Water for Pharmaceutical Use

Part 2:

Water purification engineering

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Water for Pharmaceutical Use

Objectives

To examine the basic technology and requirements for:

1. Water treatment systems
2. Storage requirements
3. Sampling and testing
4. Different types of water used in pharmaceuticals
5. Microbial limits, disinfection

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Water system design

1. Pipes sloped so water does not pool and can drain easily
2. Sanitary fittings & connections
3. Constructed of suitable materials such as stainless steel
4. Circulate the water
5. Incorporate non-return valves (NRV)

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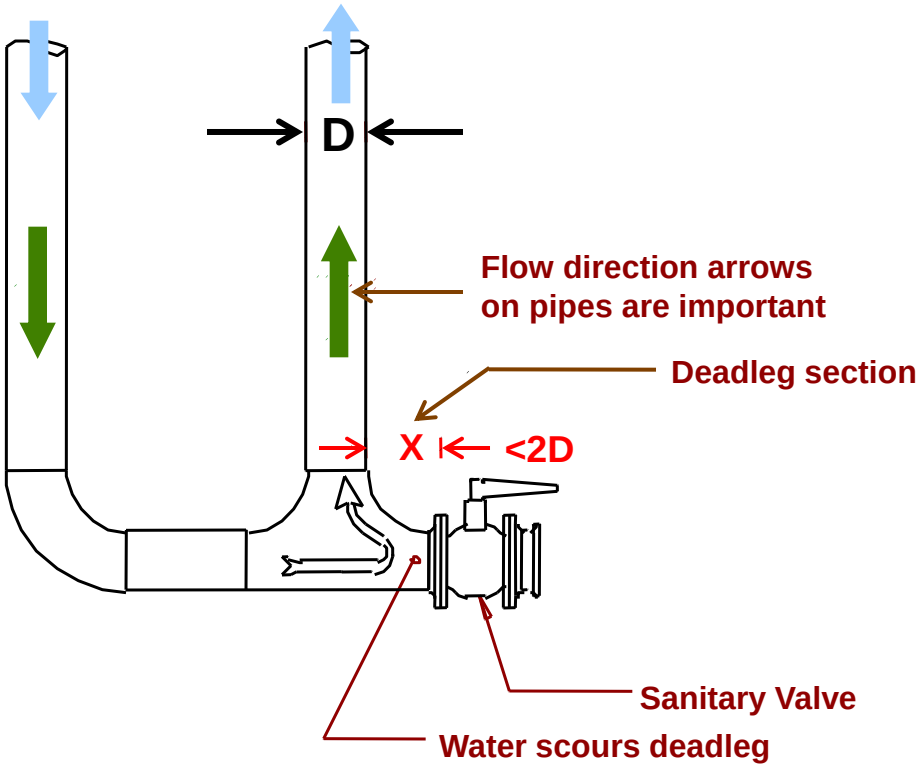
Further water treatment purification stages downstream of the pre-treatment system

1. Filtration
2. Disinfection
3. Reverse osmosis or de-ionization
4. Distillation or ultra-filtration

Water system design (1)

There should be no dead legs



If D=25mm & distance X is greater than 50mm, we have a dead leg that is too long.

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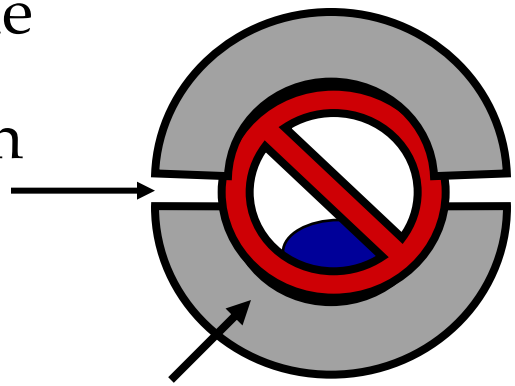
Water system design (2)

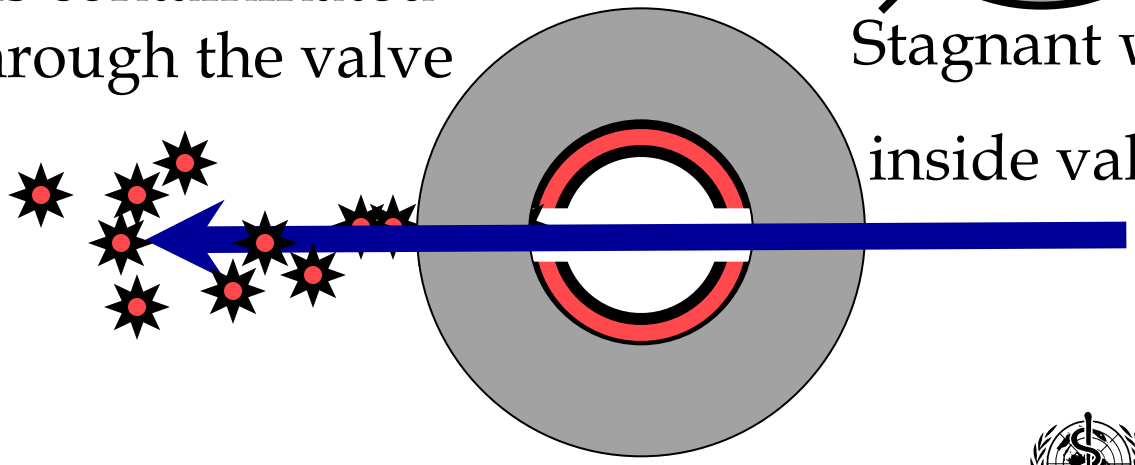
1. Ball valves are unacceptable

2. Bacteria can grow when the valve is closed



Stagnant water inside valve

3. The water is contaminated as it passes through the valve



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Water system design (3)

1. Sanitary pumps
2. Clamps and O rings
   versus threaded fittings
3. Heat exchangers
4. Side arm level measuring devices are
   unacceptable

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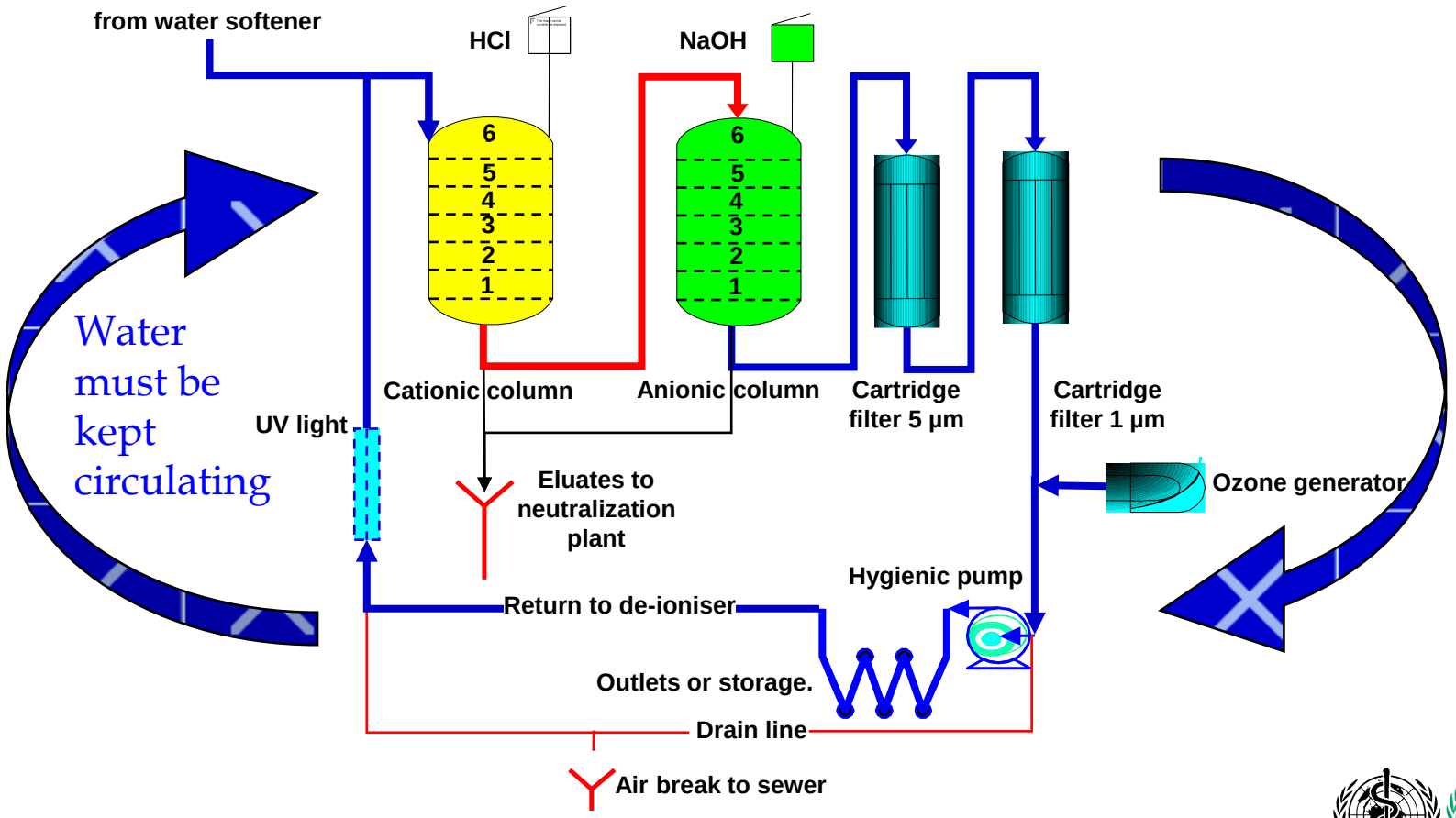
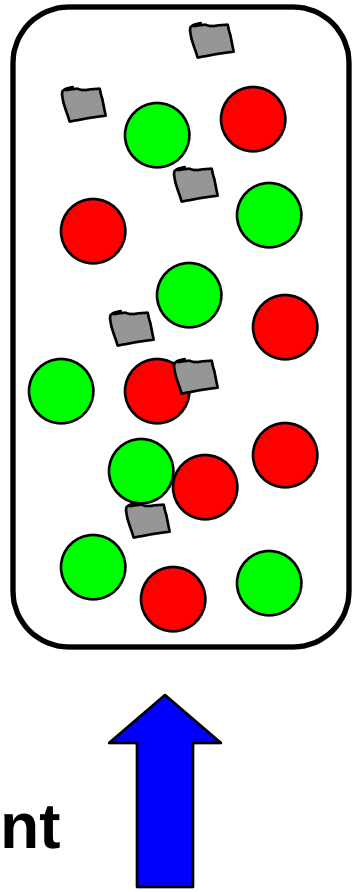
Typical de-ionizer schematic

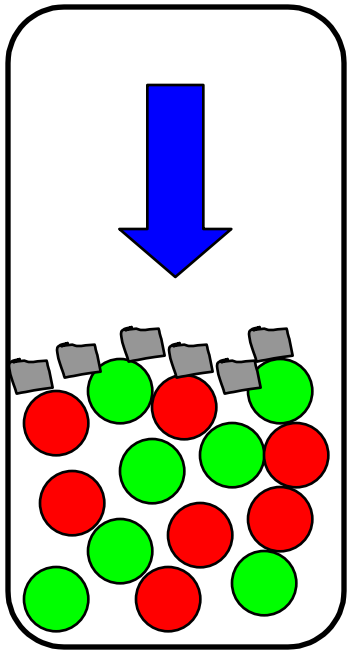


Up and Down Flow

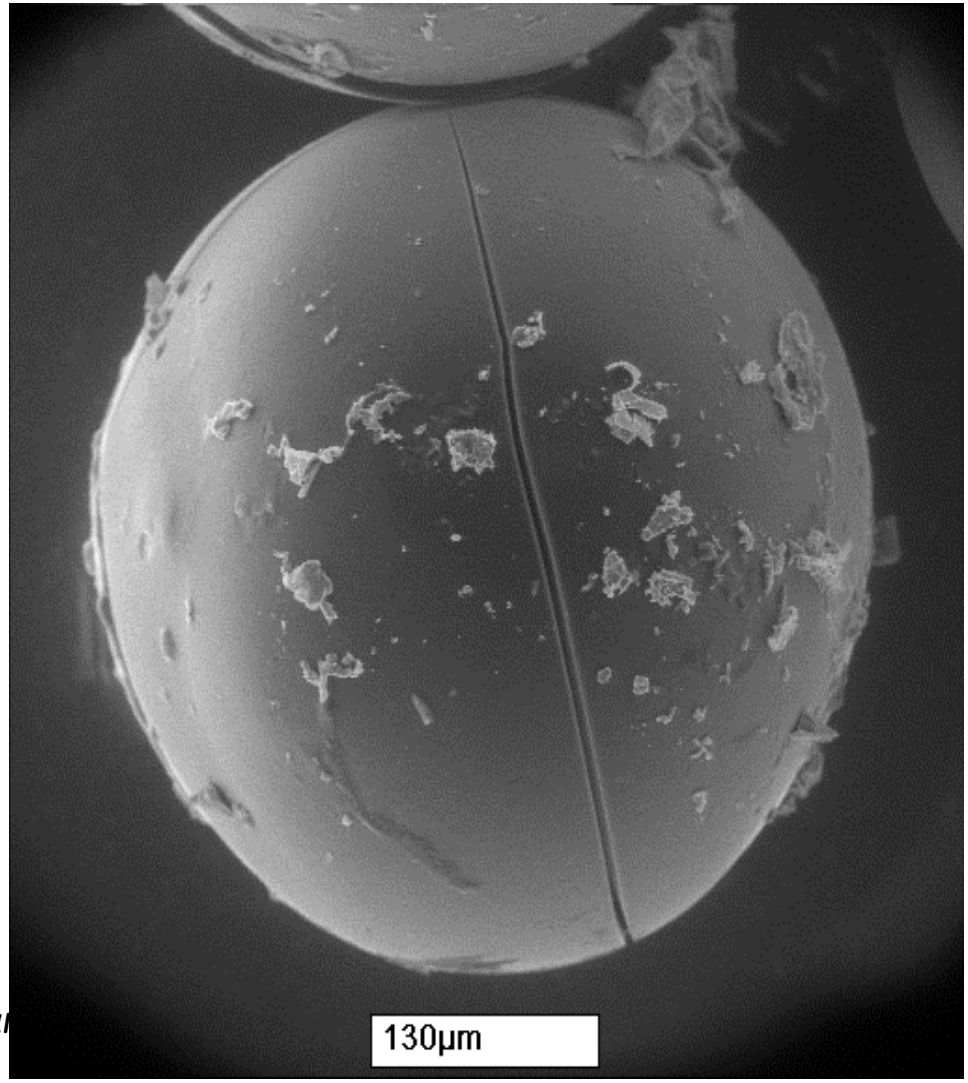
UPFLOW:
Channeling
but lower
risk of
clogging
Used in
Pretreatment



DOWNFLOW:
No channeling
and better ion
capture,
but higher
risk of
clogging
Used in
Polishing



SEM of Ion-Exchange Resin Bead

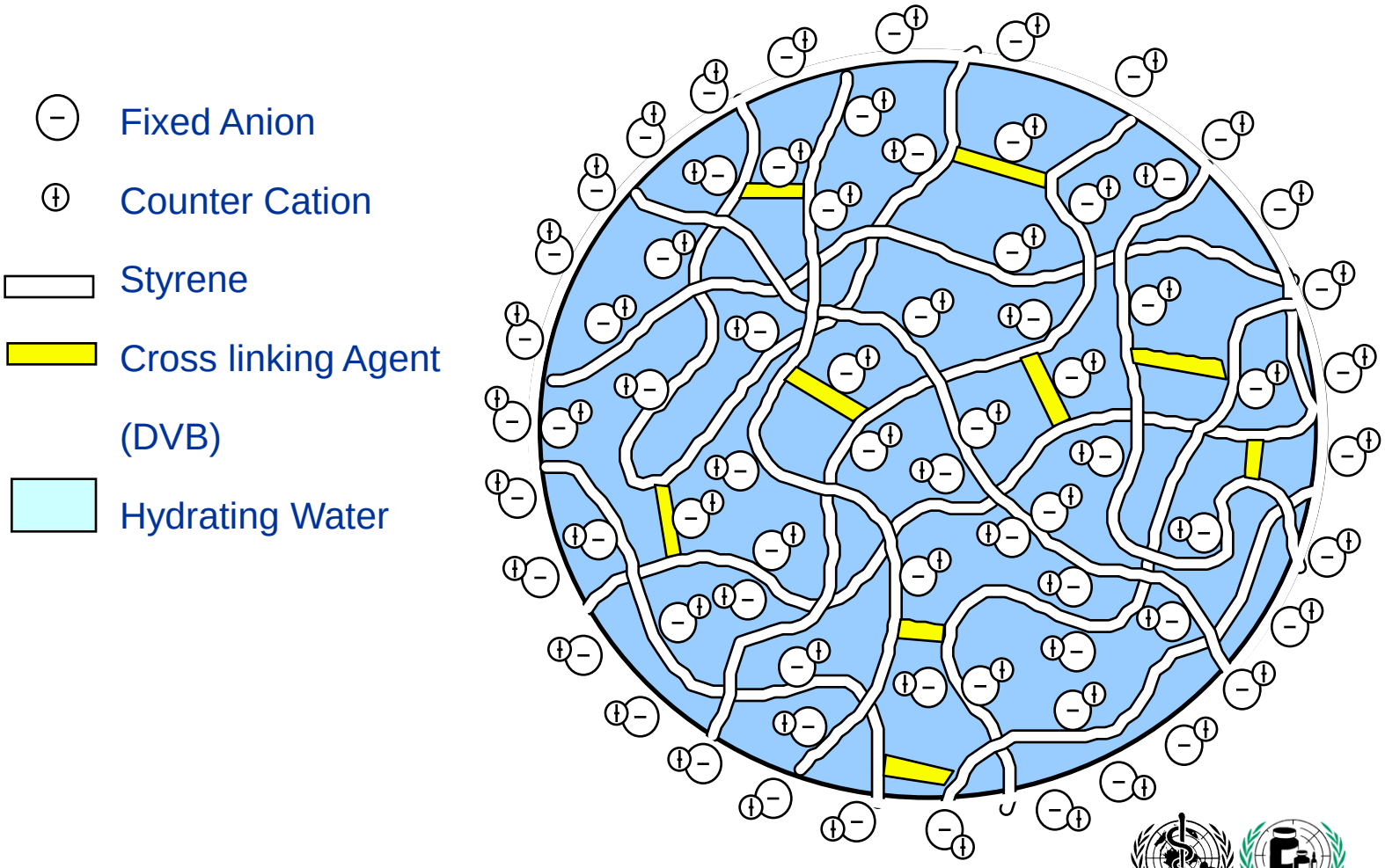


Bead diameter:
300 to 1200 µm
(0.3 to 1.2 mm)

Beads pores:
1 to 100 nm
(0.001 to 0.1 µm)

Bead dry weight
40 to 60%

Ion-Exchange Resin Bead model



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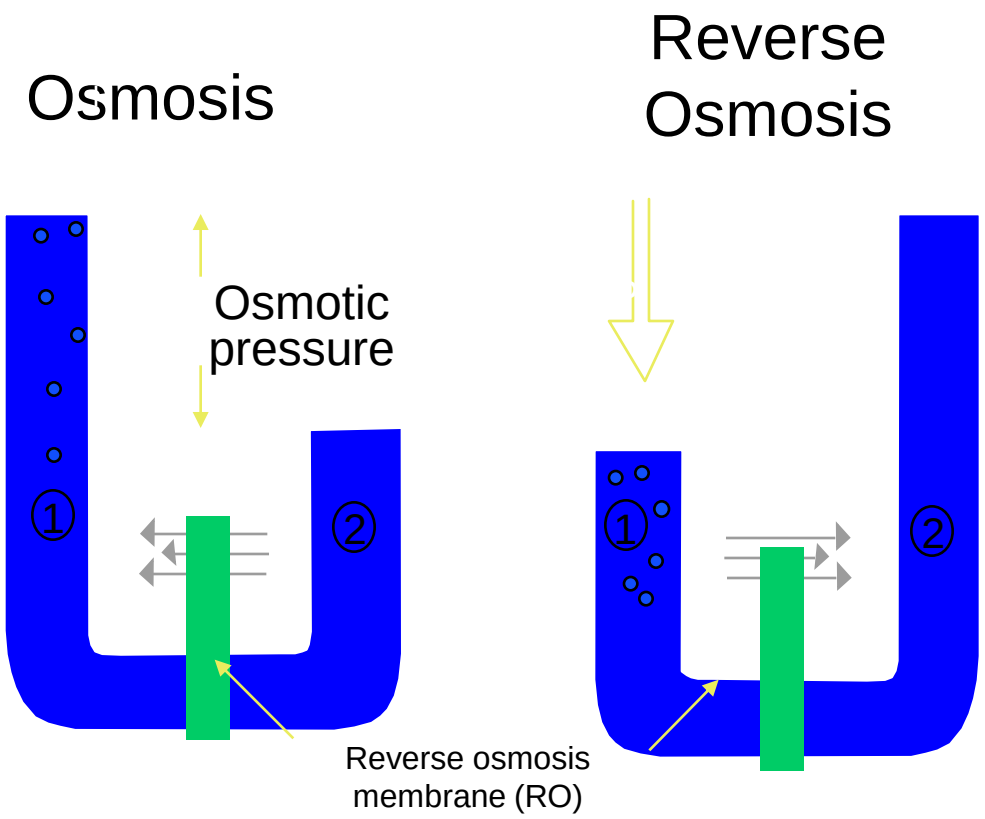
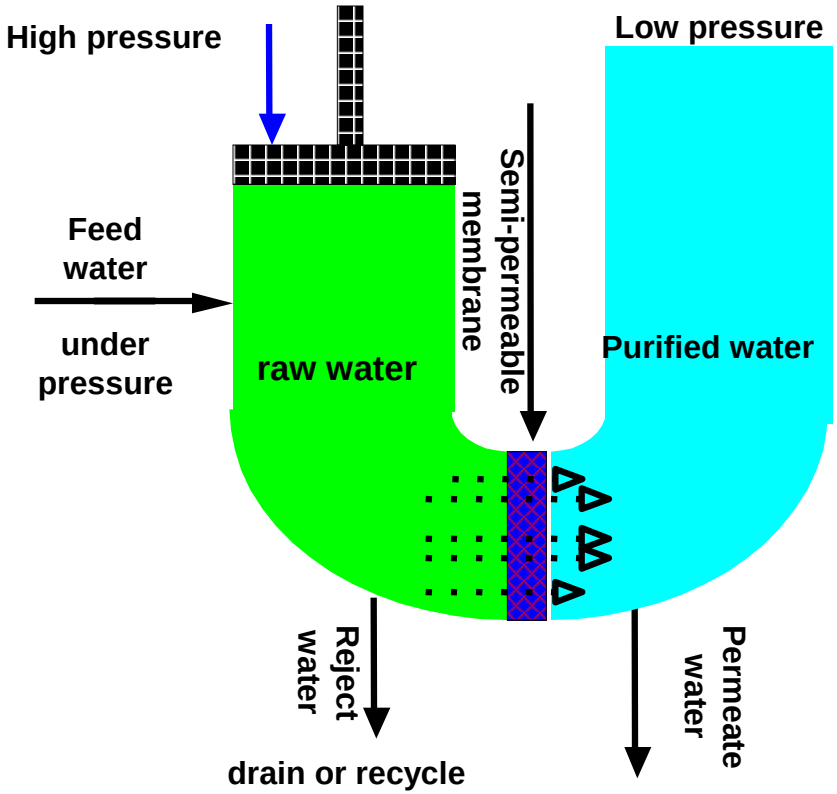
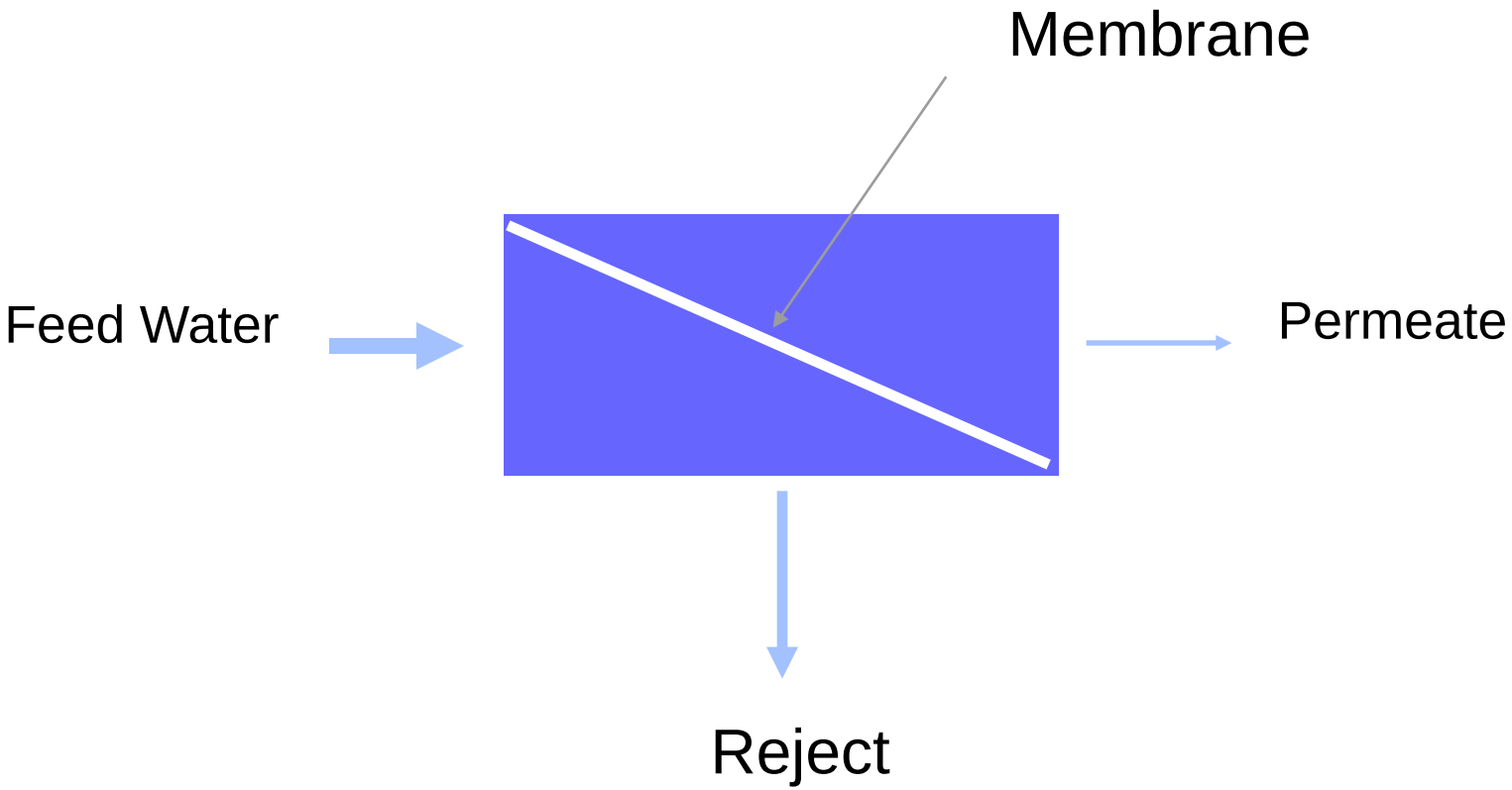


Water for Pharmaceutical Use

Reverse osmosis (RO) theory

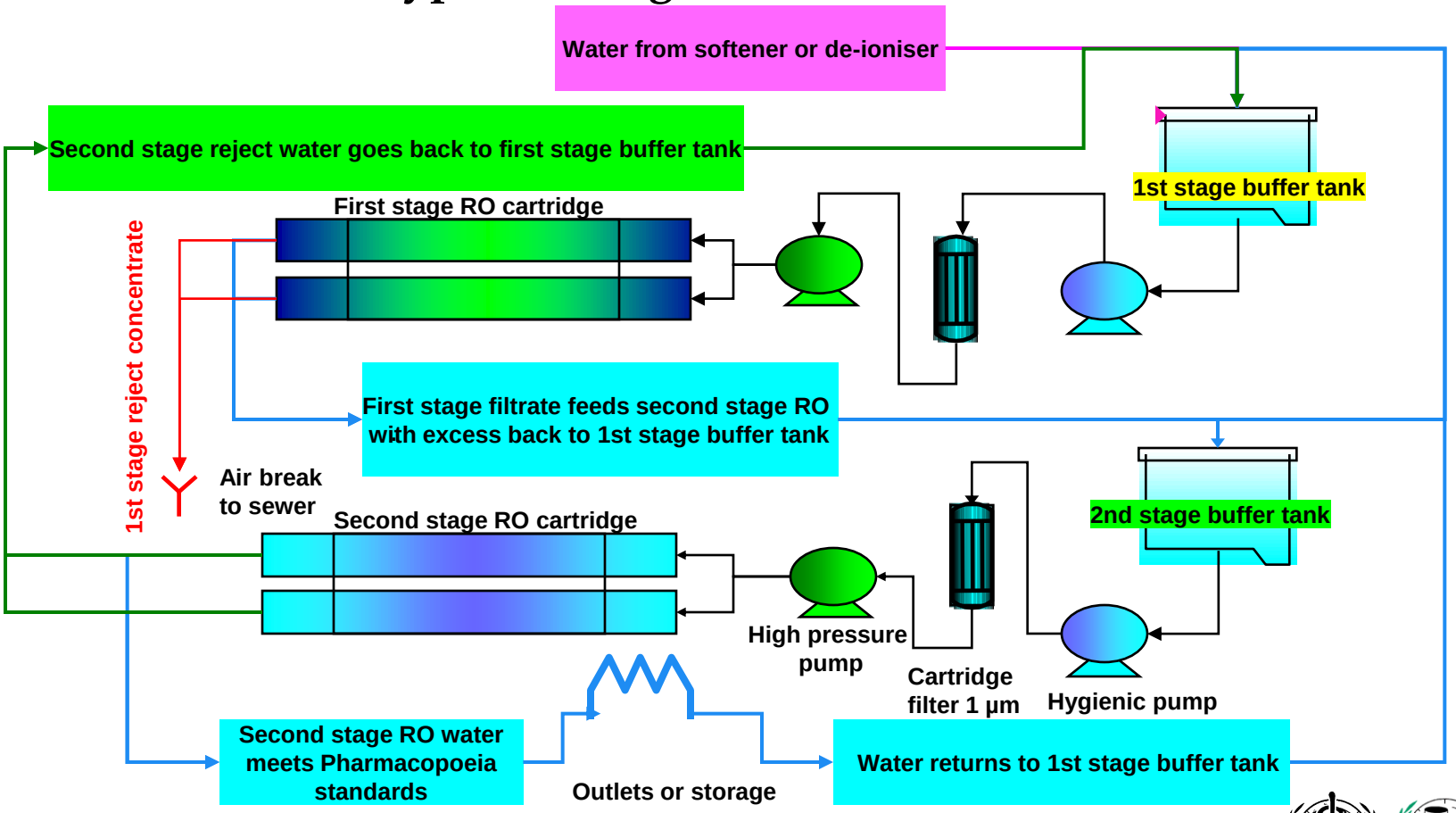


Water for Pharmaceutical Use



Water for Pharmaceutical Use

Typical 2-stage RO schematic



Water for Pharmaceutical Use

Use of reverse osmosis

- Advantages
- Disadvantages
- Many uses
  - *purified water*
  - *feeding of distillation units or ultra-filtration units*
  - *Water for Final Rinse*
  - *Water for Injections (if permissible)*

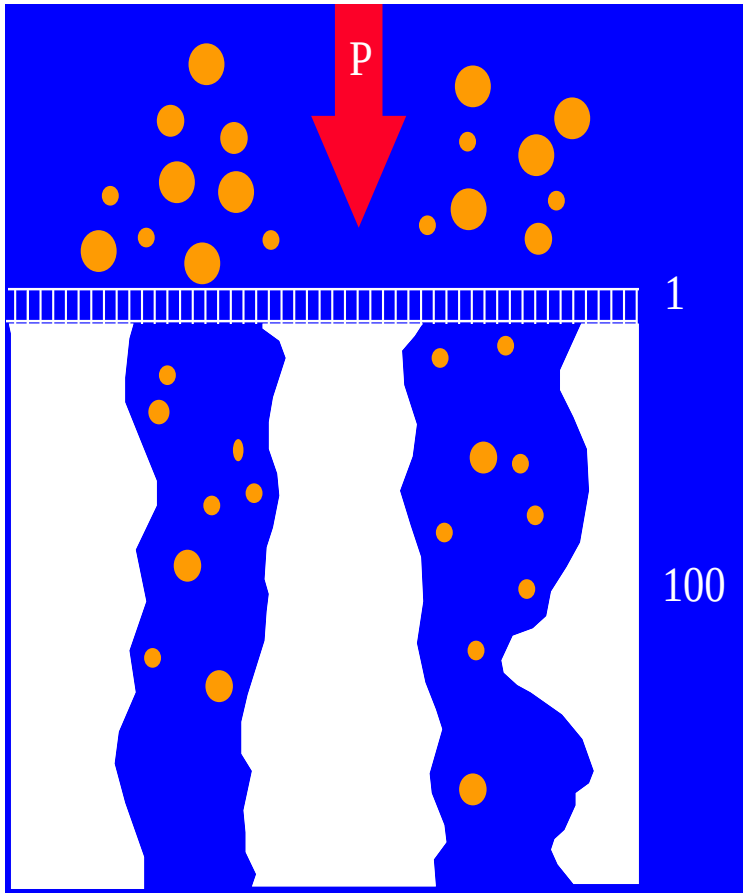
Water for Pharmaceutical Use

Ultra-filtration

- Can be used for WFI or for Water For Final Rinsing for parenteral manufacturing (if permitted)
- Removes organic contaminants, such as endotoxins
- Operation at 80°C, and sterilization at 121 °C

Water for Pharmaceutical Use

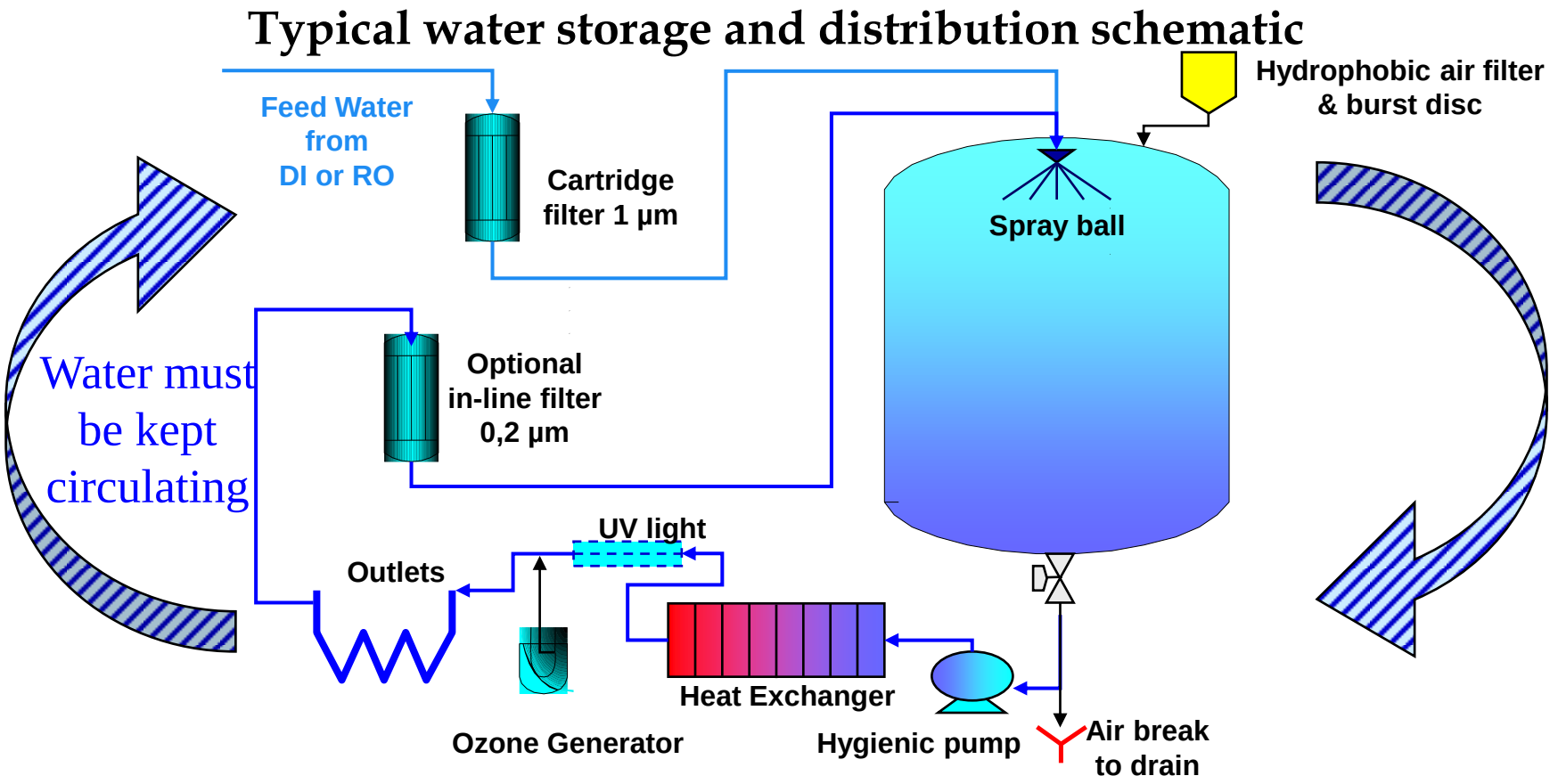
- Ultrafilters are asymetric membranes, sometimes composite
- Under pressure,small size molecules go through the membrane,whereas molecules larger then the NMWL are retained



Water for Pharmaceutical Use

1. Single-effect distillation
   - *simple distillation, single effect*
   - *vapour compression, thermo compression*
2. Multi effect distillation
   - *multiple effect stills*
3. Clean steam generators
   - *used where steam can come into contact with product contact surfaces, e.g. sterilization-in-place (SIP)*

Water for Pharmaceutical Use



Water for Pharmaceutical Use

Disinfection (1)

Heat

- One of the most reliable methods of disinfection of water systems

Ozone

- Produced easily
- Leaves no residue

Water for Pharmaceutical Use

Disinfection (2)

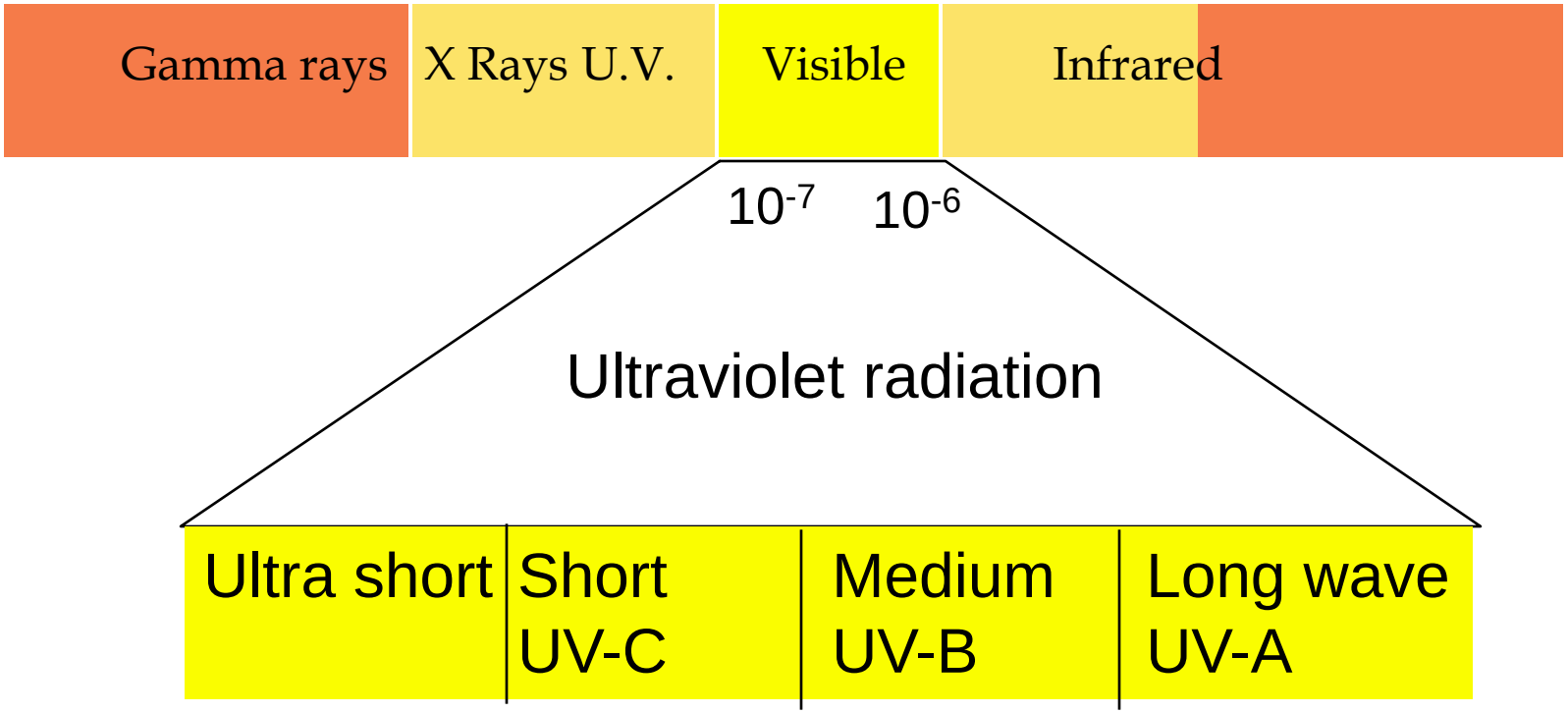
UV

1. UV does not "sterilize"
2. Flow rate critical
3. Post-irradiation recontamination may be an issue
4. Lamps have finite life

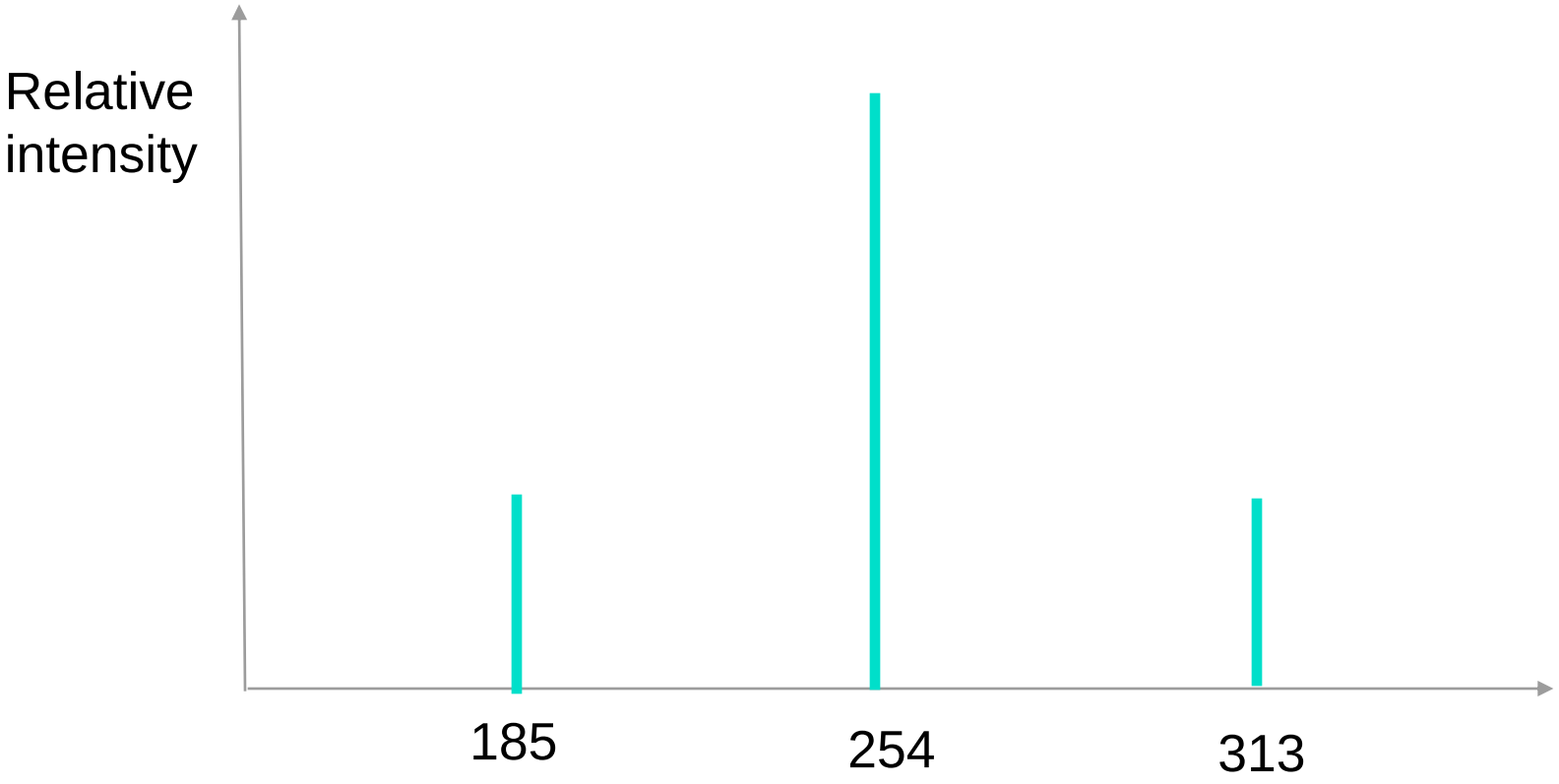
Other chemicals

1. XO_2
2. Halogen
3. Formaldehyde

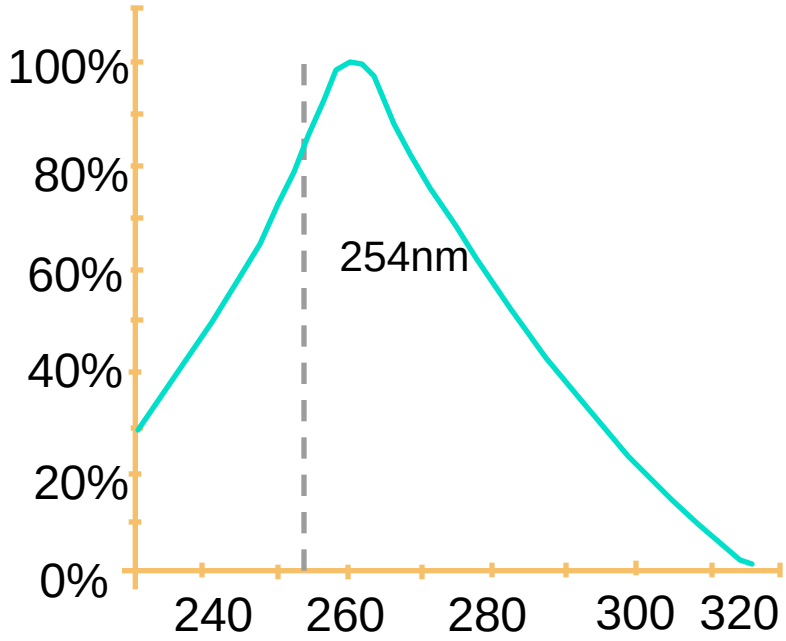
Water for Pharmaceutical Use



Water for Pharmaceutical Use



Water for Pharmaceutical Use



UV Technology
(185 + 254 nm)

Water for Pharmaceutical Use

- **Conversion of traces of organic contaminants to charged species and ultimately CO2 (185 + 254)**
- **Limited destruction of micro-organisms and viruses (254)**
- **Limited energy use**
- **Easy to operate**
- **Polishing technique only: may be overwhelmed if organics concentration in feed water is too high. Organics are converted, not removed.**
- **Limited effect on other contaminants**
- **Good design required for optimum performance.**

Water for Pharmaceutical Use

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

Water for Pharmaceutical Use

Sampling (1)

1. There must be a sampling procedure
2. Sample integrity must be assured
3. Sampler training
4. Sample point
5. Sample size

Water for Pharmaceutical Use

Sampling (2)

1. Sample container
2. Sample label
3. Sample storage and transport
4. Arrival at the laboratory
5. Start of test

Water for Pharmaceutical Use

Testing - setting specifications for purified water or WFI - (1)

	Ph. Eur.	JP	USP	Int. Ph.
pH	5.0-7.0	5.0-7.0	5.0-7.0	pass test
Cl	< 0.5	pass test	-	pass test
SO_4	pass test	pass test	-	pass test
NH_4	< 0.2	< 0.05	-	pass test
Ca/Mg	pass test	-	-	pass test
Nitrates	< 0,2	pass test	-	pass test
Nitrites	-	pass test	-	-

Water for Pharmaceutical Use

Testing - setting specifications for purified water or WFI (2)

	Ph. Eur.	JP	USP	Int. Ph
Conductivity (µS/cm)	-	-	< 1.3	-
Oxidizable subs.	pass test	pass test	-	pass test
Solids (ppm)	< 10	< 10	-	nmt(*) 10
TOC (ppm)	-	< 0.5	< 0.5	-
Heavy metals	-	-	-	pass test
CO_2	-	-	-	pass test

Water for Pharmaceutical Use

Testing

1. Method verification
2. Chemical testing
3. Microbiological testing
   - *test method*
   - *types of media used*
   - *incubation time and temperature*
   - *objectionable and indicator organisms*
   - *manufacturer must set specifications*

Water for Pharmaceutical Use

Water for Injections

1. International pharmacopoeia requirements for WFI are those for purified water plus it must be free from pyrogens
2. Usually prepared by distillation
3. Storage time should be less than 24 hours
4. Microbial limits must be specified

Water for Pharmaceutical Use

Water for Final Rinse

- Water for final rinse must be of the same quality as the water required for pharmaceutical preparation

Water for Pharmaceutical Use

Pyrogens and endotoxins

1. Any compound injected into mammals which gives rise to fever is a "Pyrogen"
2. Endotoxins are pyrogenic, come from Gram negative bacterial cell wall fragments
3. Detect endotoxins using a test for *lipopolysaccharides (LPS)*
   - *rabbit test detects pyrogens*
   - *LAL test detects endotoxins*
4. Ultrafiltration, distillation, & RO may remove pyrogens

Water for Pharmaceutical Use

Suggested bacterial limits *(CFU/mL)*

Sampling location	Target	Alert	Action
Raw water	200	300	500
Post multimedia filter	100	300	500
Post softener	100	300	500
Post activated carbon filter	50	300	500
Feed to RO	20	200	500
RO permeate	10	50	100
Points of Use	1	10	100