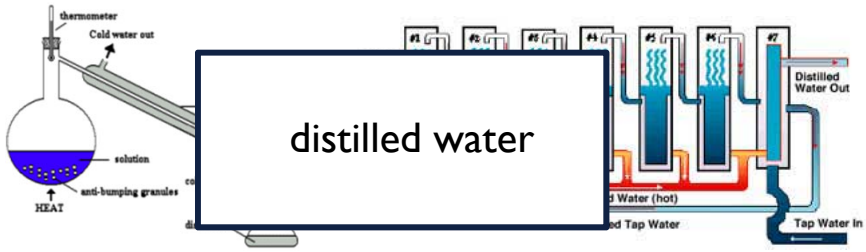
- effective removal of a large range of organic substances
- large capacity

DISADVANTAGES

- very little effect on other contaminants
- possibility of bacterial contamination
- sanitization of carbon bed should be performed often
- equilibrium after all active sites are occupied

DISTILLATION

- a process of separating the components by selective evaporation and condensation



single-effect

multiple-effect – re-using the heat energy

ADVANTAGES	DISADVANTAGES
• removes a large percentage of all types of contaminants • average investment • perceived as easy to operate	• contaminants can be generated during process • high operating costs – heating and cooling • regular maintenance (acid) • pretreatment (DI) required

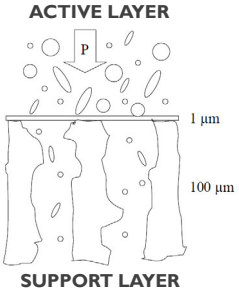
MICROFILTRATION

- a filtration method used to separate microorganisms and suspended particles from process water
- used in conjunction with other separation processes
- typical particle size used for microfiltration ranges from about 0.05 to 10 μm

ADVANTAGES	DISADVANTAGES
• 100% removal of bacteria and particles larger than pore size • **sterilizing filtration (0.22 μm membranes)** • minimum maintenance – replace when required • high flow rates	• minimum effect on other contaminants • surface of the membrane may be subject to fouling or plugging

ULTRAFILTRATION

- a filtration method relies on similar principles as reverse osmosis but uses lower pressures and more permeable membranes
- ultrafilters are asymmetric membranes
- small size molecules go through the membrane, whereas larger molecules (above NMWL) are retained



ADVANTAGES

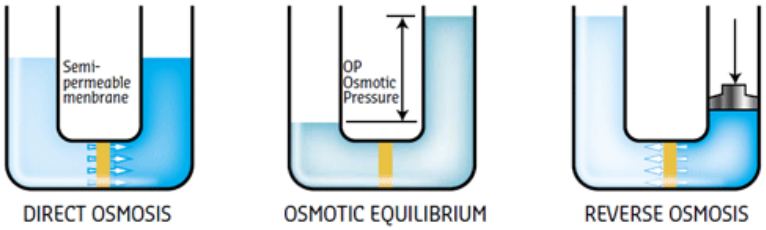
- effective removal (> 99%) of organics above NMWL
- very efficient at removing pyrogens
- low risk of scaling
- low use of energy

DISADVANTAGES

- almost no removal of ions, gases and low MW organics
- regular back flushing is necessary to remove retained particles
- high quality feed water is desirable

REVERSE OSMOSIS

- a membrane filtration method that removes many types of large molecules (bacteria, pyrogens, organics) and ions from water solutions



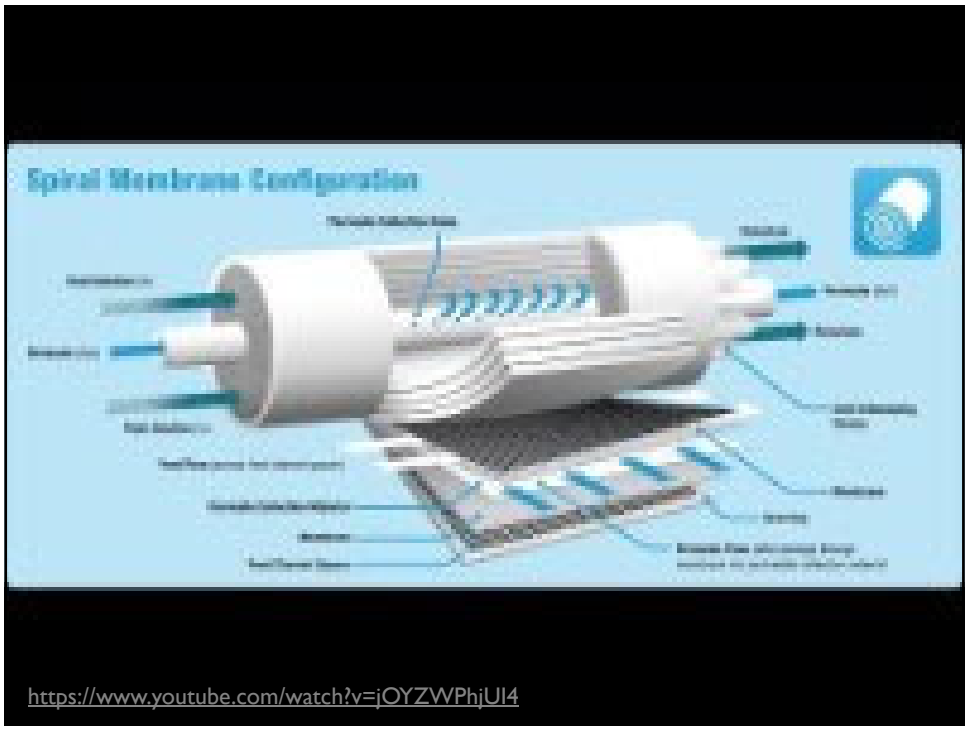
Reverse Osmosis operating principle

Ions: rejection > 97%

Organics (MW > 100 Da): rejection > 99%

Particles, bacteria: rejection > 99%

https://www.youtube.com/watch?v=aVdWqbpbv_Y&t=1s



https://www.youtube.com/watch?v=jOYZWPhjUI4

REVERSE OSMOSIS

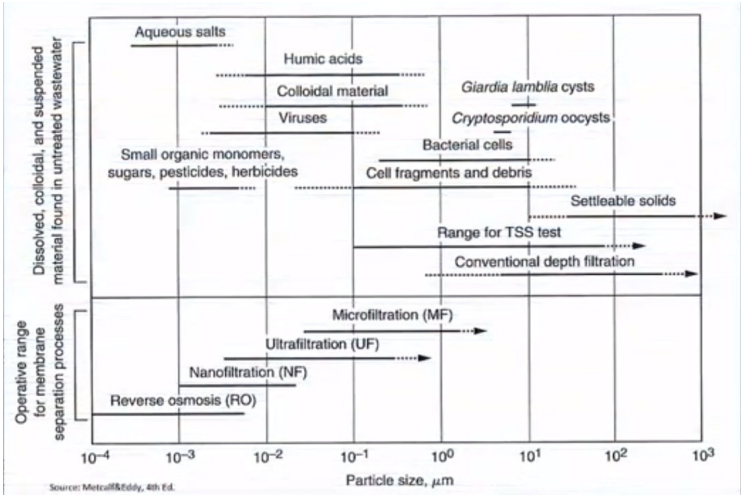
- the purity of the feed water and the effectiveness of the filter membrane define the quality of the product water
- a selection of reverse osmosis membranes are available to address varying water conditions and requirements

ADVANTAGES	DISADVANTAGES
• removes a fair percentage of all contaminants • low operating costs (low energy needs) • no need for strong acid and bases cleaning • good control of operating parameters (flow, pressure, conductivity)	• RO membranes are subject to plugging, fouling, piercing (particles, chemical attack) and scaling • high water consumption • danger of microbial growth on membrane • gases are not effectively removed

- Membrane pore sizes can vary depending on filter type.

- **Particle filtration** removes particles of **> 1 µm**
- **Microfiltration** removes particles of **> 50 nm**
- **Ultrafiltration** removes particles of **> ~3 nm**
- **Nanofiltration** removes particles of **> 1 nm**
- **Reverse osmosis** removes particles **> 0.1 nm**

WATER PURIFICATION METHODS



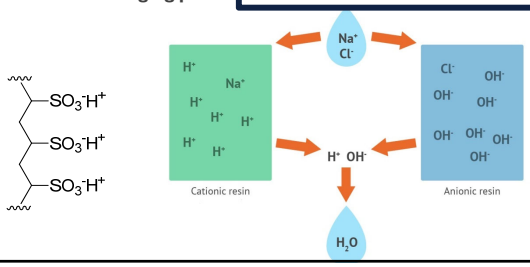
DEIONIZATION (or demineralization or ion exchange)

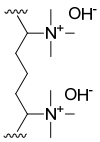
- a process by which both positive and negative ions are removed and replaced by H^+ and OH^-
- predominantly us[illegible] method for reverse osmosis
- ion exchange resi[illegible]mm)

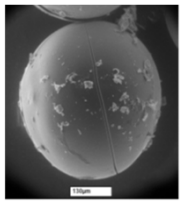
CATION RES
Functional sites c[illegible]
exchanging positiv[illegible]

demineralised water

dionised water

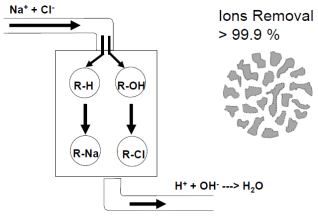






DEIONIZATION (or demineralization or ion exchange)

- mixed-bed deionization – a 50/50 mixture of cation and anion resin combined in a single ion exchange column



Ions Removal
> 99.9 %

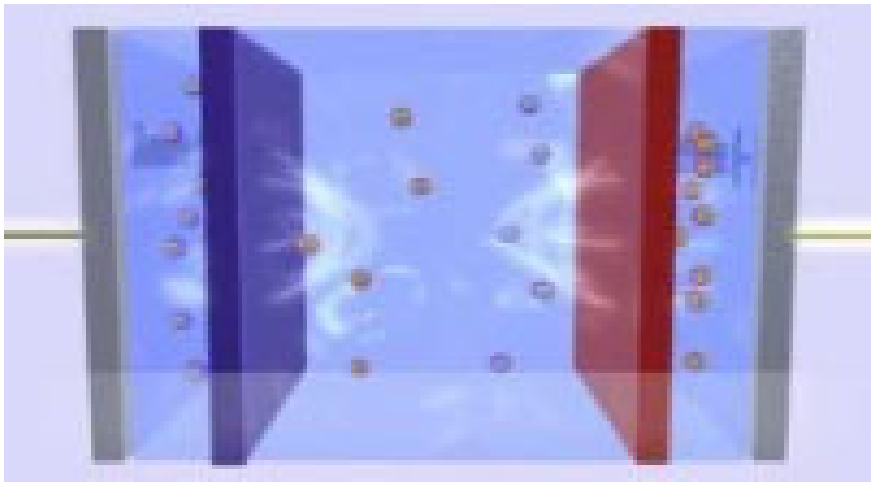
ADVANTAGES

- very effective method at removing ions (final conductivity: 0.1 – 1.0 µS/cm)

DISADVANTAGES

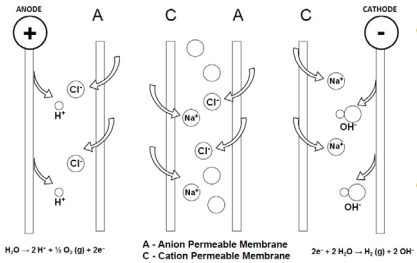
- does not eliminate other contaminants
- limited capacity depending on binding sites density (good feed water necessary)
- resin is a haven for microbial growth
- possibility of particles release

ELECTRODEIONIZATION



https://www.youtube.com/watch?v=wNCcpx9leG4

ELECTRODEIONIZATION



- a continuous deionization, where ion selective permeable membranes, mixed-bed ion exchange resin and electric current are used
- the resin is permanently regenerated by a weak electric current

ADVANTAGES

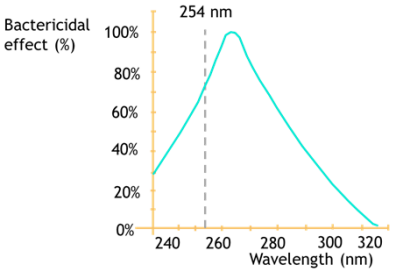
- very efficient removal of ions (< 0.2 µS/cm)
- low energy consumption
- high water recovery
- low maintenance
- less prone to microbial contamination

DISADVANTAGES

- does not eliminate other contaminants
- good feed water is a must to prevent plugging or fouling of resins and scaling at electrodes

UV TECHNOLOGY

- photochemical oxidation
- eliminates trace organics at 185 nm → typically converted to CO_2, which equilibriates to HCO_3^- (removed by ion exchange resins)
- eliminates microorganisms at 254 nm by breaking the DNA chains
- the device must be propery sized for the water flow



ADVANTAGES

- traces of organics converted to HCO_3^-
- can be used to continously ‚sanitize' circulating water
- easy to operate
- limited energy use

DISADVANTAGES

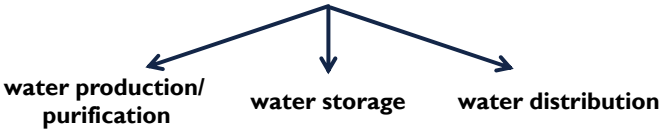
- polishing technique only – may be overwhelmed if organics conc. is high
- organics converted, not removed
- limited effect on other contaminants
- good design required for optimum work

WATER PURIFICATION METHODS

CONTAMINANT	STILL	DI	RO	UF	MF	AC
IONS						
ORGANICS						
PARTICLES COLLOIDS						
BACTERIA VIRUSES						
GASES						

PHARMACEUTICAL WATER SYSTEMS

prevent unacceptable microbial and chemical contamination



* QA involved in approval of use after installation and maintenance work
* **regular monitoring** of water sources and treated water
  - **chemical and microbiological**
  - **endotoxin** level where relevant
* monitoring **documentantion** of system performance
* validated **sanitization** procedure followed on a routine basis

WATER STORAGE AND DISTRIBUTION SYSTEMS

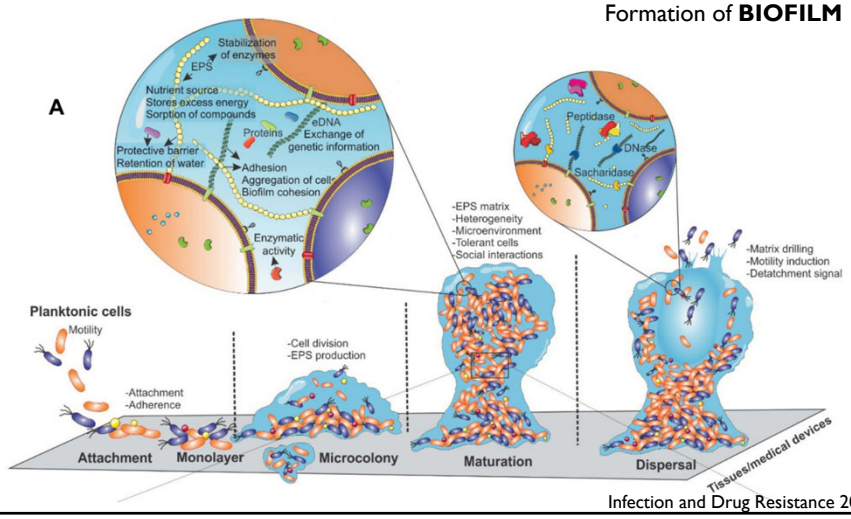
Once purified, water can be used directly or is fed into a storage vessel (more frequently!) for subsequent distribution.

GENERAL:

* water storage and distribution should work in conjunction with the purification plant → delivery of water of **consistent** quality
* this system should be configured to prevent microbial proliferation and recontamination
* **on-line and off-line monitoring** is necessary to ensure that the specifications are maintained (**flow, pressure, temperature, conductivity, pH and total organic carbon**)

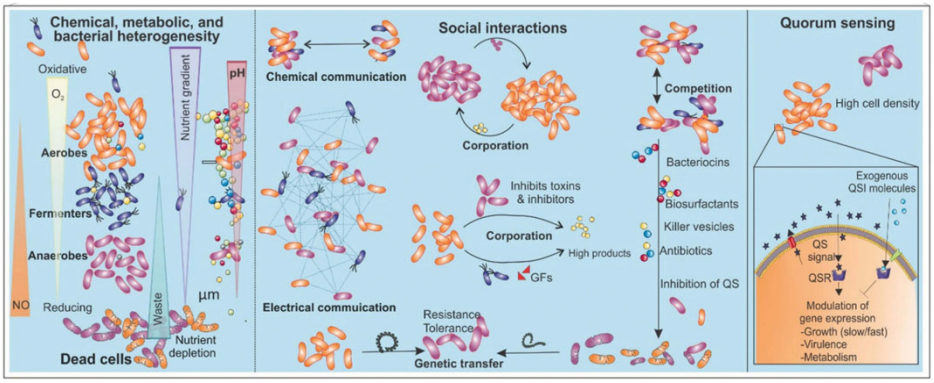
MICROBIAL CONTAMINATION

Formation of **BIOFILM**



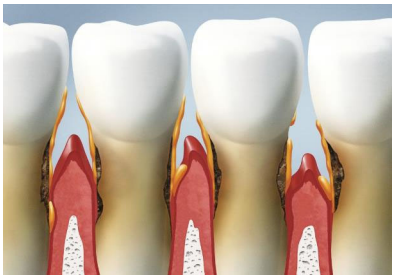
Infection and Drug Resistance 2020:13

BIOFILM



WHY BIOFILM PRESENTS A BIG PROBLEM?

https://www.membraworld.com/biofilm/?lang=en



https://www.dentist-lieberman.com/palm-harbor-dentist/2014/12/22/myths-about-gum-disease-palm-harbor-dentist/

HOW TO PREVENT THE GROWTH OF BIOFILM?

Water treatment equipment, storage and distribution systems should have:

* features to control the proliferation of microorganisms
* techniques for sanitizing the system

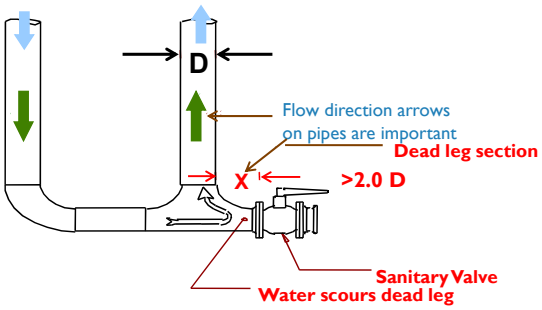
CONTAMINATION CONTROL TECHNIQUES (1):

* continuous **turbulent flow** circulation
* **avoid dead legs**
* **hygienic pattern diaphragm valves**
* **shortest possible length** of pipe work
* pipe work of ambient temperatures system should be isolated from hot pipes
* pipework systems should be **sloped and fully drainable**

HOW TO PREVENT THE GROWTH OF BIOFILM?

* **dead legs** are stagnant areas where there is no flow → this allows microbial contamination
* a consensus in the industry that a dead leg should not be greater than twice the diameter of the pipe

If **D = 25mm** and **X > 50mm**, we have a dead leg that is too long.



HOW TO PREVENT THE GROWTH OF BIOFILM?

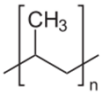
MATERIALS:

* compatibility
* prevention of leaching
* corrosion resistance

} in the full range of the working and sanitization temperature of the water system

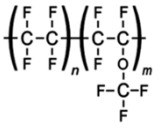
Appropriate WPU system contact materials include:

* *stainless steel Grade 315 L (low carbon)*
* *polypropylenes (PP)*



* *polyvinylidene-difluorides (PVDF)*

* *perfluoroalkoxyl alkanes (PFA)*



HOW TO PREVENT THE GROWTH OF BIOFILM?

CONTAMINATION CONTROL TECHNIQUES:

- the growth of microorganisms can be inhibited by:
  - **ultraviolet** radiation sources in pipework
  - maintaining the system heated (65-80 °C)
  - sanitizing the system periodically using hot water (guidance temperature > 70 °C)
  - sterilizing or sanitizing the system periodically using superheated hot water or clean steam
  - routine chemical sanitization using **ozone** or other suitable chemical agents

HOW TO PREVENT THE GROWTH OF BIOFILM?

- on-line and off-line monitoring is necessary to ensure that the specifications are maintained (flow, pressure, temperature, conductivity, pH and total organic carbon)

Planktonic bacteria
G^- microorganisms
- need < 1 mg/L organic carbon
- sensitive to ↑ T

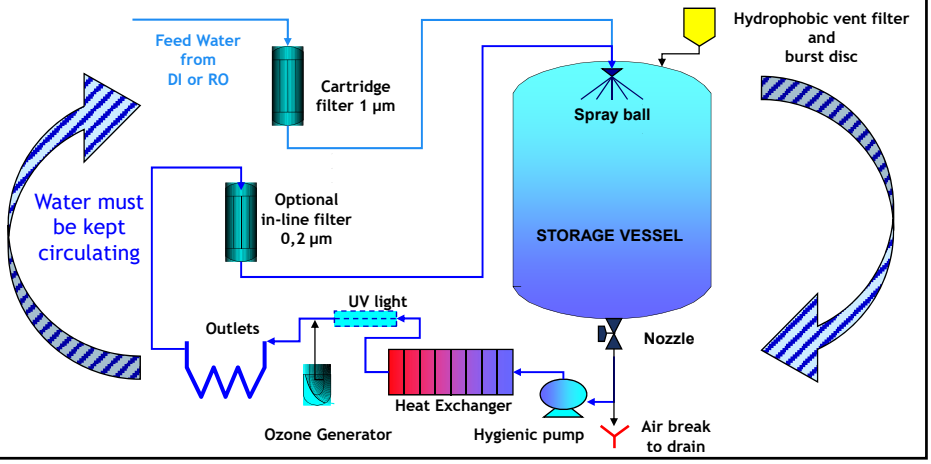
← Prevention: ↑ T

G^+ microorganisms
- need more organic molecules
- thermophiles – some can survive over 100 °C

← Prevention: ↓ TOC

WATER STORAGE AND DISTRIBUTION SYSTEMS

Typical water storage and distribution schematic



WATER QUALITY SPECIFICATIONS

- the standards (for bulk and dosage form types) are provided in the pharmacopoeias
- the **limits for various impurities** or classes of impurities are either specified or recommended
- companies should meet the **strict requirements** from the relevant pharmacopoeia
- potable water
  - not covered by a monograph
  - must comply with the regulations laid down by the competent authority
  - testing at the manufacturing site
  - in the production care should be taken to control microbiological contamination
  - source feed water for pharmacopoeial waters

WATERS IN EUROPEAN PHARMACOPOEIA

PURIFIED WATER (Aqua purificata)
- PURIFIED WATER IN BULK
- PURIFIED WATER IN CONTAINERS

WATER FOR INJECTIONS (Aqua ad iniectabile)
- WATER FOR INJECTIONS IN BULK
- STERILIZED WATER FOR INJECTIONS

WATER FOR PREPARATION OF EXTRACTS (Aqua ad extracta praeparanda)

Concentrated water for diluting haemodialysis solutions

Water (^{15}O) injection

WATERS IN US PHARMACOPOEIA (USP40-NF35)

Water used in the pharmaceutical industry and related disciplines is classified by the US Pharmacopoeia (USP) as follows:

BULK MONOGRAPHED WATERS
* USP Purified Water
* USP Water for Injection
* USP Water for Hemodialysis
* USP Pure stream

STERILE MONOGRAPHED WATERS
* USP Sterile Purified Water
* USP Sterile Water for Injection
* USP Bacteriostatic Water for Injection
* USP Sterile Water for Irrigation
* USP Sterile Water for Inhalation

WATERS IN EUROPEAN PHARMACOPOEIA 11

DEFINITION

Water, purified (Ph. Eur. 0008) PW	Water for preparation of extracts (Ph. Eur. 2249)	Water for Injections (Ph. Eur. 0169) WFI
Water for the preparation of **medicines other than those** that are required to be both **sterile and apyrogenic**, unless otherwise justified or authorised.	Water intended for the preparation of ***Herbal drug extracts (0765)*** complies with the section **PW in bulk or PW in containers** in the monograph PW (0008), or is water intended for human consumption of a quality equivalent to that defined in **Directive 98/83/EC.**	Water for the preparation of medicines for **parenteral administration** when water is used as **vehicle** (WFI in bulk) and for **dissolving or diluting substances or preparations for parenteral administration** (sterilized water for injections).

WATERS IN EUROPEAN PHARMACOPOEIA 11

PRODUCTION

Water, purified (Ph. Eur. 0008) PW	Water for preparation of extracts (Ph. Eur. 2249)	Water for Injections (Ph. Eur. 0169) WFI
prepared by **distillation**, by **ion exchange**, by **reverse osmosis OR** by any other suitable method …	When water intended for human consumption is used as water for preparation of extracts it is **clear, colourless liquid**.	**<u>Water for injections in bulk</u>** Obtained from water that complies with the regulations on water intended for human consumption or from purified water: - **by distillation** - **by a purification process that is eqivalent to distillation.** Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electrodionisation, ultrafiltration or nanofiltration. **<u>Sterilized water for injection</u>** WFI in bulk has been distributed into suitable containers, closed and **sterilized by heat** in conditions that the product still complies with the test for bacterial endotoxins

	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins (2.6.14)	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 50 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)

	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins (2.6.14)	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 50 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)

2.2.44. TOTAL ORGANIC CARBON IN WATER FOR PHARMACEUTICAL USE

- TOC – determination is an indirect measure of organic substances in water
- General method: complete oxidation of the organic molecules in the samples water to produce CO_2 followed by measurement of the amount of CO_2 produced.
- Need to discriminate between organic and inorganic carbon (present as carbonate)
- Limit of detection: 0.05 mg/L

	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 50 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)

CONDUCTIVITY

Table 0169.-2. – *Stage 1*
Temperature and conductivity requirements (for non-temperature-compensated conductivity measurements)

Temperature (°C)	Conductivity ($\mu S \cdot cm^{-1}$)
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

Table 0169.-3. – *Stage 3*
pH and conductivity requirements (for atmosphere- and temperature-equilibrated samples)

pH	Conductivity ($\mu S \cdot cm^{-1}$)
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins (2.6.14)	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 50 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)


DRUG DELIVERY SYSTEMS
Important excipient
Different roles of water


RADIOPHARMACEUTICALS

WATER FOR PHARMACEUTICAL USE

Water can be used:

- for cleaning agent for rinsing vessels, equipment, primary packaging material
- during synthesis of active ingredient
- during production of final product
- as an excipient
- for reconstitution of the product

We can choose between:

- Potable water
- Water for preparation of extracts
- Purified water
- Water for injections

WHERE TO FIND INFORMATION

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2020
EMA/CHMP/CVMP/QWP/496873/2018

Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the quality of water for pharmaceutical use

WHICH WATER TO USE?

Water present as an excipient in the final formulation

STERILE MEDICINAL PRODUCTS

Sterile medicinal products	Minimum acceptable quality of water
Parenteral	WFI
Biologics (including vaccines and ATMP)	WFI
Ophthalmic (excluding ATMP)	Purified
Haemofiltration solutions Haemodiafiltration solutions	WFI
Peritoneal dialysis solutions	WFI
Irrigation solutions	WFI
Nasal/Ear preparations	Purified
Cutaneous preparations	Purified

WHICH WATER TO USE?

NON-STERILE MEDICINAL PRODUCTS

Non-sterile medicinal products	Minimun acceptable quality of water
Vaccines for non-parenteral use	Purified*
Oral preparations	Purified
Nebuliser solutions	Purified**
Cutaneous preparations	Purified***
Nasal/ear preparations	Purified
Rectal/vaginal preparations	Purified

* **WFI** is recommended in order to ensure the vaccines' safety and product quality

** **In certain disease states (eg. cystic fibrosis),** medicinal products administered by nebulisation are required to be sterile and non-pyrogenic. In such cases, **WFI** should be used.

*** For some products such as **veterinary teat dips**, it may be **acceptable to use potable water** where justified and authorised taking account of the variability in chemical composition and microbiological quality.

WHICH WATER TO USE?

Water used during manufacture of medicinal products but not present in the final formulation.

Manufacture	Minimun acceptable quality of water
Granulation	Purified*
Tablet coating	Purified
Used in formulation prior to non-sterile lyophilisation	Purified
Used in formulation prior to sterile lyophilisation	WFI

* For some veterinary premix products eg. granulated concentrates it may be acceptable to use potable water where justified and authorised taking account of the variability in chemical composition and microbiological quality.

WHICH WATER TO USE?

Water used for cleaning/rinsing.

Cleaning/Rinsing of Equipment, Containers, Closures	Minimun acceptable quality of water
Initial rinse for non-sterile products	Potable
Initial rinse for sterile products	Purified
Final rinse	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water

More details in EMA Guidline on the quality of water for pharmaceutical use

WHICH WATER TO USE?

Water used during the manufacture of Active Substances (AS)

Type of manufacture	Product requirements	Minimun acceptable quality of water
Synthesis of all intermediates of AS prior to final isolation and purification steps	No requirement for sterility or apyrogenicity in AS or the pharmaceutical product in which it will be used.	Potable*
Final isolation and purification	No requirement for sterility or apyrogenicity in AS or the pharmaceutical product in which it will be used.	Potable
Final isolation and purification	AS is not sterile, but is intended for use in a sterile, non-parenteral product	Purified

More details in EMA Guidline on the quality of water for pharmaceutical use

* Purified Water should be used where there are technical requirements for greater chemical purity.

CONCLUSIONS – ‚TAKE-HOME' MESSAGES

- water has unique chemical properties
- **potable water** is feed water for all waters for pharmaceutical use
- water purification techniques depend on the **type of contaminants in feed water**
- **distillation and reverse osmosis** target the whole range of contaminants with good efficiency
- pharmaceutical water systems should be configured to **prevent microbial proliferation and recontamination**
- standards for waters for pharmaceutical use are provided in pharmacopoeias
- WFI is the highest quality of pharmacopoeial waters
- radiopharmaceuticals
  - parenteral administration – sterile water for injection
  - oral delivery – purified water

PERC 2023 Water for pharmaceuti cal use

HTTPS://FORMS.OFFICE.COM/E/ZJCWBQKVRM