Microbiological quality of pharmaceutical water

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Part I

➔ Water chemistry

➔ Regulatory reminders

➔ Water generation methods

Water source

Surface

- High level of pollution
- Low mineralization

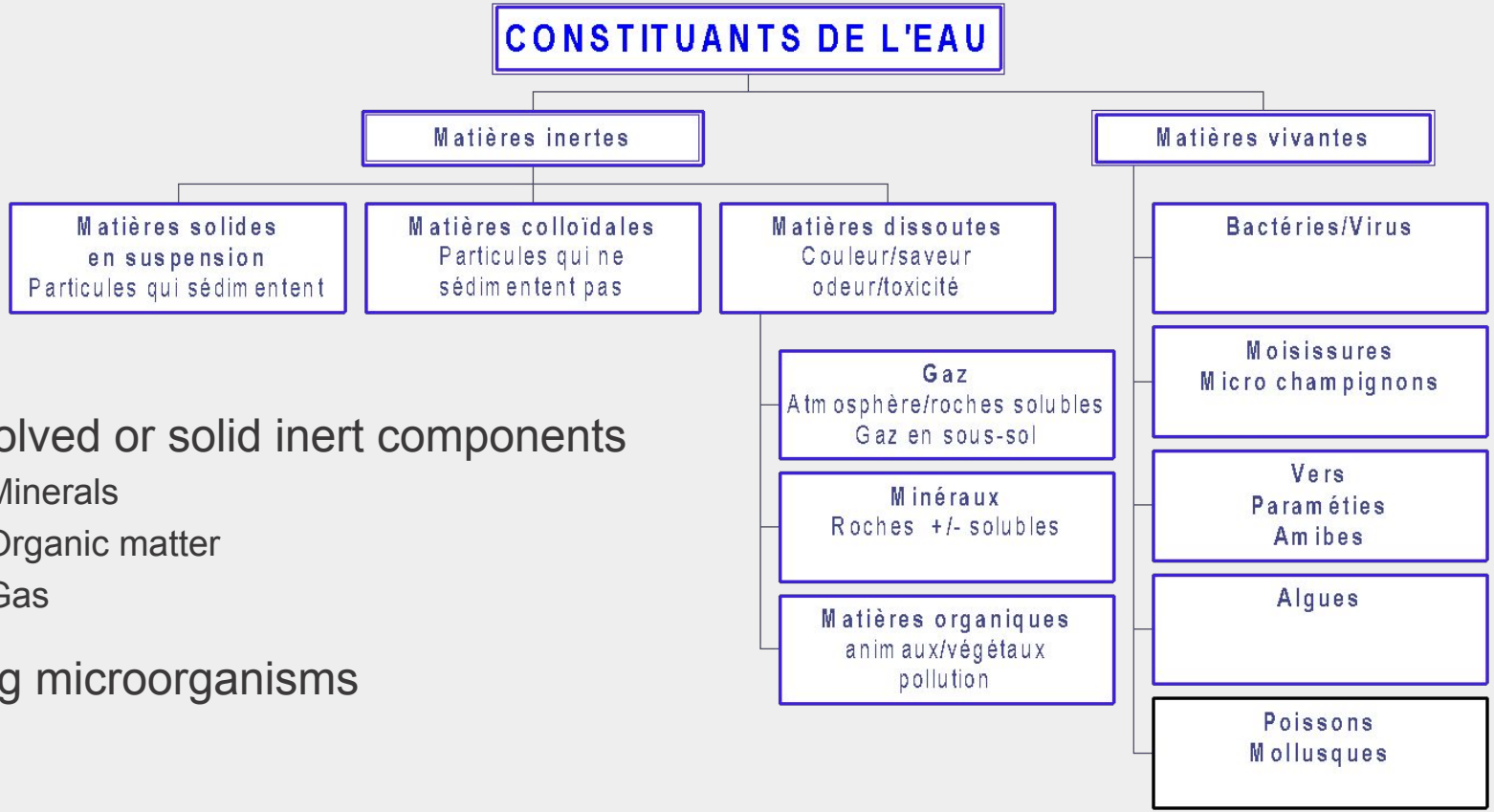
Well

- Good microbiological quality
- Highly mineralized

City water

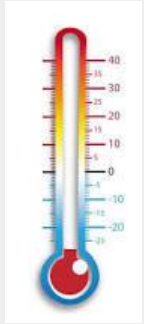
- Meets drinking water specifications

Water constituents



- ➔ Dissolved or solid inert components
  - Minerals
  - Organic matter
  - Gas
- ➔ Living microorganisms

Physical parameters



1. TEMPERATURE

- chemical reactions (kinetic, solubility, ...)
- growth of microorganisms

2. ORGANOLEPTIC CHARACTERS

Flavor, smell, color

3. TURBIDITY

- suspended solids

4. CLOGGING POWER

- fouling index
- colloids

Ionic balance

➔ CATIONS

- **Hardness**
  - Calcium Ca^{2+}
  - Magnesium Mg^{2+}
- **Monovalents**
  - Sodium Na^{+}
  - Potassium K^{+}

➔ ANIONS

- **TAC**
  - Carbonates CO_3^{2-}
  - Bicarbonates HCO^{3-}
- **Salt of strong acid**
  - Chlorides Cl^{-}
  - Sulfates SO_4^{2-}
  - Nitrates NO_3^{-}

Gas

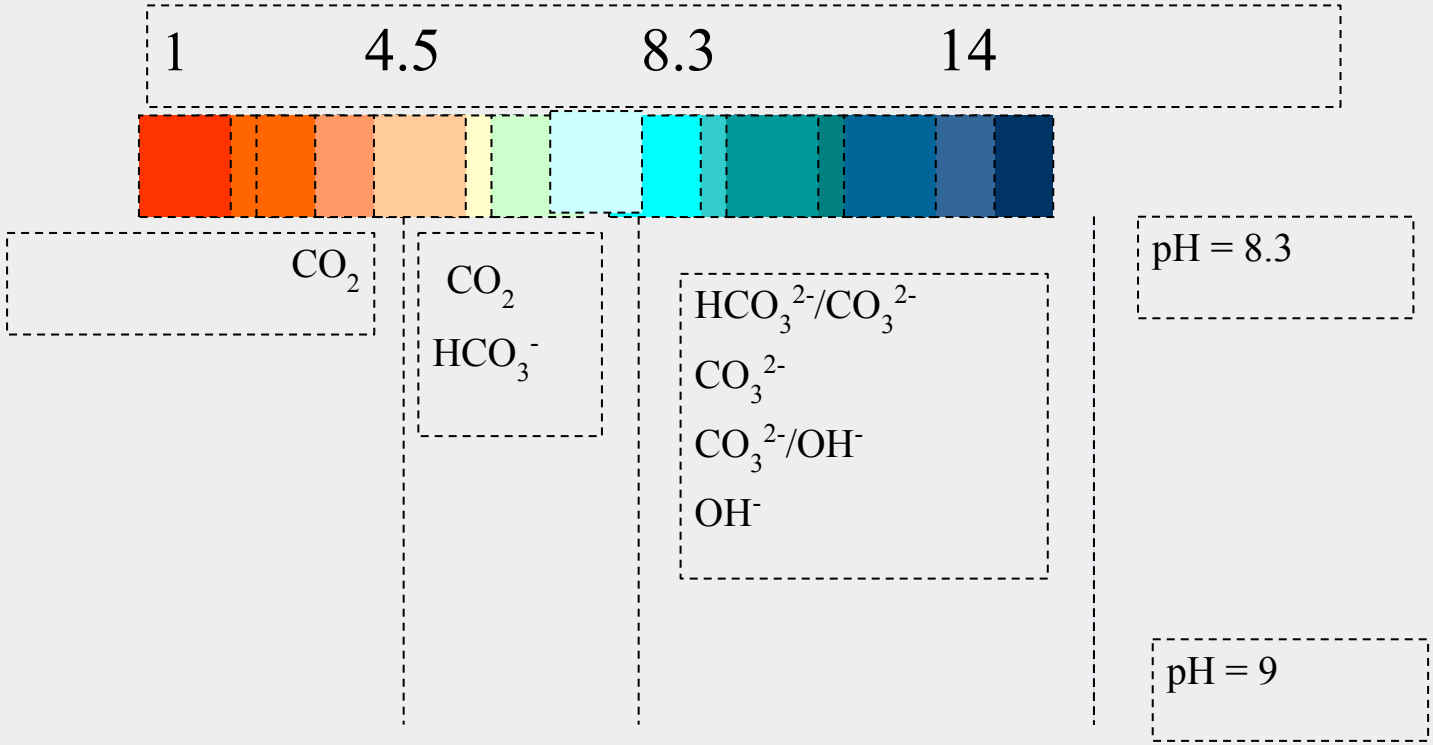
➔ Oxygen (O2)

expressed in mg/l (ppm); It varies from 0 to saturation; maximum content decreases with temperature

➔ Carbon dioxide (CO2)

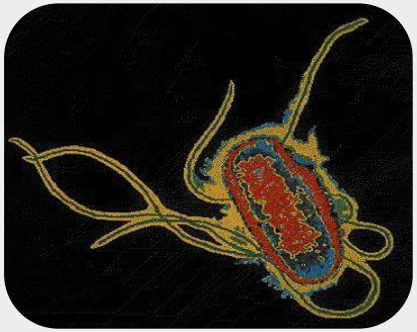
expressed in mg/l in balance with carbonates and bicarbonates. Balance depends on pH

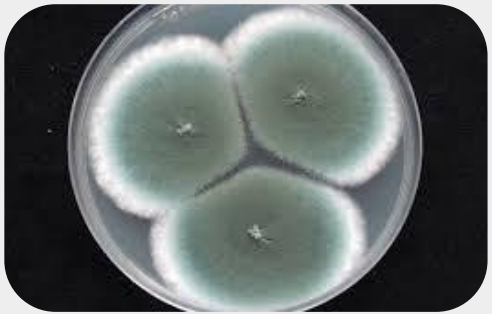
The PH



Microorganisms

- Virus
- Bacteria
- Yeast
- Mold

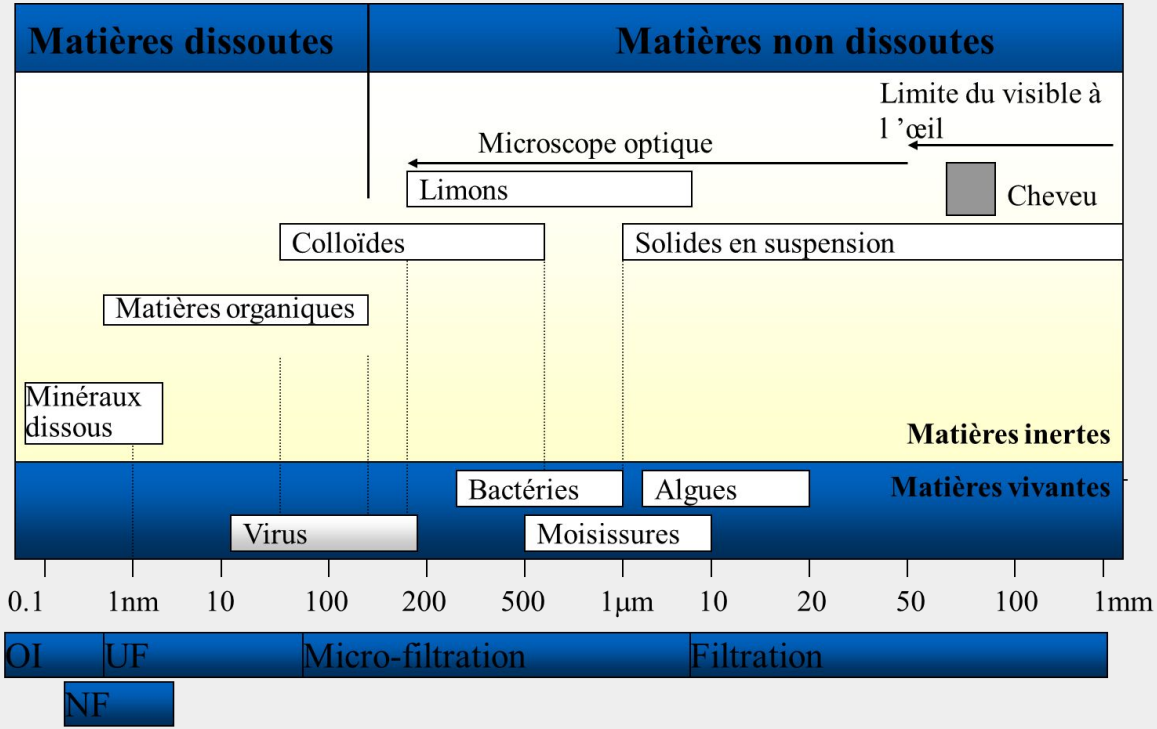




Growth factors

- ➔ pH (algae: pH - 5 - 6, bacteria: pH - 7 - 9)
- ➔ High temperature
- ➔ Light
- ➔ Absence or presence of oxygen (aerobic, anaerobic species)
- ➔ Nutrient (organic element, biofilm ...)
- ➔ Lack of growth inhibitors (biocides)

Particles in water



Water for pharmaceutical use

Waters for pharmaceutical use

- → Purified water
- → Water for injection

Bulk purified water (Aqua Purificata)

DÉFINITION

Eau destinée à la préparation de médicaments autres que ceux qui doivent être stériles et exempts de pyrogènes, sauf exception justifiée et autorisée.

PRODUCTION

L'eau purifiée en vrac est préparée par distillation, par échange d'ions, par osmose inverse ou par tout autre procédé approprié à partir d'une eau destinée à la consommation humaine comme établi par l'Autorité compétente.

L'eau purifiée en vrac est conservée et distribuée dans des conditions visant à empêcher la croissance de microorganismes et à éviter toute autre contamination.

Extrait Pharmacopée européenne

Definition

Water for injection

DÉFINITION

Eau destinée soit à la préparation de médicaments pour administration parentérale à véhicule aqueux (eau pour préparations injectables en vrac), soit à la dissolution ou la dilution de substances ou préparations pour administration parentérale (eau stérilisée pour préparations injectables).

Extrait Pharmacopée européenne

Eau pour préparations injectables en vrac

PRODUCTION

L'eau pour préparations injectables en vrac est obtenue soit à partir d'une eau destinée à la consommation humaine, comme établi par l'Autorité compétente, soit à partir d'une eau purifiée. Elle est produite :

- soit par distillation dans un appareil dont les composants en contact avec l'eau sont constitués de verre neutre, de quartz ou d'un métal approprié ; également, l'appareil est muni d'un dispositif efficace pour empêcher le primage ;
- soit par un procédé de purification équivalent à la distillation. Une osmose inverse, en simple ou double passage et couplée à d'autres techniques appropriées comme l'électrodésionisation, l'ultrafiltration ou la nanofiltration, convient. L'autorité de supervision du fabricant est informée préalablement à la mise en application du procédé.

Quelle que soit la méthode de production employée, le bon suivi des opérations et l'entretien correct du système sont essentiels. Afin de garantir l'obtention d'une eau de qualité appropriée, des méthodes validées sont appliquées et un suivi en cours de production de la conductivité électrique, ainsi que des contrôles réguliers du carbone organique total et de la contamination microbienne sont effectués.

Definition

Quality requirements

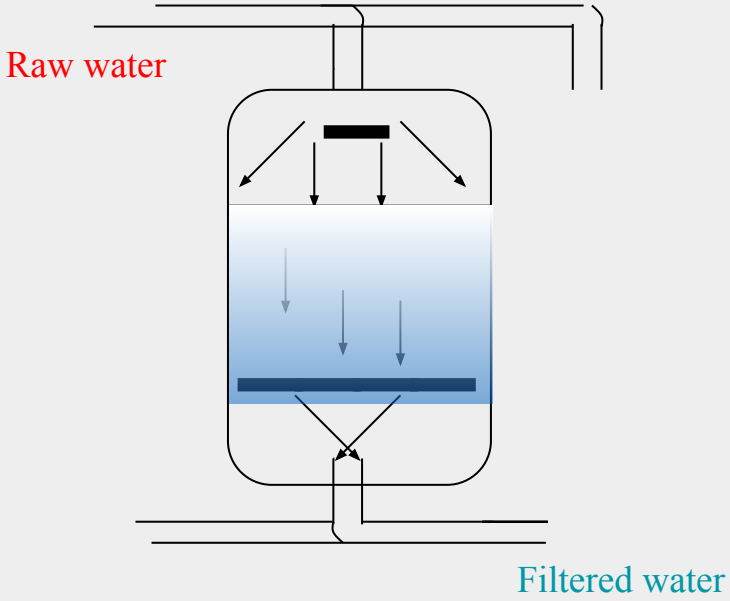
PARAMÈTRES	ORIGINE	PW	WFI
Origin	PE / USP	Potable water	Potable water
Color	PE	Clear, Colorless	Clear, Colorless
Odor	PE	Odorless	Odorless
Taste	PE	Insipid	Insipid
Conductivity (µS/cm à 20°C)	PE	≤ 4,3	≤ 1,1
Conductivity (µS/cm à 25°C)	USP	≤ 1,3	≤ 1,3
Total Organic Carbon (TOC)	PE / USP	≤ 500 ppb	≤ 500 ppb
Nitrates NO_3^-	PE	≤ 0,2 ppm	≤ 0,2 ppm
Heavy metals(équivalent Pb ppm)	PE	≤ 0,1	≤ 0,1
Germes aérobies viables totaux	PE / USP	≤ 100 UFC / ml	≤ 10 UFC / 100 ml
Endotoxins	PE / USP	ND	≤ 0,25 UI / ml

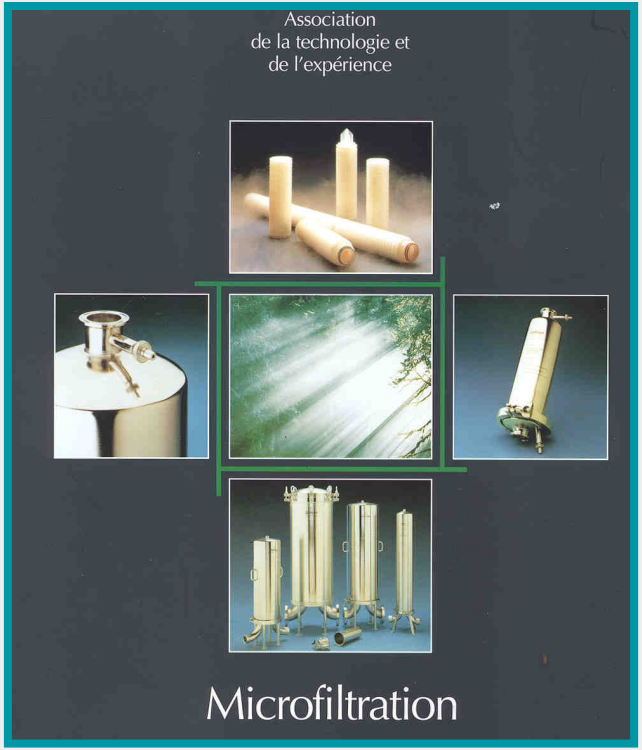
Purified water generation

Water treatment techniques

- → Filtration
- → Softening
- → Ion exchange
- → Reverse osmosis
- → Electrodeionisation

Sand filtration / Cartridges





Retention of particles : size from 10 to 0.2 µm

Softening

→ Objective:

Replace Calcium and Magnesium by another cation: SODIUM.

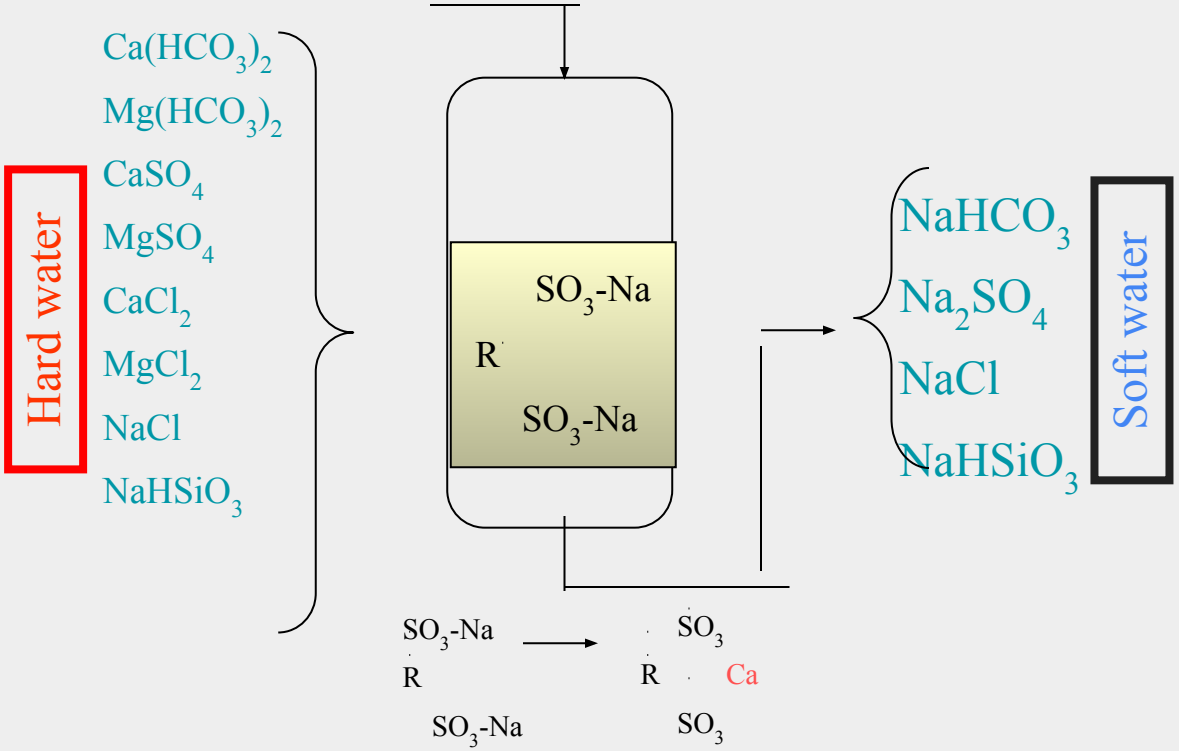
→ Principle

$$R\text{-}SO_3\text{-}Na + Ca^{2+} \longrightarrow R\text{-}SO_3\text{-}Ca + Na^{+}$$

→ Regeneration

$$R\text{-}SO_3\text{-}Ca + Na^{+} \longrightarrow R\text{-}SO_3\text{-}Na + Ca^{2+}$$

Principle of softening



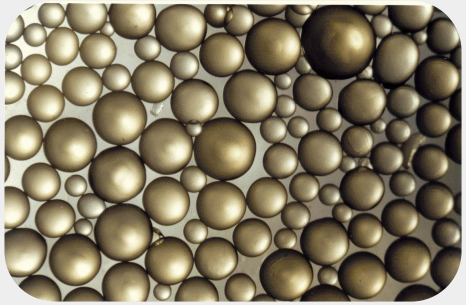
Demineralization by ion exchange process

➔ Strong cationic resin for the cations elimination

$$R\text{-}SO_3\text{-}H + Ca^{2+} \longrightarrow R\text{-}SO_3\text{-}Ca + H^+$$

➔ Strong anionic resin for anions elimination

$$R\text{-}OH + Cl^- \longrightarrow R\text{-}Cl + OH^-$$



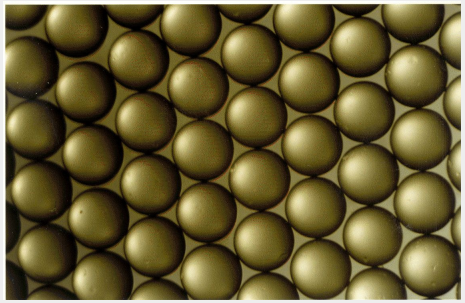
➔ Regeneration

Cationic resin: HCl, H_2SO_4, HNO_3

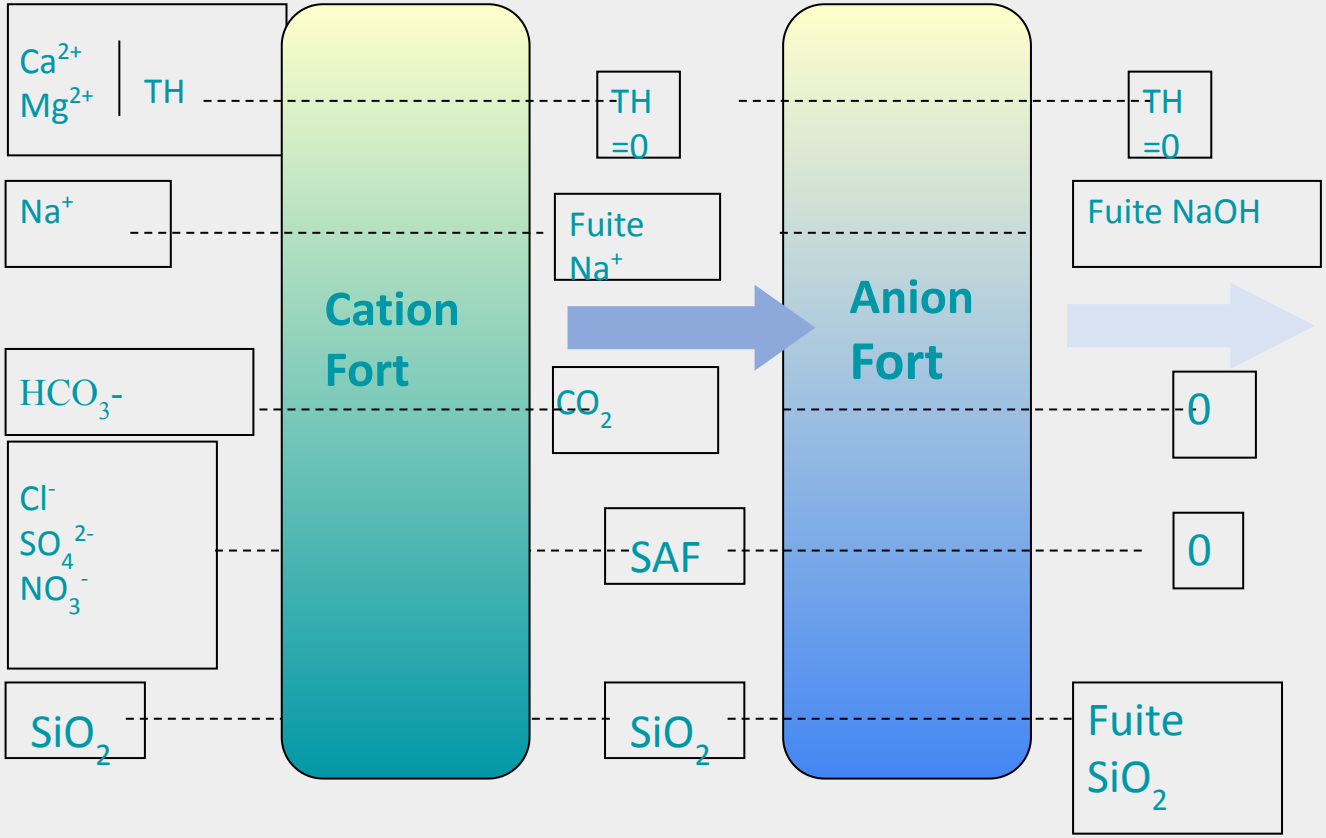
$$R\text{-}SO_3\text{-}Ca + H^+ \longrightarrow R\text{-}SO_3\text{-}H + Ca^{2+}$$

Anionic resin: NaOH, KOH

$$R\text{-}Cl + OH^- \longrightarrow R\text{-}OH + Cl^-$$

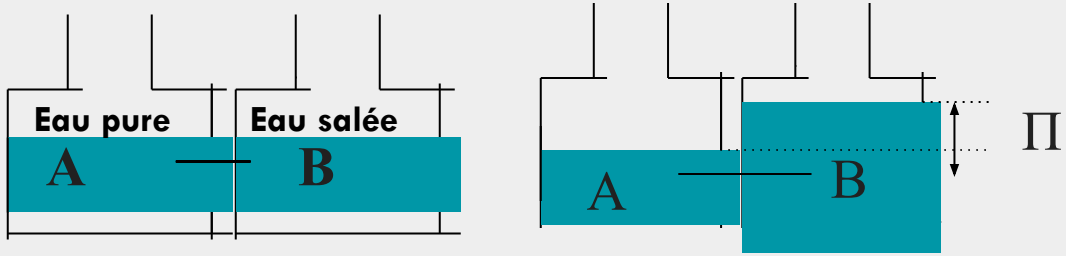


Demineralization



Reverse osmosis

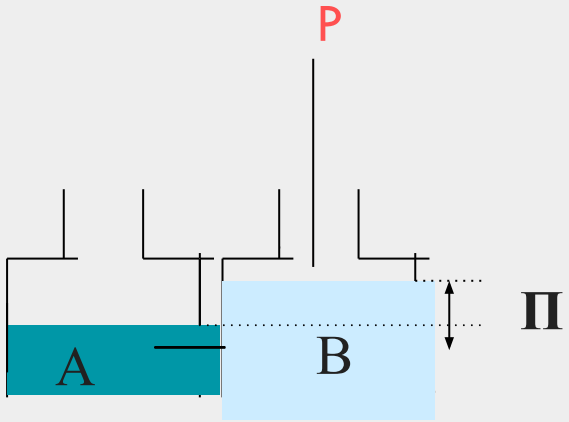
Direct osmosis is a natural phenomenon of diffusion between two solutions of different concentrations through a semipermeable membrane that acts as a partition of separation



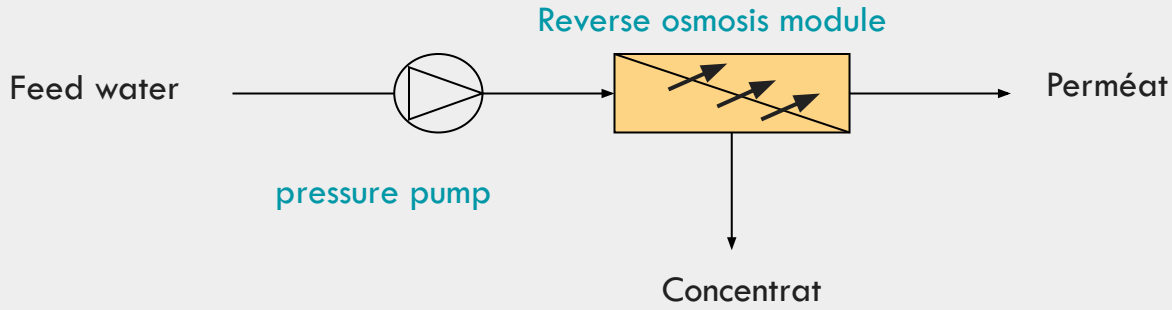
Reverse osmosis

- Need to apply to the most concentrated solution a pressure P greater than its osmotic pressure to reverse the natural flow.

- By applying pressure P to the B part containing the dissolved material, the water molecules diffuse to purified water (part A), simultaneously, the concentration of dissolved material in the water on the other side of the membrane increases in part B.

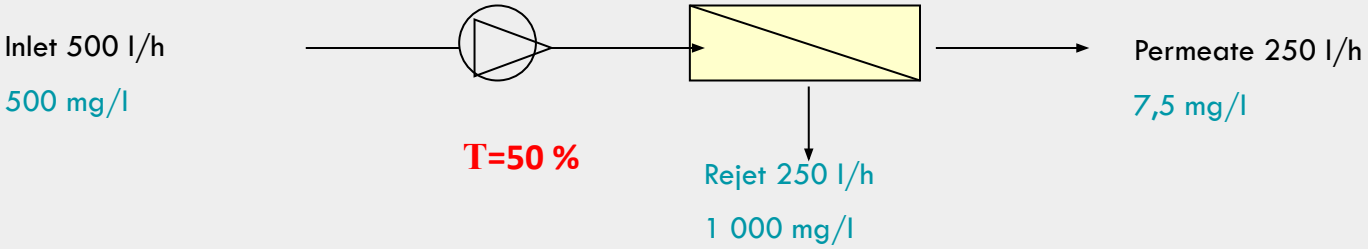


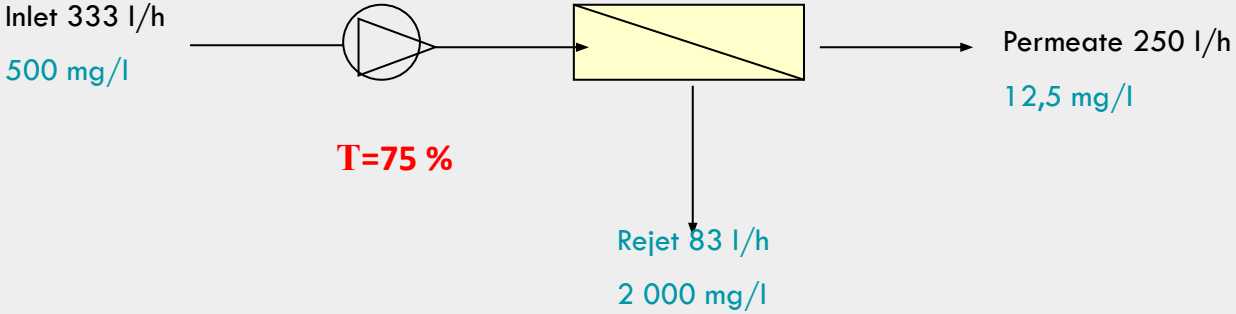
Representation



Conversion rate = (Permeate /feed water) x 100

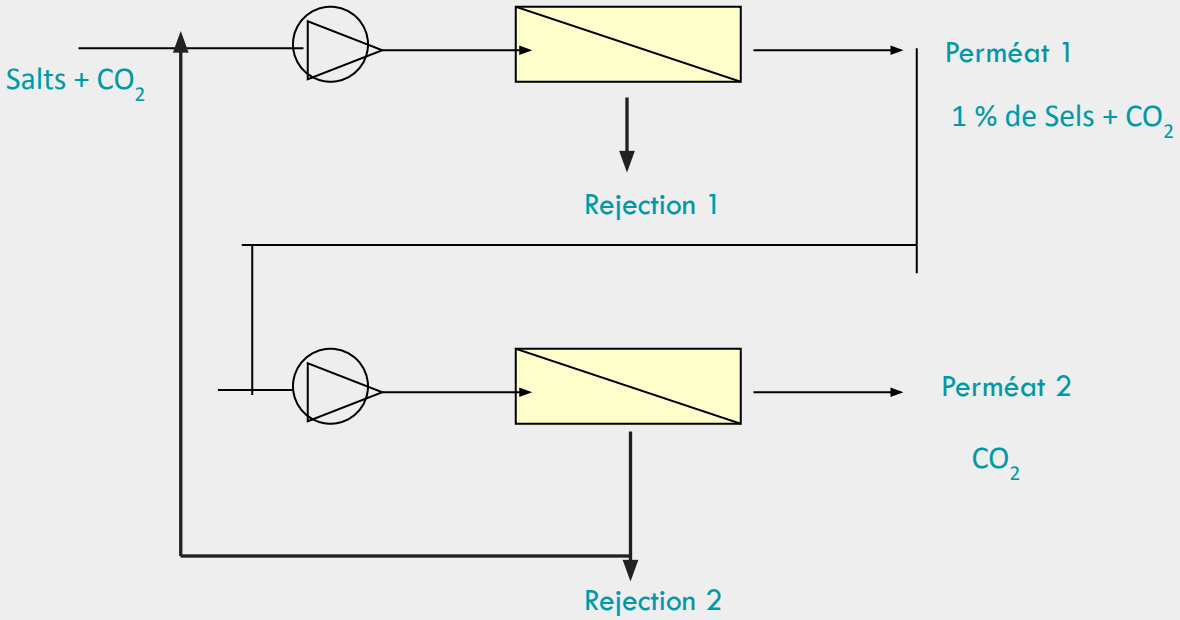
Concentration of salts





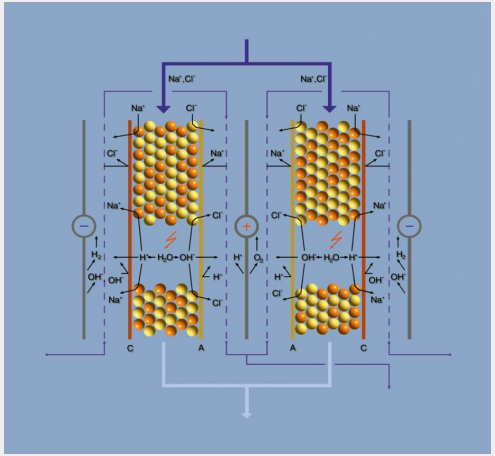
The saving of discharge water implies a lower quality of the permeate

Double pass RO



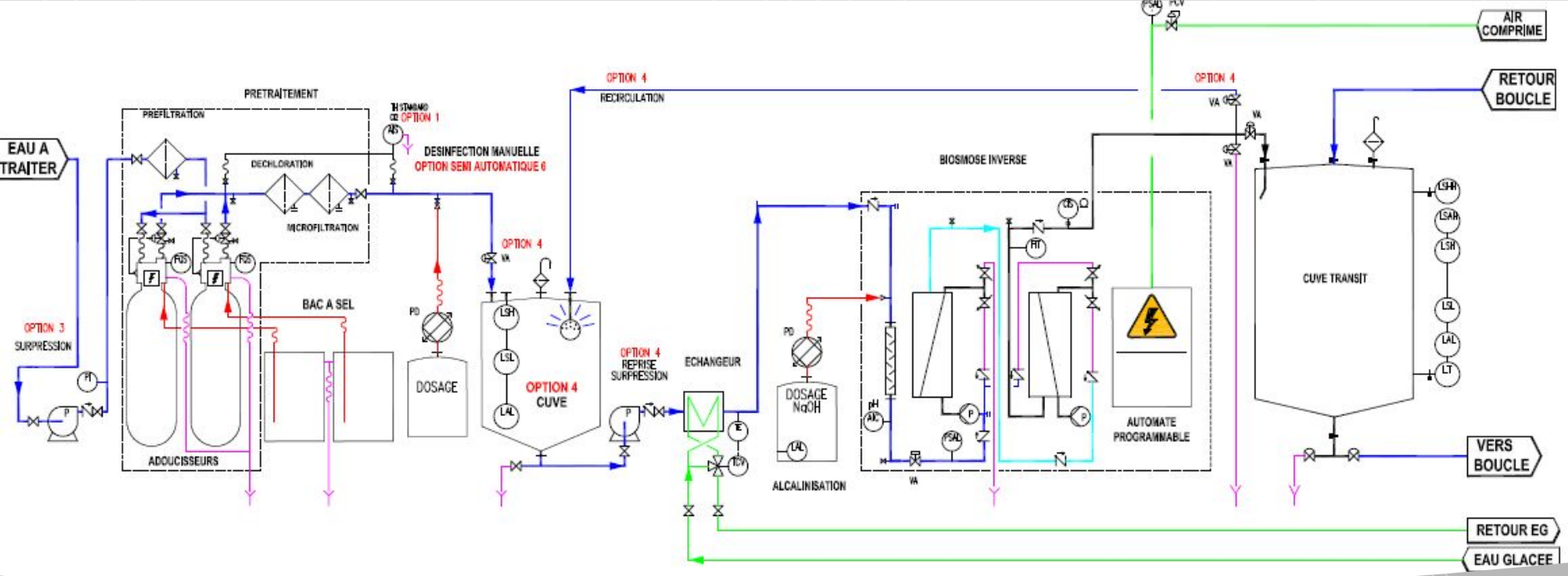
Electrodeionization

- EDI is a process combining ion exchange resins, selective ion membranes and electrolysis.
- The resin used is a mixed bed made up of cationic and anionic resins. It is constantly regenerated by the H+and OH- ions from the electrolysis of the water.
- Under the influence of an electric field, the anions and cations are attracted respectively to the anode and the cathode and pass through the selective membranes.

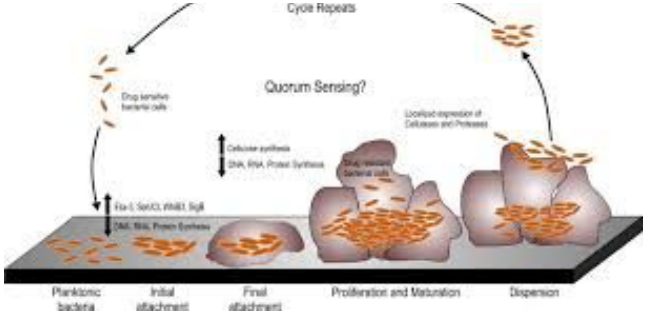


Purified water production systems

Examples



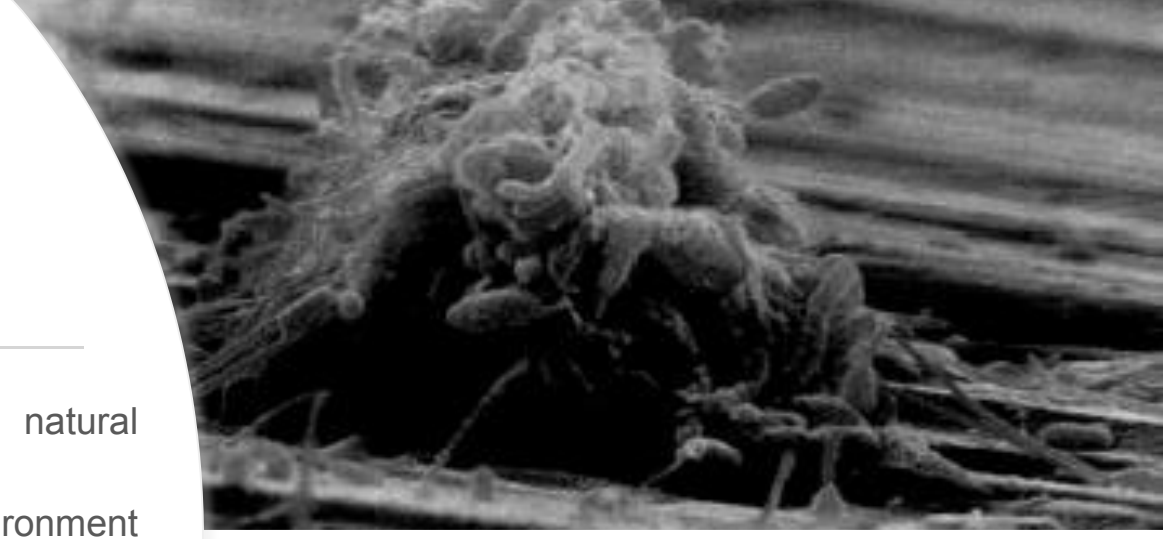
Double pass RO



Part II

BIOFILMS & BIOCONTAMINATIONS

Biofilm generation

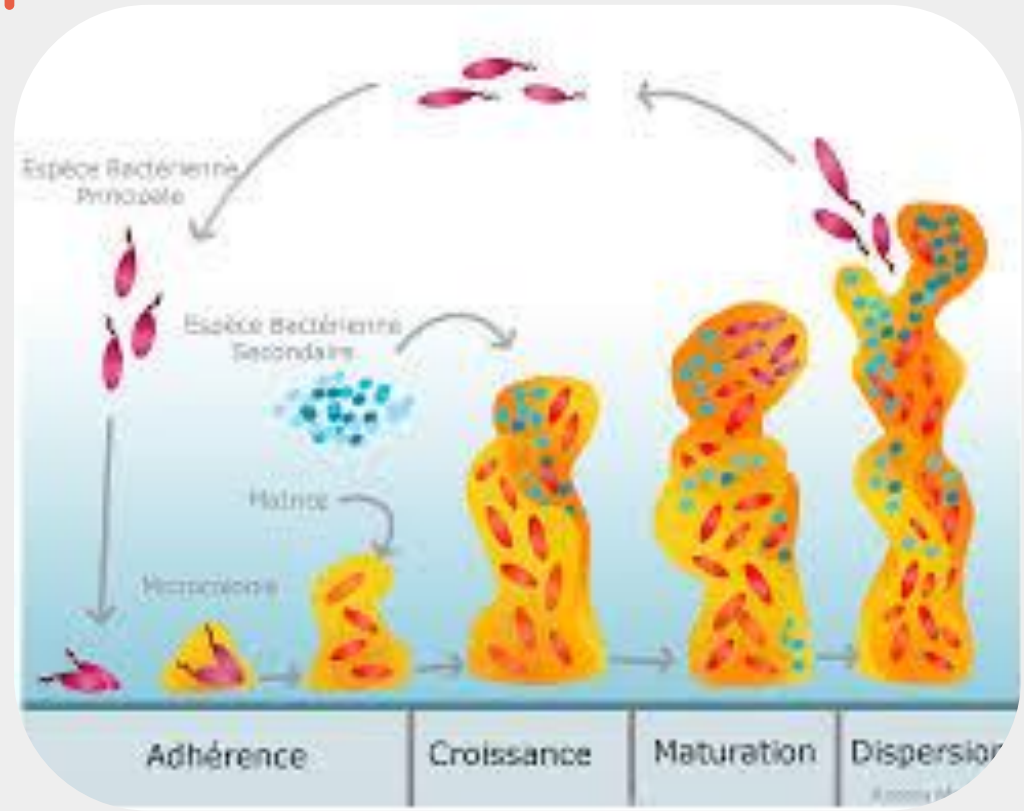


The adhesion of microorganisms is a natural process observed regardless of the nature

- of the environment
- of microorganisms
- Support material

Matrix based on organic polymers of microbial origin

Biofilm generation



➔ Reversible attachment

➔ Irreversible attachment

➔ Mature biofilm community

➔ Re-colonization

Detection

- **Physical and chemical analysis**
  - TOC
- **Microbiological**
  - Endotoxin testing
  - Total viable aerobic germs

Solutions

→ Design

→ Preventive solutions

→ Curative solutions

Conception

- Preventing adhesion of microorganisms
- Reducing their proliferation
- Installation design
- Limitation of dead legs
- Lack of stagnation
- Continuous operation
- Turbulent mode
- Equipment design (Drainability
- Disinfection
- Surface roughness (Ra) : distribution loop, Welds, equipment …
- Specific materials (316L stainless steel)

Preventive solutions

→ **Physical methods**

Temperature : Maintaining the distribution loop at T :70- 80°C
Ultraviolet ray

→ **Chemical methods**

Ozone : Protection of the storage tank and distribution loop by micro-ozonation

Objective: Maintaining the quality

Chemical treatment

Benefits

- Effective because it is possible to choose the disinfectant based on the contaminant nature
- Low cost solution

Disadvantages

- Requires to stop the production
- Long operation
- Requires validation
- Handling and storing chemicals

Preventive or curative treatment

Thermal treatment

Benefits

- Maintaining microbiological quality all times
- Efficiency
- No chemical handling and storage

Disadvantages

- Expensive solution(specific equipment)
- Operational safety
- Significant energy consumption
- Requires a point-of-use cooling device

Maintaining the distribution temperature at up tp 70°C
Sterilization at T 121°C

Ozone treatment

- → Disinfectant effect
- → Destroying the bacteria envelope
- → Destroying the virus envelope
- → Destroying of bacterial endotoxins
- → Fast action (less than 4 min)
- → Oxidizing effect (Potential of 2.08V)
- → Reducing the TOC

Characteristics

- ➔ Quick action
- ➔ Unstable Gas (in situ production)
- ➔ Destruction by UV radiation : 254 nm to 120 mJ/cm

- ➔ Dosing

  - Use period:

10 to 30 ppb in the outlet of the storage tank
Destruction of ozone by UV radiation

  - Disinfection phase

Maintaining concentration during non-use periods
Disinfection phase with a dose at 80 - 100 ppb for 20 to 30 min

Benefits

- → No chemicals
- → No storage of hazardous product
- → Automatic operation
- → Traceability
- → Safety
- → Compatible with SS 316 L , Silicone, EPDM, PTFE, PVDF...

Microbiological quality monitoring

➔ Establishing a microbiological control card

- Defining trends
- Highlighting fluctuations in the quality of water

➔ Monitoring microbial contamination

- Establishing a flora map / identification of germs
- Definition of background noise
- Defining alert thresholds and action thresholds
- Defining the frequencies of cleaning/disinfection

➔ Establishing the routine control and sampling plan

Conclusion

Qualification of a purified water production and distribution unit

Part III

➔Design qualification

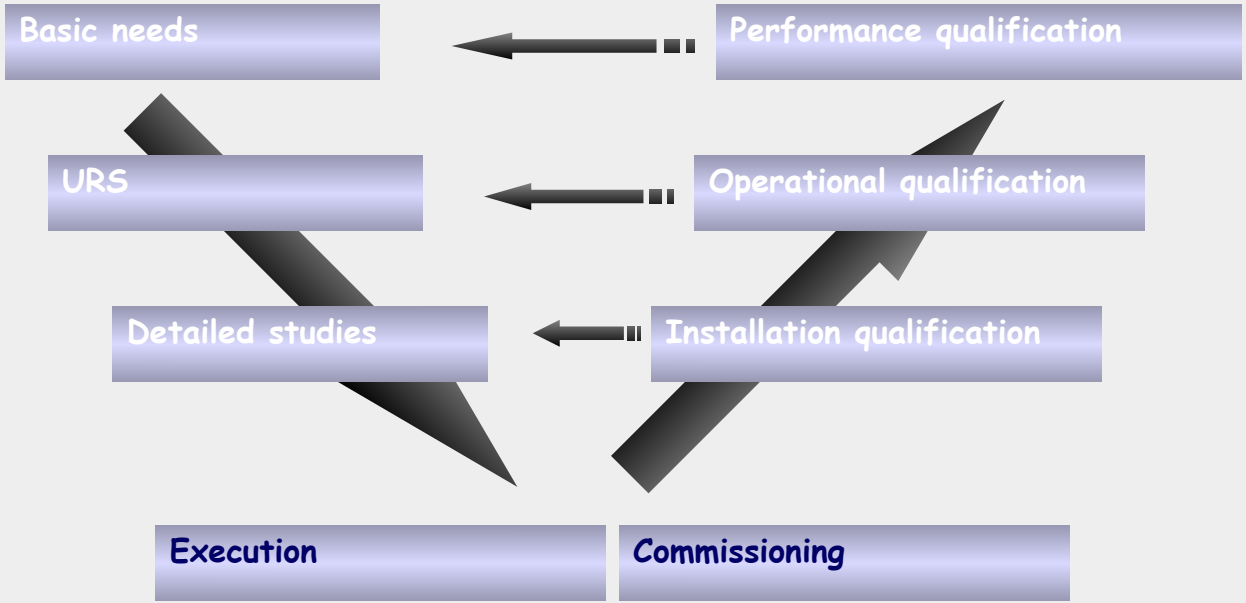
➔Installation qualification

➔Operational qualification

➔Performance qualification

Complex installation

Qualification approach



Design qualification

➔ The purpose of the design qualification is to provide **documented evidence** that a systematic study of needs and constraints associated to the process has been conducted in order to achieve the predetermined objectives.

➔ The design qualification must deliver a **protocol** and a **report**.

Design qualification

Objective

- confirm technical choices based on regulatory needs and requirements (pharmacopeia, cGMP/ GMP)

Methodology

- Defining needs
- Identification of constraints

Points to be defined

- PID scheme
- Process calculation sheet
- Mechanical and electrical performance
- Choosing materials
- Measurement techniques

Installation qualification

To check the presence and right positioning of components, their identification and compliance with the specifications previously defined by the specifications.

Installation qualification

Static verification of supply

- ➔ Presence of all elements as provided in the specifications
- ➔ Positioning in relation the P&ID
- ➔ Identifying the elements of the installation

Documentary verification

- ➔ Plans and diagrams in their TQC version
- ➔ Nomenclature / technical specifications
- ➔ Material Certificates EN 10204
- ➔ Weld control

Operational qualification

Through operational qualification, it is the dynamic function of the equipment that is verified.

Each function of the equipment must be operational in accordance with the specifications previously defined in the specifications.

Operational qualification

Dynamic checking

➔ How the elements work individually

➔ How the whole thing works

Checking safety device

➔ System response to standard incidents

➔ Alarm systems

Automatism

➔ Regulation: Temperature, Flow… etc.

➔ Valves: Opening, Closing

Performance qualification

Objective

Ability to produce water that meets pre-defined specifications under normal operating conditions

Methodology

Intensive water quality control program at all stages of treatment

Performance qualification

Phase I (2 to 4 weeks)

- ➔ Sampling under standard operating conditions
- ➔ Daily sampling
- ➔ All stages of purification
- ➔ All point of use
- ➔ Controlling the quality of raw water

Water shouldn't be used

Performance qualification

Phase II (2 to 4 weeks)

- ➔ Sampling under standard operating condition
- ➔ Daily sampling
- ➔ All stages of purification
- ➔ All POU
- ➔ Controlling the quality of raw water

Water could be used if the results of the first period are consistent

Performance qualification

Phase III (1 year)

- Establishing a control card for critical settings
  - Highlighting fluctuations in water quality
  - Setting alert thresholds and action thresholds
- Tracking microbiological contamination
  - Establishing a flora map
  - Defining the frequencies of cleaning/disinfection
- Establishing the routine control and sampling plan
- Establishing preventive maintenance schedules

Thank you
for your attention