

# Pure Media and Process Systems – State of the Art Solutions for Vaccine Manufacturing

DCVMN – Workshop Engineering and GMP compliant systems

30<sup>th</sup> October 2014, Delhi



## Portfolio for Complete Production Lines

### Clean Utilities



**Bosch – Pharma Liquid**, Crailsheim/Germany

**Bosch – Pharma Solid**, Waiblingen/Germany

**Pharmatec**, Dresden/Germany

**SBM**, Ternitz/Austria

### Process Technology



**Moeller & Devicon**, Sandved/Denmark

**Manesty**, Knowsley/UK

**Hüttlin**, Schopfheim/Germany

### Primary Packaging



**Eisai Machinery**, Japan

**Bosch Packaging USA**, Minneapolis/USA

**Bosch Packaging CHINA**, Hangzhou/China

**Bosch Packaging JAPAN**, Japan

### Secondary packaging



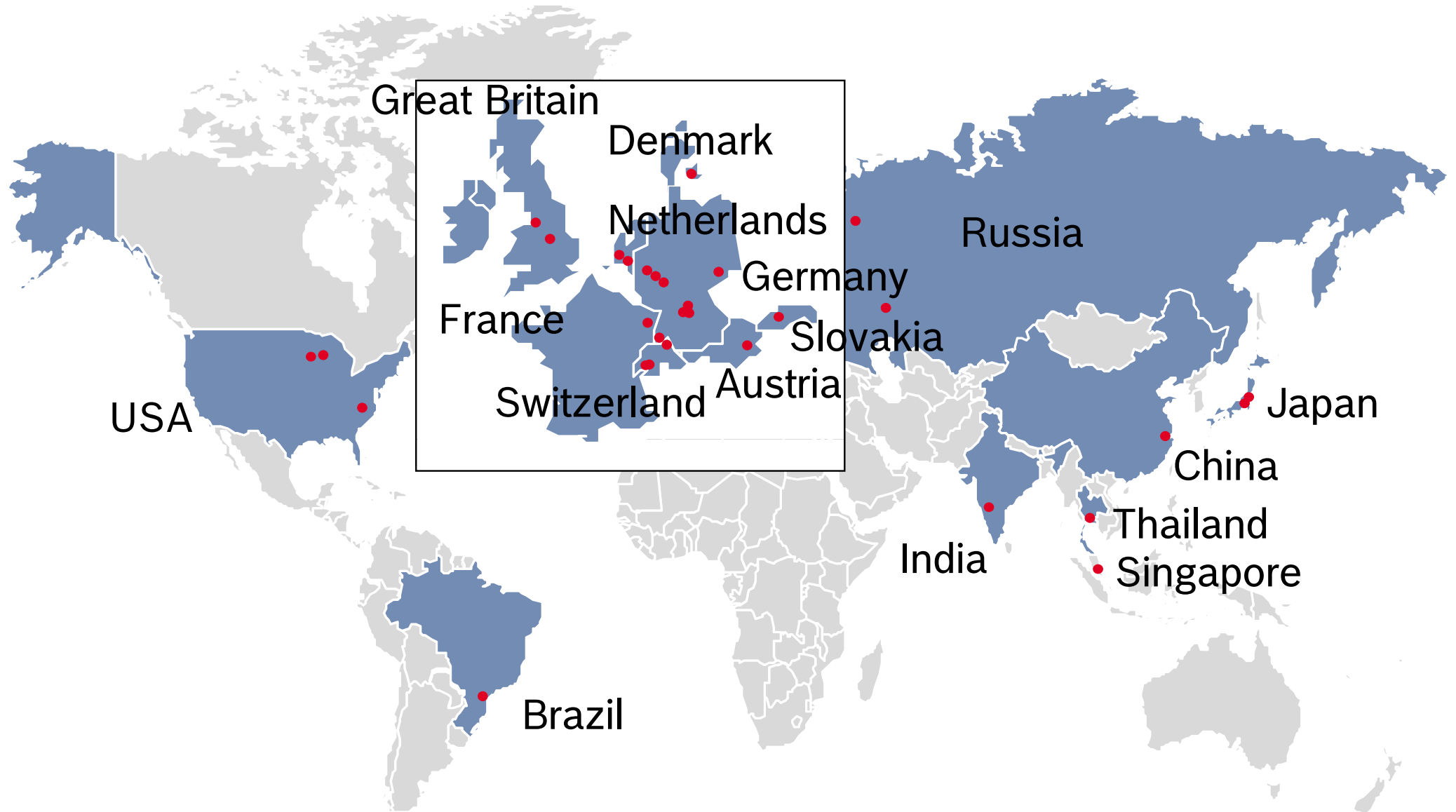
**Bosch Packaging INDIA**, Verna/India

**Bosch Packaging Systems**, Beringen/CH

**Bosch Chemical & Cosmetics**, Viersen/Germany

**Valicare**, Frankfurt/Germany

## Worldwide Presence

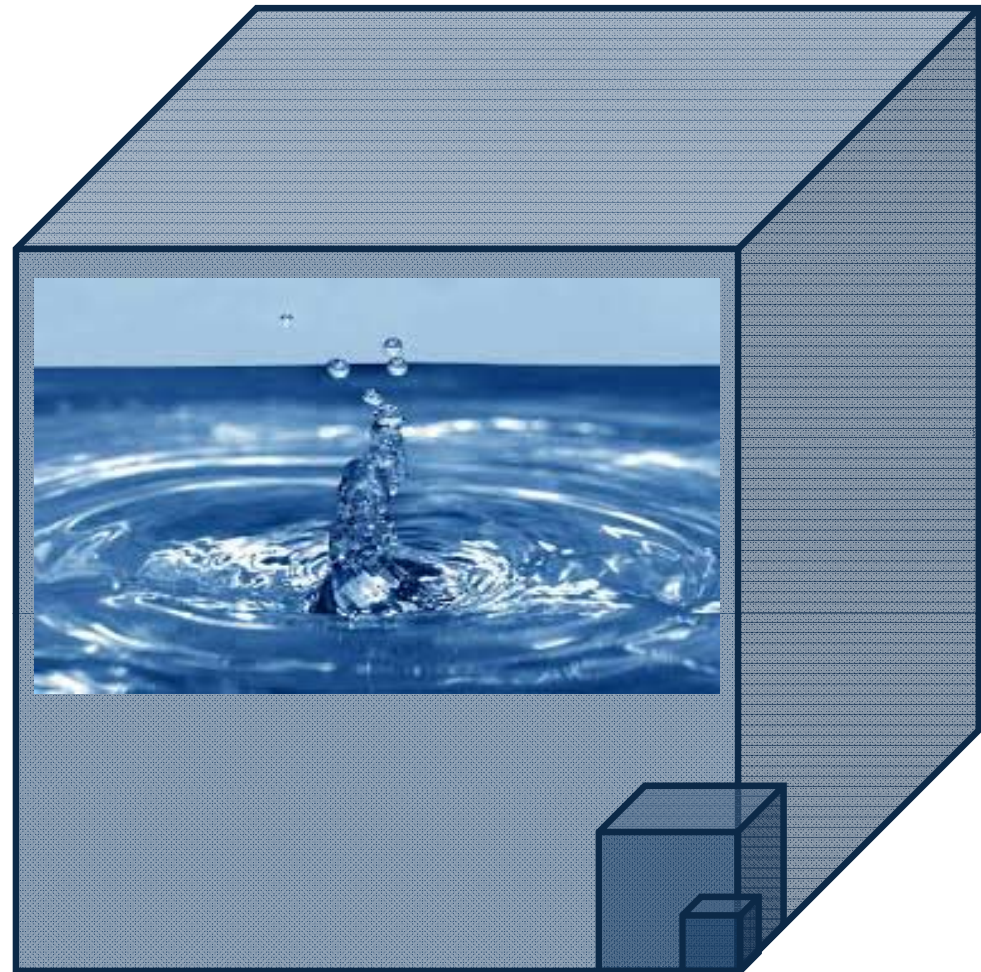


# NATURAL SOURCE WATER - H<sub>2</sub>O

Total volume approx.  
1,36 billion km<sup>3</sup> (cube  
of 1.116 km length)

Fresh water volume  
approx. 40 million km<sup>3</sup>  
(cube of 340 km  
length) -> 3%

Useable as Potable  
Water approx. 8  
million km<sup>3</sup> (cube of  
200 km length) ->  
0,6%

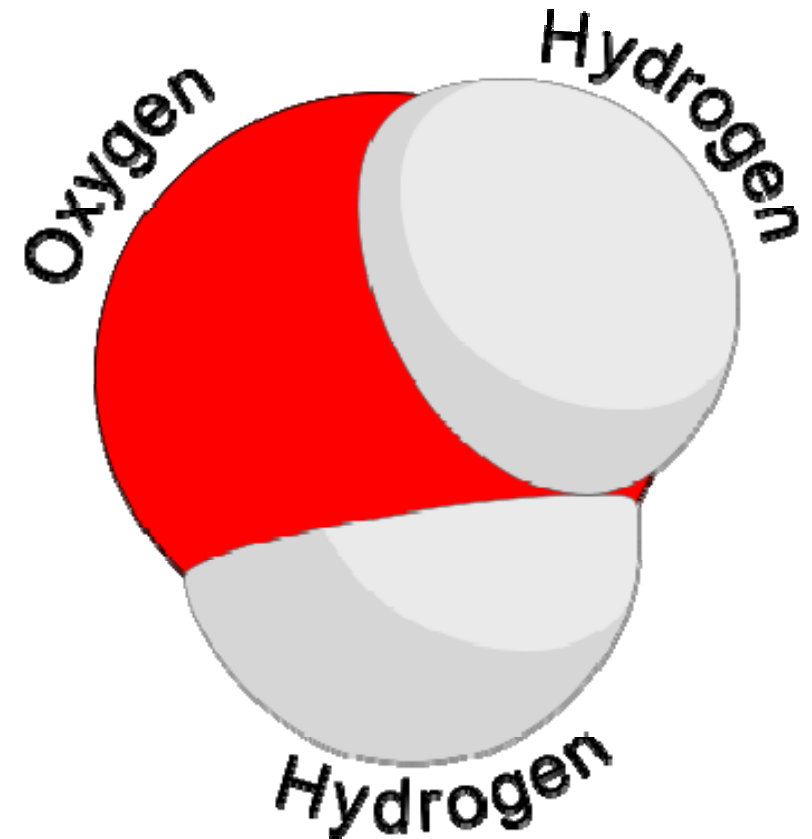


Many substances dissolve in water and it is commonly referred to as **the universal solvent**.

Therefore **all natural waters contain**, in various concentrations, dissolved salts which dissociate in water to form charged ions. Positively charged ions are called **cations**; negatively charged ions are called **anions**.

In general, ionic and polar substances such as acids, alcohols and salts are relatively soluble in water, and nonpolar substances such as fats and oils are not.

**Water molecule (H<sub>2</sub>O)**



## Definition:

- Potable water is water **intended for human consumption**
- Potable water **is not defined in a Pharmacopoeia**, it is specified in the local regulations for drinking water
- Potable water provides a **basis for all water qualities defined in the Pharmacopoeias**



## Potable water

Potable water varies by country and region. The quality is depending on methods of sourcing and treatment

### Methods of potable water sourcing:

- Well water from municipal supplier
- Well water from a local source (at site)
- Surface water from:
  - Fresh water lakes
  - Filtrate from river banks
  - Sea water desalination
  - Other sources



**Further treatment steps have to be individually designed according to the analysis of the potable water!**

## → Definition of Water Qualities in the Pharmacopoeias:

- National Pharmacopoeias
- European Pharmacopoeia (Ph. Eur.)
- American Pharmacopoeia (USP)



## → International regulations and guidelines

- ISPE Pharmaceutical Engineering guides
- FDA Guide for Inspection of High Purity Water Systems
- EMEA/CPMP/QWP Note for Guidance on Quality of Water for Pharmaceutical Use

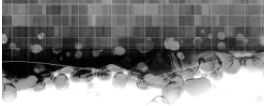


# PHARMACEUTICAL WATER CATEGORIES

## Four water categories are used in the pharmaceutical industry:

- Potable water
- Purified water\*
- Highly purified water\* (→ Ph. Eur. only)
- Water for injection\*

\* Compendial water qualities (according to the Pharmacopoeias)



**A Comparison of Ph. Eur. and USP Requirements**

Purified Water and Water for Injection are similar grades of pharmaceutical water with slightly differing specifications in the European Pharmacopoeia (Ph. Eur.) and the United States Pharmacopoeia (USP). The implementation of the Ph. Eur. 7<sup>th</sup> Edition from the 1<sup>st</sup> January 2002 not only provides guidance to ranges of particular grades, but also introduces a new grade of water called "Highly Purified Water". Highly Purified Water is to be used in the preparation of medicinal products in instances where water of high biological quality is needed but WFI is not required.

The following summaries are based on the current requirements of the European and United States Pharmacopoeias.

Purified Water	USP	Ph. Eur.
Process	Distillation, reverse osmosis, ion exchange, any other suitable process	Distillation, ion exchange, any other suitable process
Conductivity	≤ 1.3 µS/cm at 25°C in the measurement or equivalent values from Table A*	≤ 4.3 µS/cm at 25°C
Bacteria	≤ 100 cfu/ml guidance advice limit only	≤ 100 cfu/ml
Endotoxin	NA	≤ 0.25 IU / ml only for bulk water for dosage
TOC	≤ 500 µg/l	≤ 500 µg/l or ppm equivalent submersible test
Nitrate	NA	≤ 0.2 ppm
Heavy Metals	NA	≤ 0.1 ppm
Aluminium	NA	≤ 10 µg/ml (only for bulk water for dosage)

Highly Purified Water	USP	Ph. Eur.
Process	NA	Reverse osmosis in combination with distillation and deionisation, for example
Conductivity	NA	≤ 1.3 µS/cm at 25°C
Bacteria	NA	≤ 10 cfu / 100 ml
Endotoxin	NA	≤ 0.25 IU / ml
TOC	NA	≤ 500 µg/l
Nitrate	NA	≤ 0.2 ppm
Heavy Metals	NA	≤ 0.1 ppm
Aluminium	NA	≤ 10 µg/ml (only for bulk water for dosage)

**Water for Injection**

	USP	Ph. Eur.
Process	Distillation or reverse osmosis	Distillation
Conductivity	≤ 1.3 µS/cm at 25°C in the measurement or equivalent values from Table A*	≤ 1.3 µS/cm at 25°C
Bacteria	≤ 10 cfu / 100 ml	≤ 10 cfu / 100 ml
Endotoxin	≤ 0.25 IU / ml	≤ 0.25 IU / ml
TOC	≤ 500 µg/l	≤ 500 µg/l
Nitrate	NA	≤ 0.2 ppm
Heavy Metals	NA	≤ 0.1 ppm
Aluminium	NA	NA

**USP Three Stage Conductivity Testing**

**Stage 1: On or Off Line Testing**  
If the conductivity < 1.3 µS/cm at 25°C for tabulated values in Table A, the test is complete. If not, go to Stage 2.

**Stage 2: Lab Test**  
Equilibrate a water sample with atmospheric CO<sub>2</sub> at 25°C. If the conductivity < 2.2 µS/cm the test is complete. If not, go to Stage 3.

**Stage 3: Lab Test**  
Add sodium KCl to the previous sample and measure pH. If the conductivity does not exceed the allowable level of conductivity of the pH, based on Table B, the test is complete. If not, the water fails.

Table A		Table B	
Temperature (°C)	Conductivity Limit (µS/cm)	pH level	Conductivity Limit (µS/cm)
0	0.6	5.0	4.7
5	0.6	5.1	4.1
10	0.9	5.1	3.6
15	1.0	5.3	3.3
20	1.1	5.4	3.0
25	1.3	5.5	2.6
30	1.4	5.6	2.6
35	1.5	5.7	2.5
40	1.7	5.8	2.4
45	1.8	5.9	2.4
50	1.9	6.0	2.4
55	2.1	6.1	2.4
60	2.2	6.2	2.5
65	2.4	6.3	2.4
70	2.5	6.4	2.3
75	2.7	6.5	2.2
80	2.7	6.6	2.1
85	2.7	6.7	2.6
90	2.7	6.8	3.1
95	2.9	6.9	3.8
100	3.1	7.0	4.6



# PHARMACEUTICAL WATER CATEGORIES

Purified Water	USP	Ph Eur
Process	Distillation, reverse osmosis, any other suitable process	Distillation, ion exchange, any other suitable process
Conductivity	≤ 1,3 μS/cm at 25°C in line measurement or equivalent values from Table A*	< 4,3 μS/cm at 20°C
Bacteria	< 100 cfu / ml guidance action limit only	< 100 cfu / ml
Endotoxin	N/A	< 0.25 I.U. / ml (only for bulk water for dialysis)
TOC	< 500 ppb	< 500 ppb or pass oxidisable substances test
Nitrates	N/A	≤ 0.2 ppm
Heavy Metals	N/A	≤ 0.1 ppm
Aluminum	N/A	≤ 10 μg/ml (only for bulk water for dialysis)

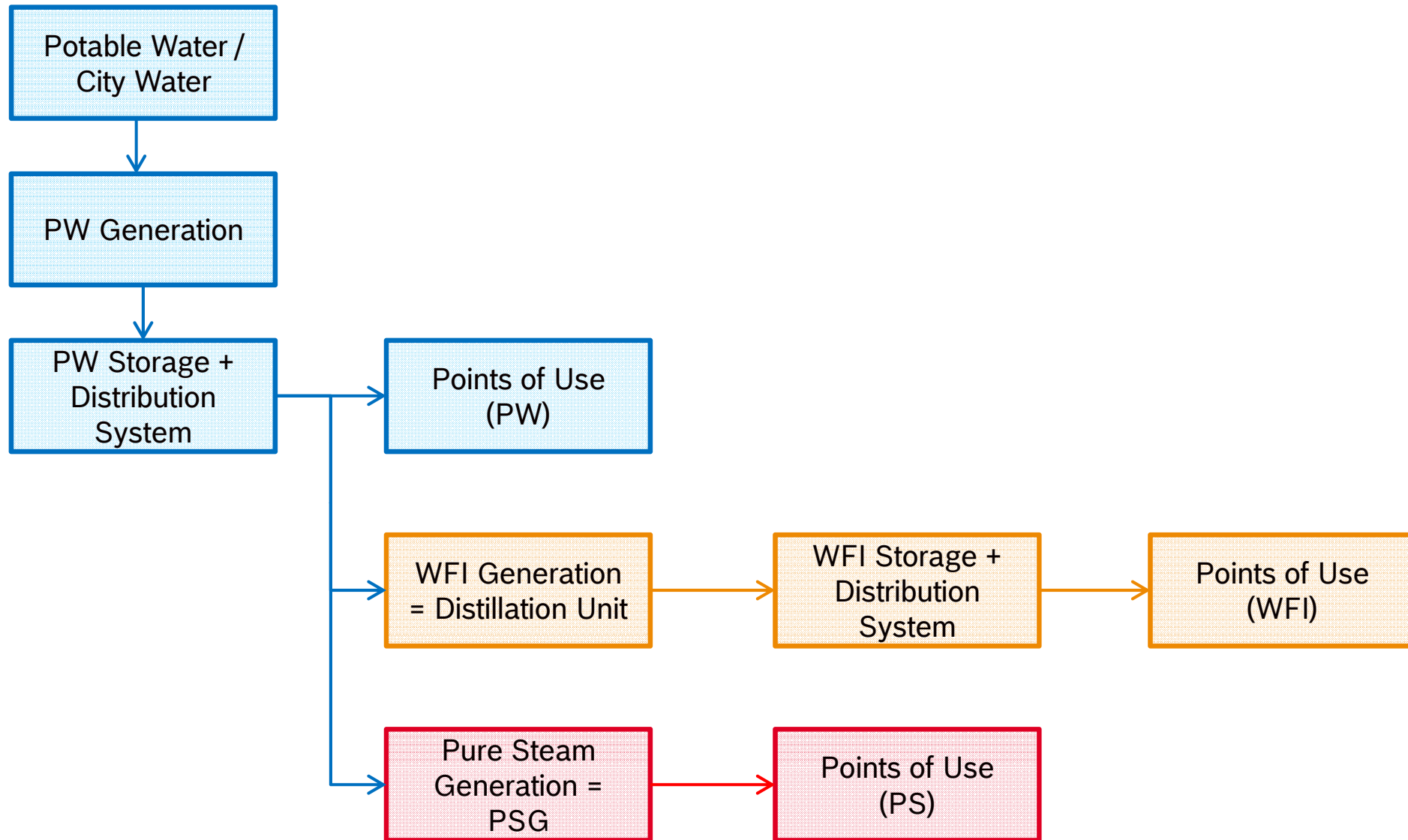


# PHARMACEUTICAL WATER CATEGORIES

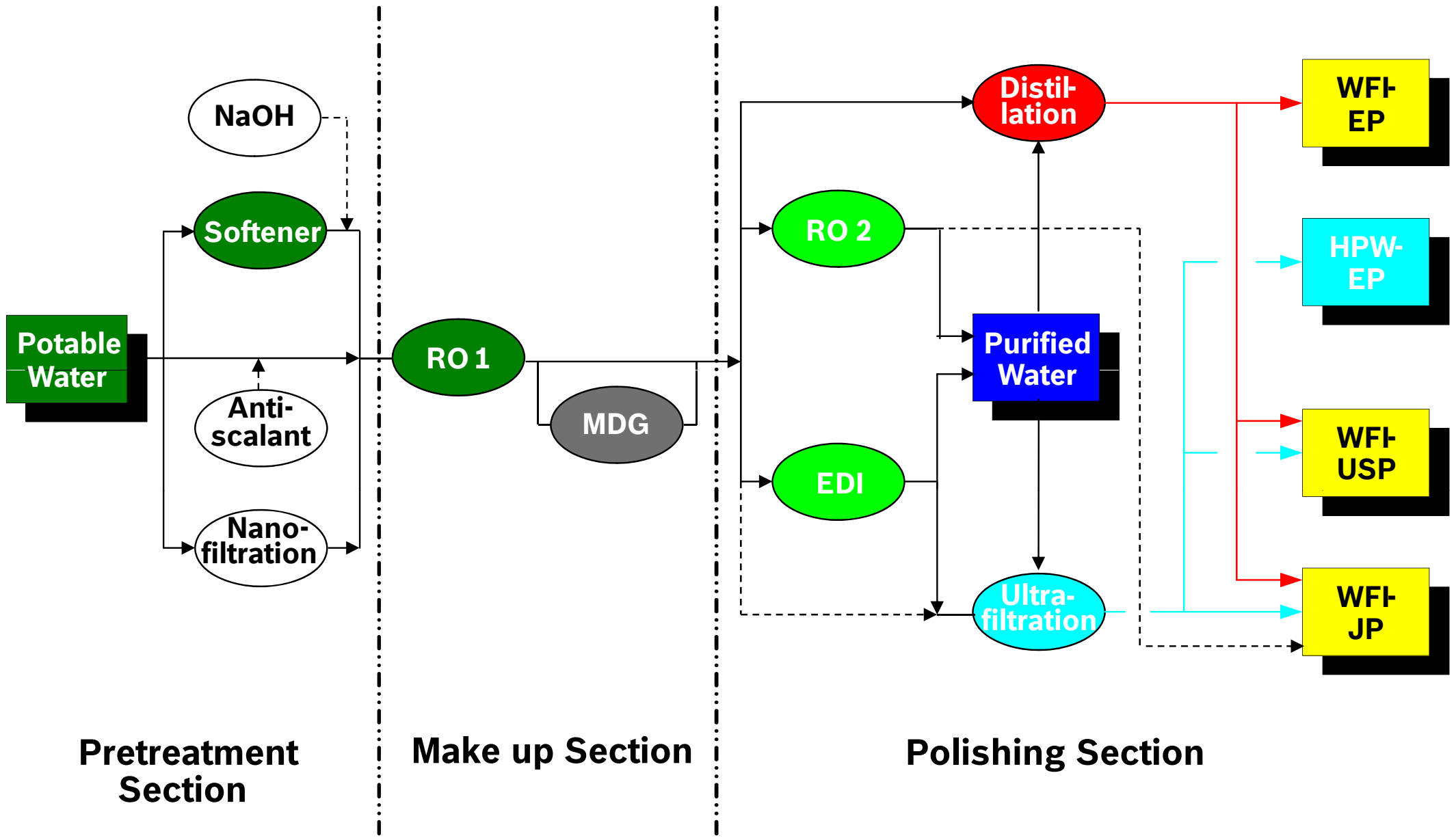
<u>Water for Injection</u>		
	USP	Ph Eur
Process	Distillation or reverse osmosis	Distillation
Conductivity	$\leq 1.3 \mu\text{S/cm}$ at 25°C in line measurement or equivalent values from Table A*	$\leq 1.1 \mu\text{S/cm}$ at 20°C
Bacteria	< 10 cfu / 100 ml	< 10 cfu / 100 ml
Endotoxin	< 0.25 EU / ml	< 0.25 I.U. / ml
TOC	< 500 ppb	< 500 ppb
Nitrates	N/A	$\leq 0.2 \text{ ppm}$
Heavy Metals	N/A	$\leq 0.1 \text{ ppm}$
Aluminum	N/A	N/A



# PHARMACEUTICAL WATER TREATMENT SYSTEMS



# PHARMACEUTICAL WATER TREATMENT SYSTEMS



- Main purpose:
  - Treatment of potable city water or raw water into water for pharmaceutical use → Purified Water according to USP (United States Pharmacopeia) and Ph Eur (European Pharmacopeia)
  
- Treatment steps:
  - Filtration and chemical treatment of incoming water
  - Softening
  - Reverse Osmosis (single or double stage RO)
  - Degassing
  - Continuous Electro Deionisation (CDI / EDI)
  - (Ultra Filtration)

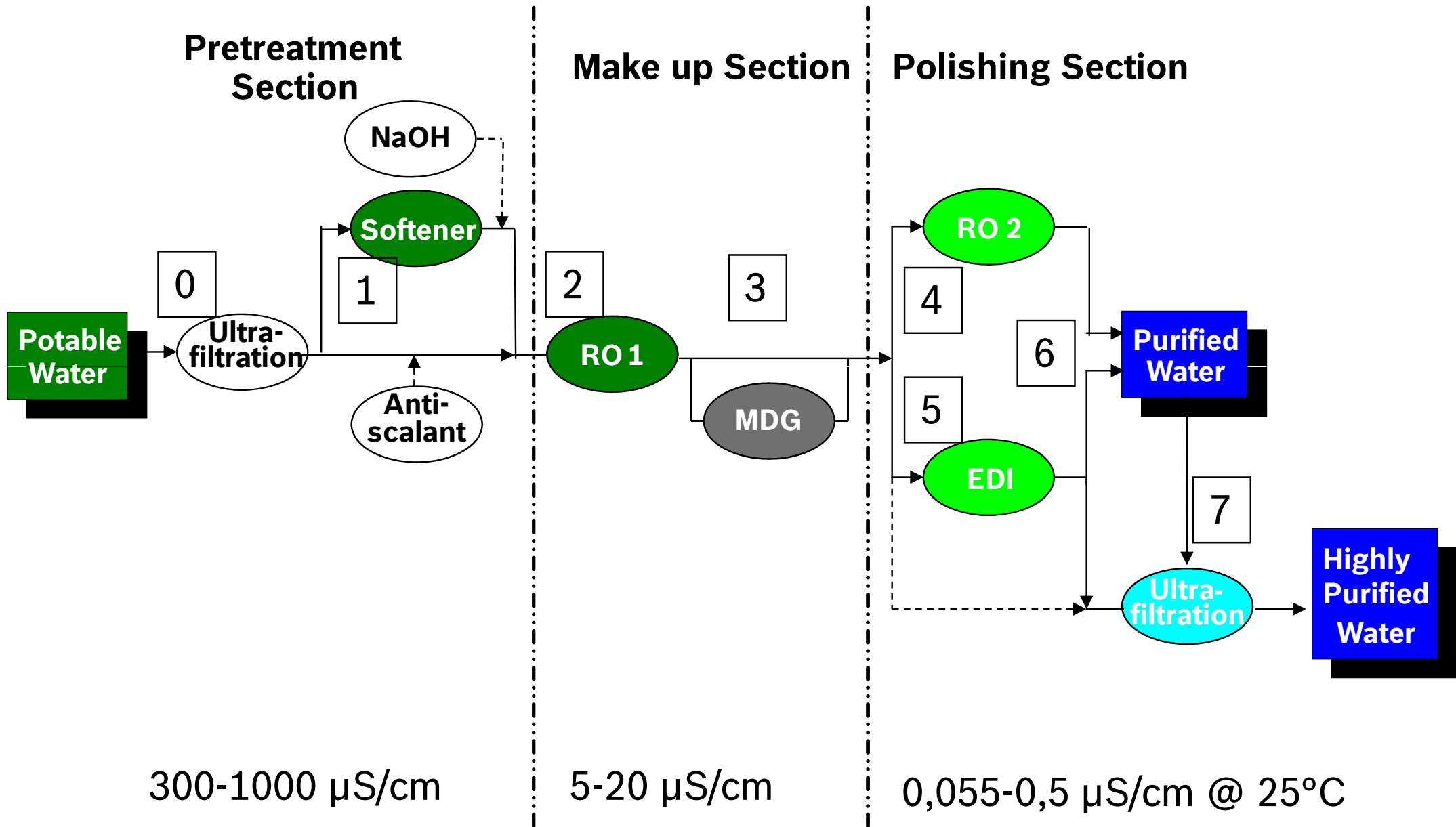
## What is needed for the design of a PW system:

- > Water analysis or
- > Sample of feed water for analysis in laboratory

## Analysis with information's on:

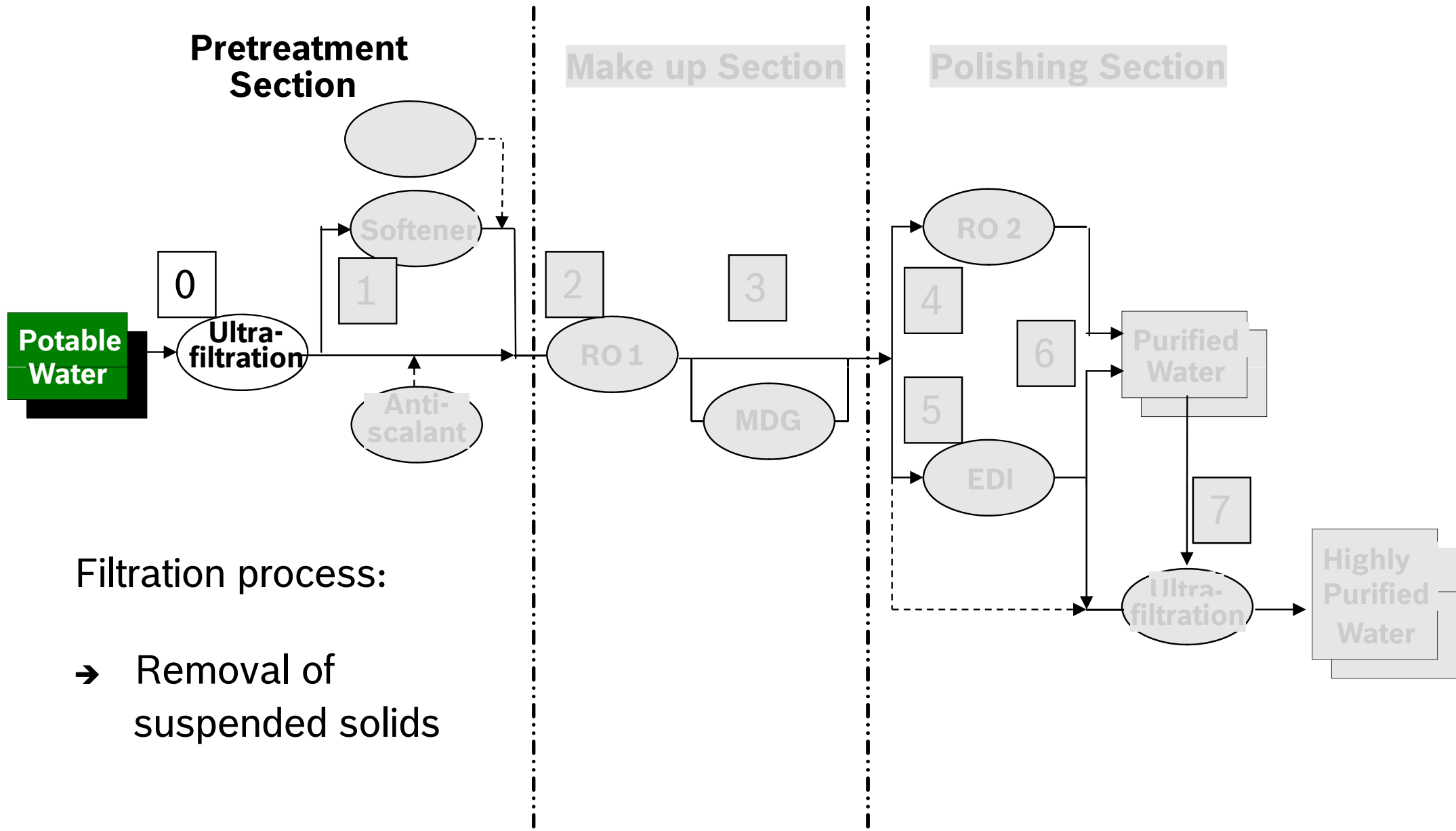
- Ions in feed water (at least conductivity)
- TSS – Total Suspended Solids = turbidity
- SDI – Silt-Density-Index (needs to be measured)
- Hardness (Ca<sup>++</sup>, Mg<sup>++</sup>, Ba<sup>++</sup>, Sr<sup>++</sup>)
- Fe, Mn
- Silica
- CO<sub>2</sub>

# PURIFIED WATER GENERATION

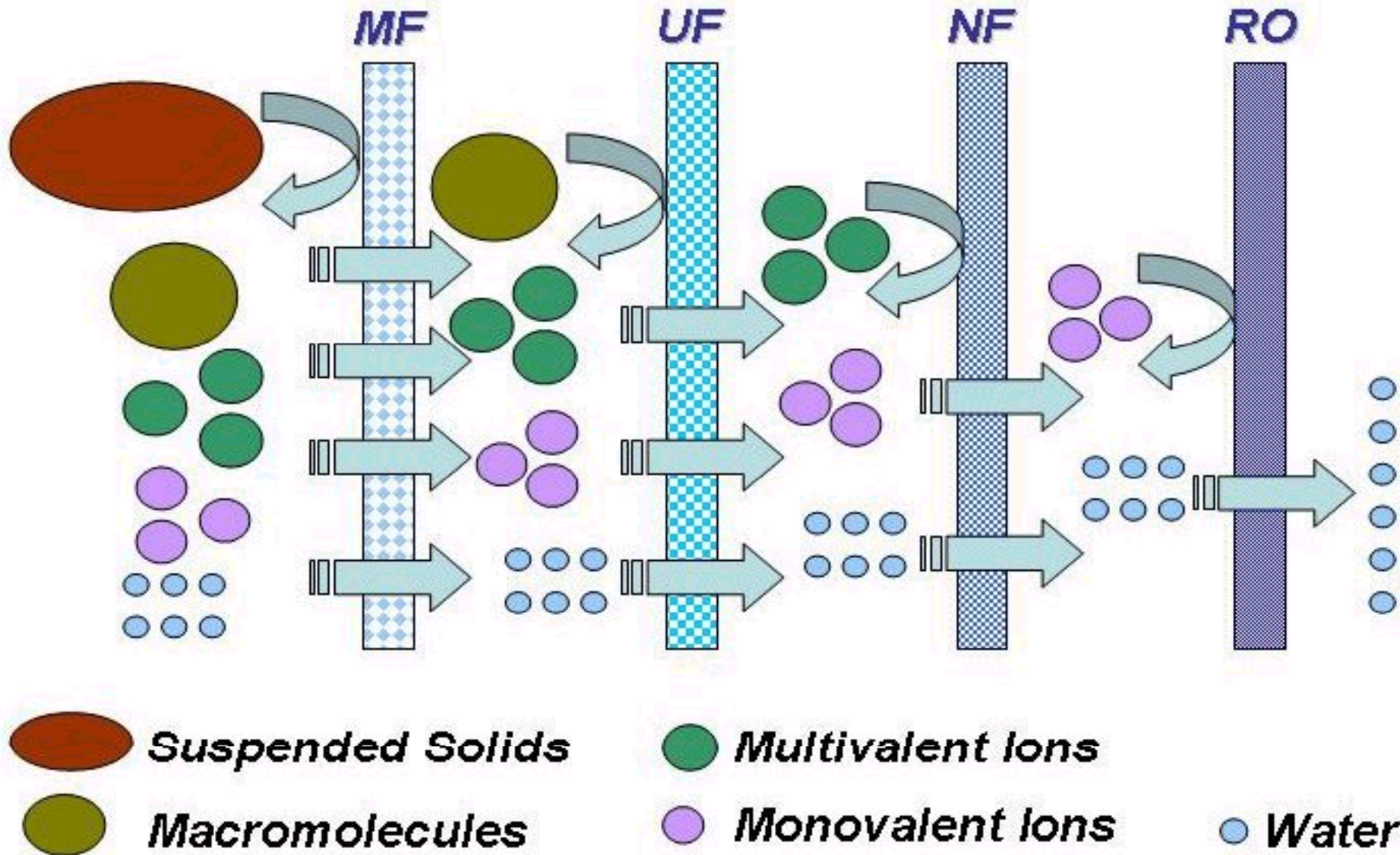




# PRE-TREATMENT: FILTRATION



# RANGE OF MEMBRANE PROCESSES



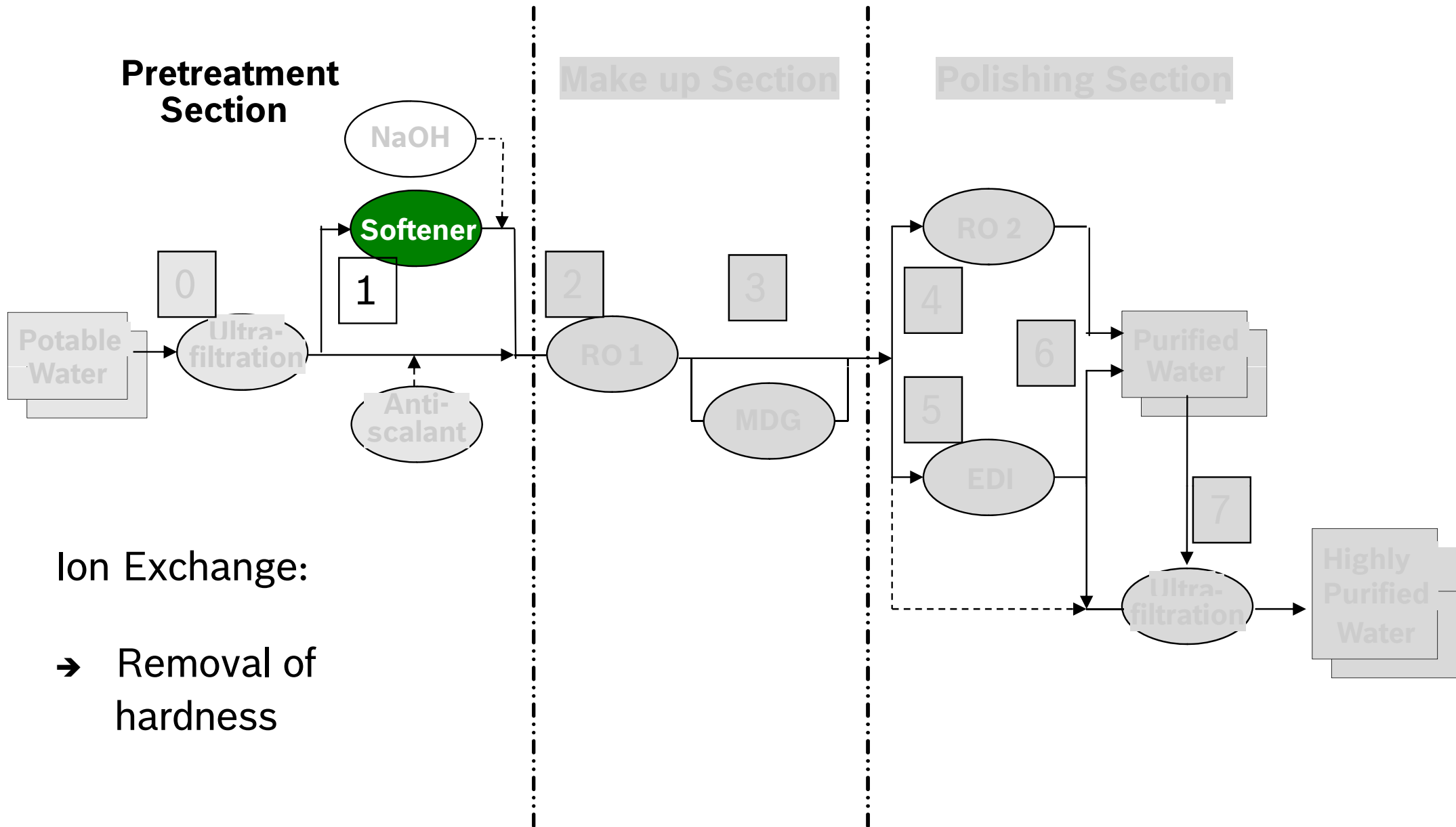
# ULTRAFILTRATION (UF)



UF module for **raw water** filtration  
Cut-off 100'000...200'000 Dalton



# WATER SOFTENING



Ion Exchange:

→ Removal of hardness



# WATER SOFTENING

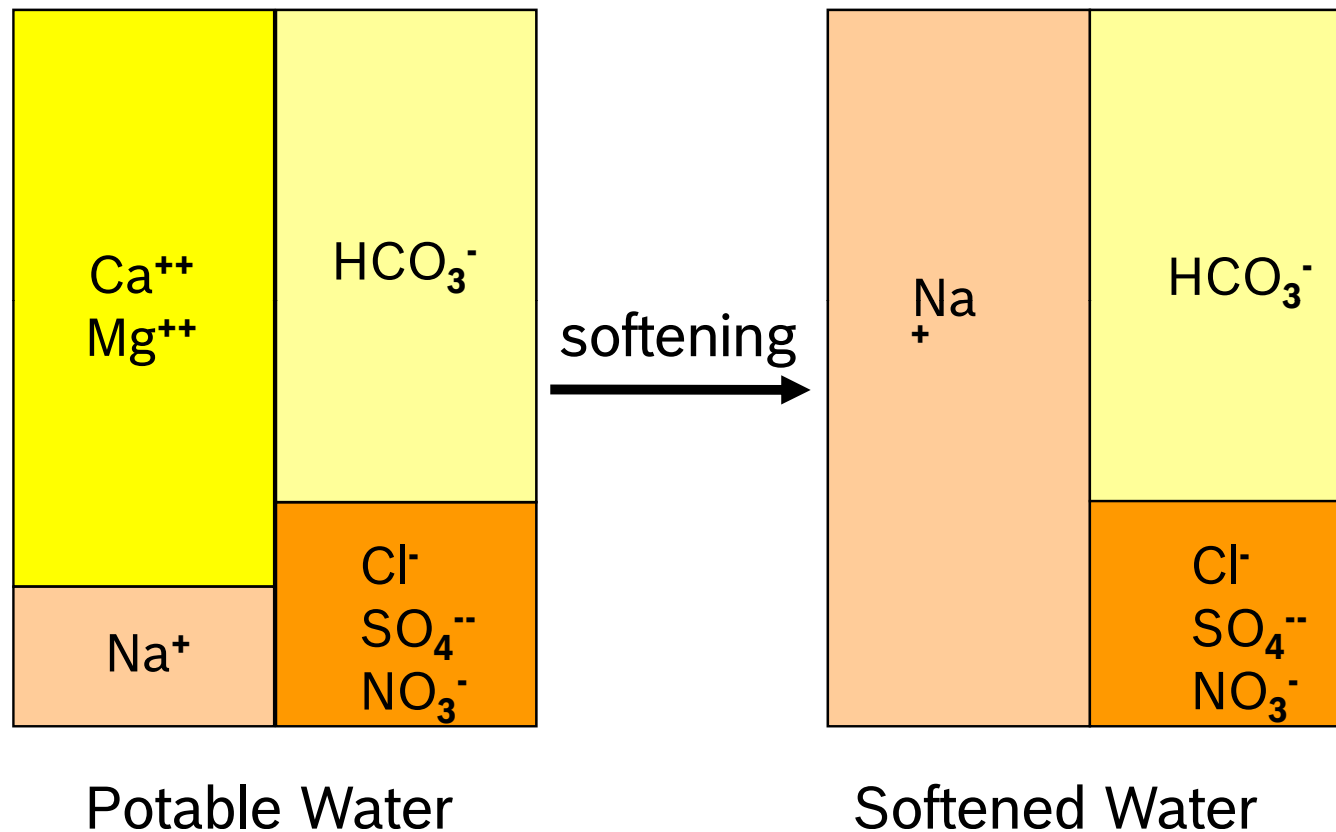


# WATER SOFTENING

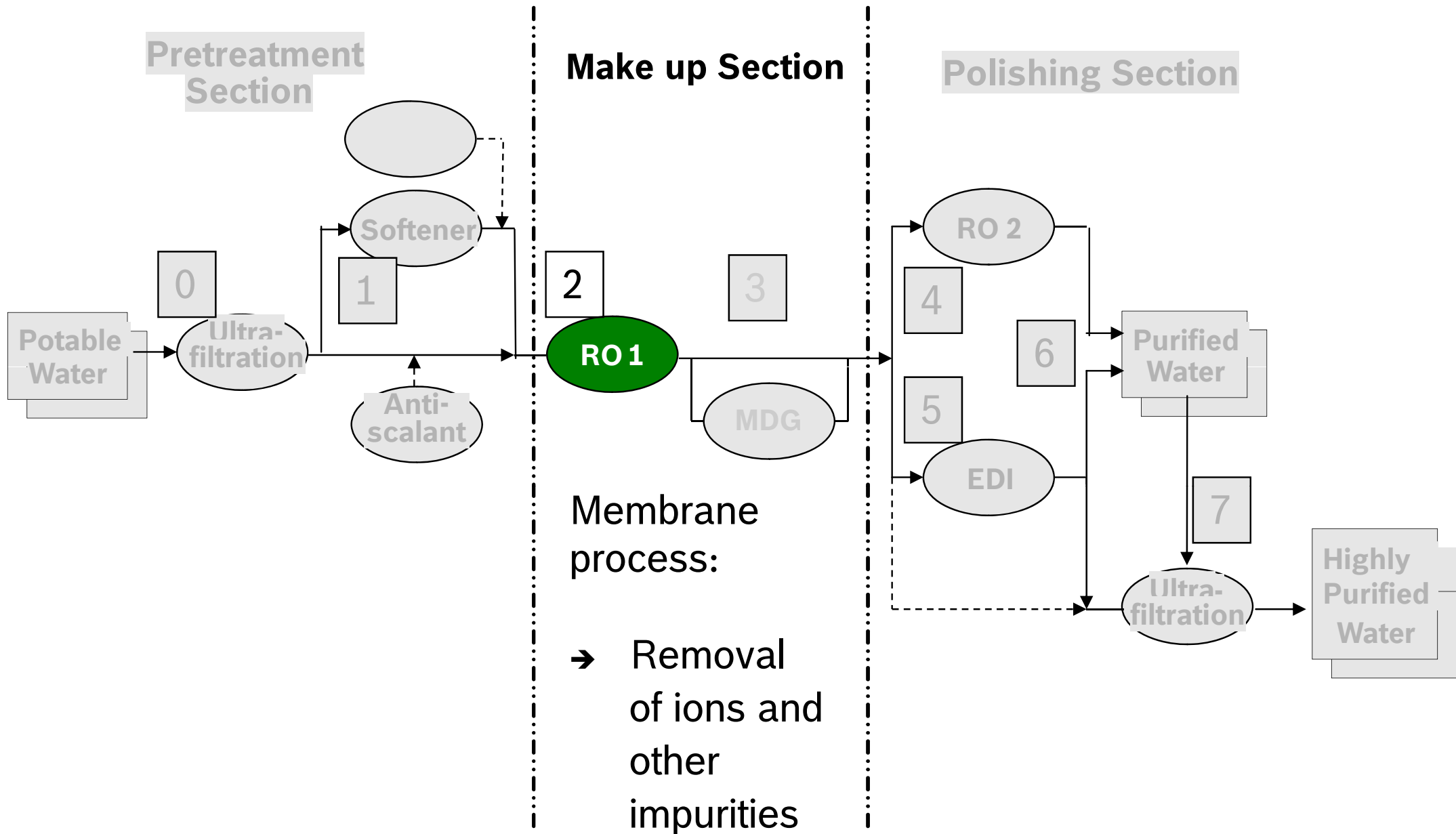


# WATER SOFTENING

Softening removes water hardness builders such as calcium and magnesium as well as metals like divalent iron ( $\text{Fe}^{++}$ ) and replaces them by sodium ions.

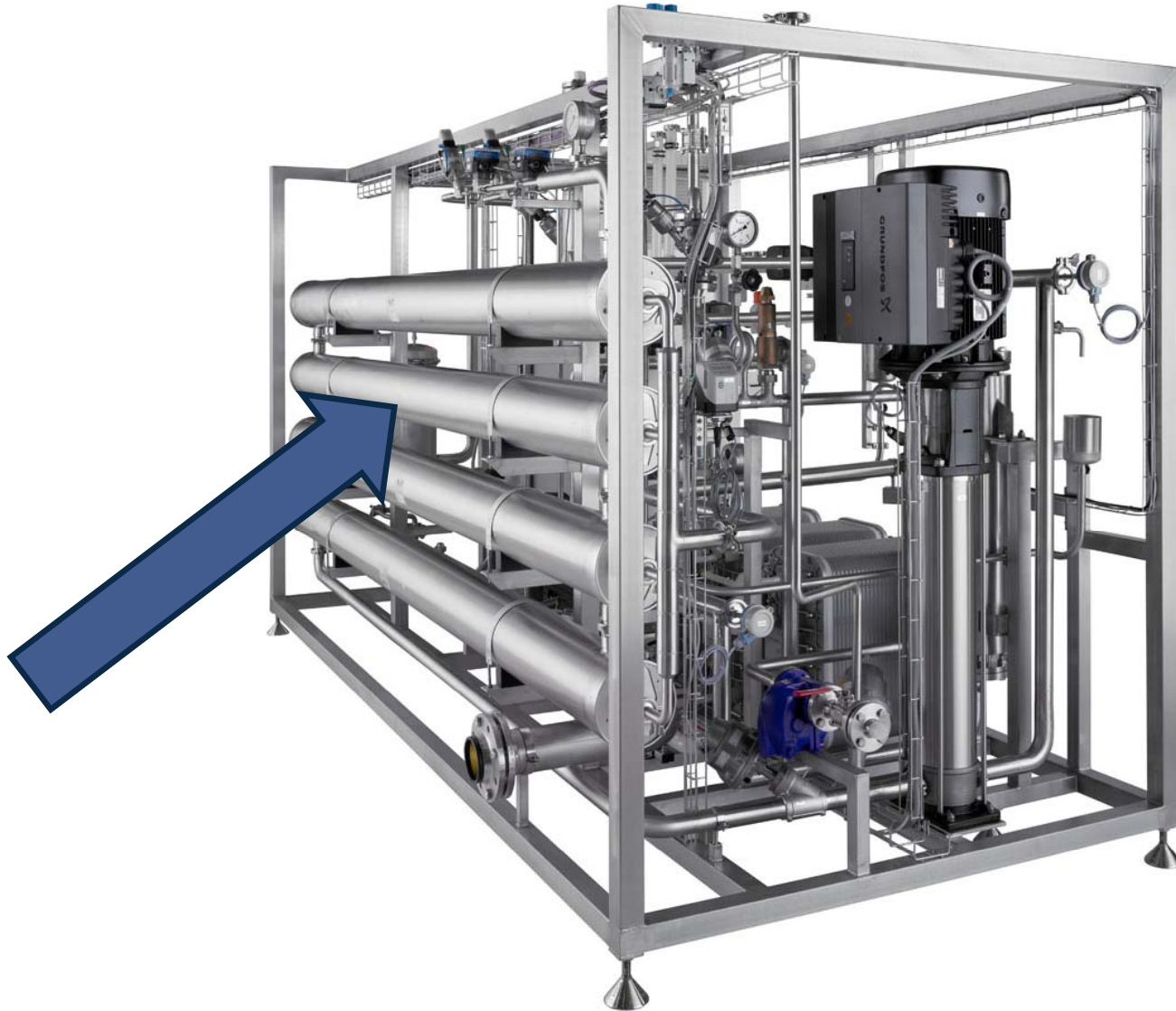


# REVERSE OSMOSIS (RO)



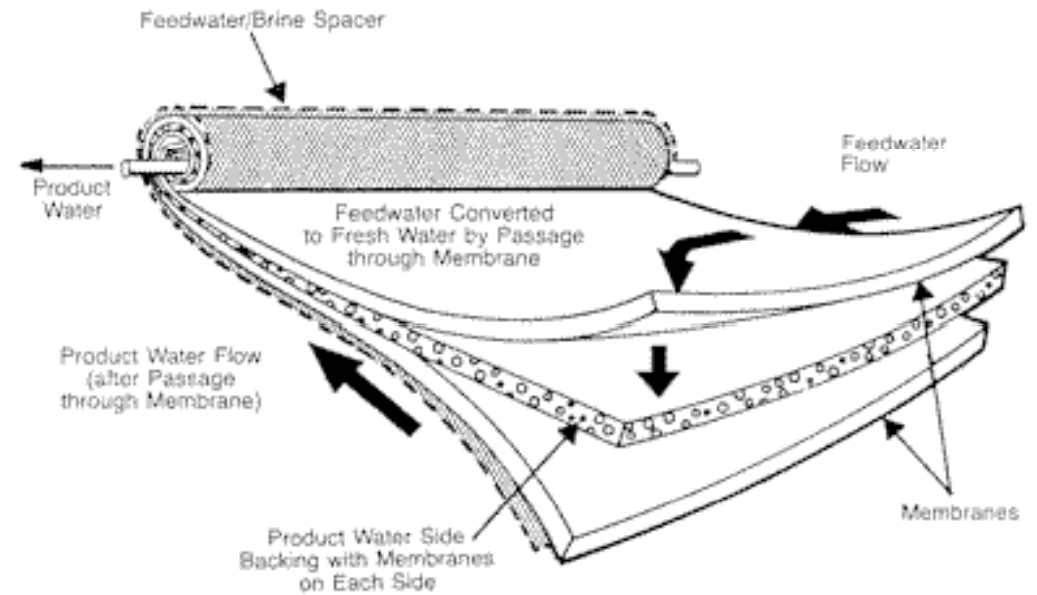


## PW Generation – RO = Reverse Osmosis



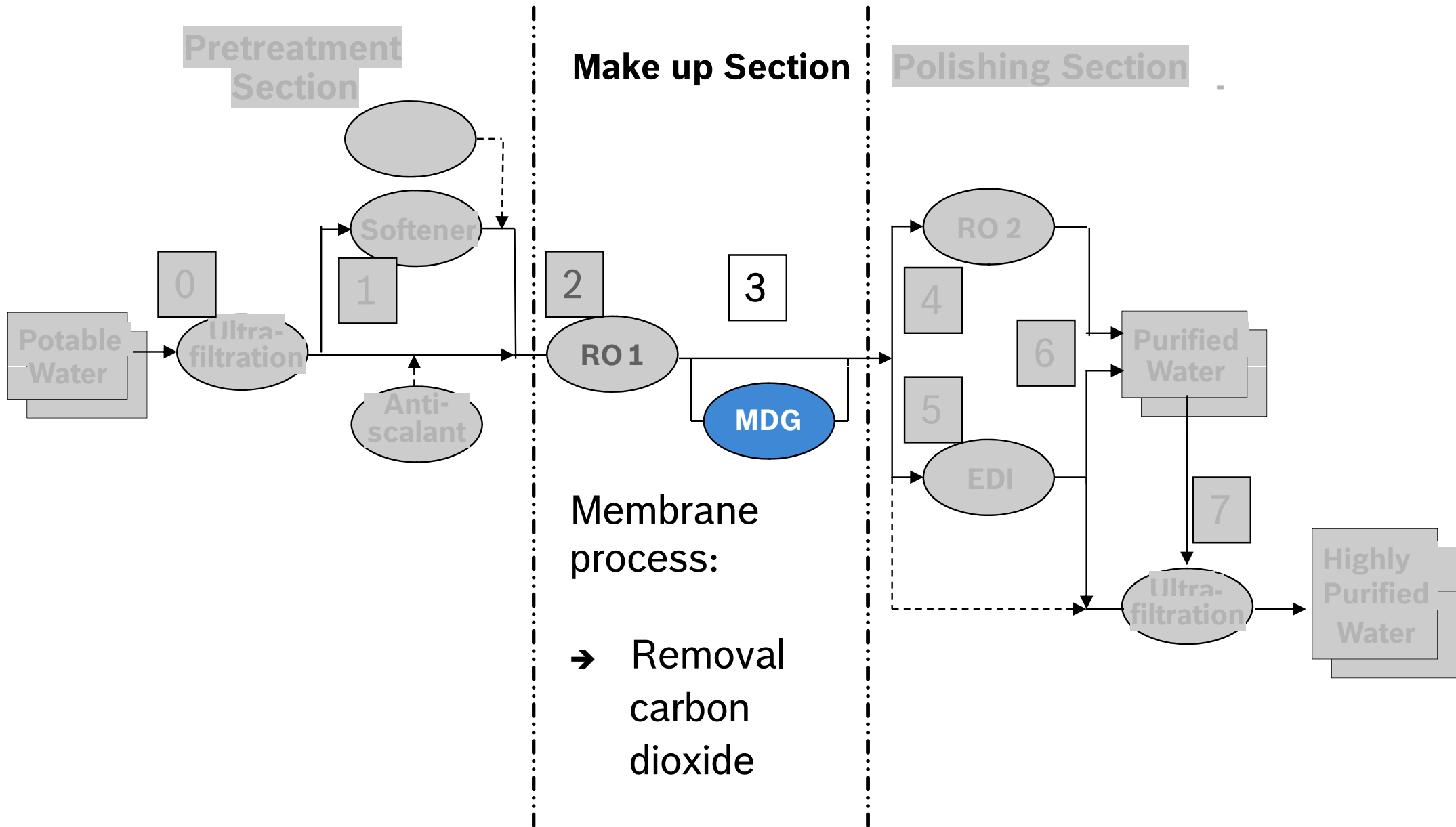
**Reverse osmosis** is a physical process where ions and other impurities in water are concentrated and where the natural process of osmosis is reversed.

# REVERSE OSMOSIS (RO)



Spiral wound module

# MEMBRANE DEGASSING ( MDG )



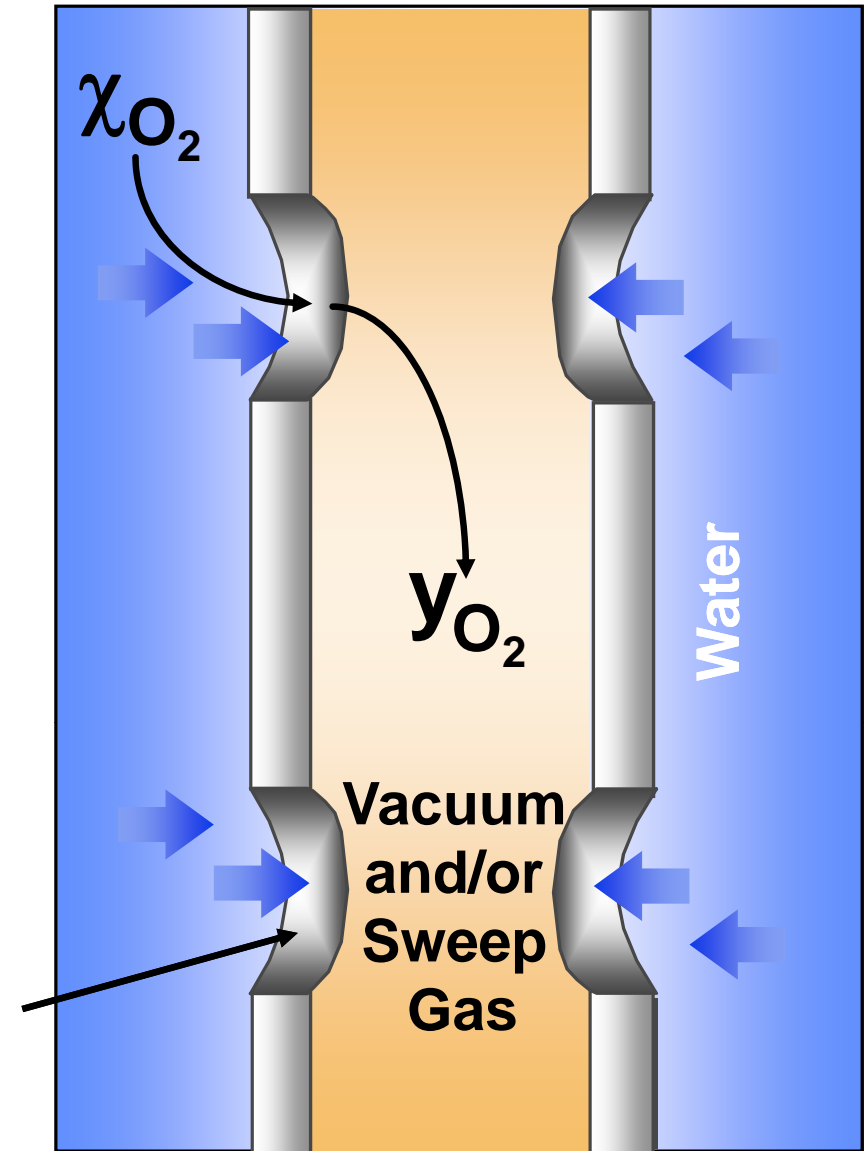
# MEMBRANE DEGASING

## Principle of the gas transfer:

Gases in the air dissolve in water until saturation is reached.

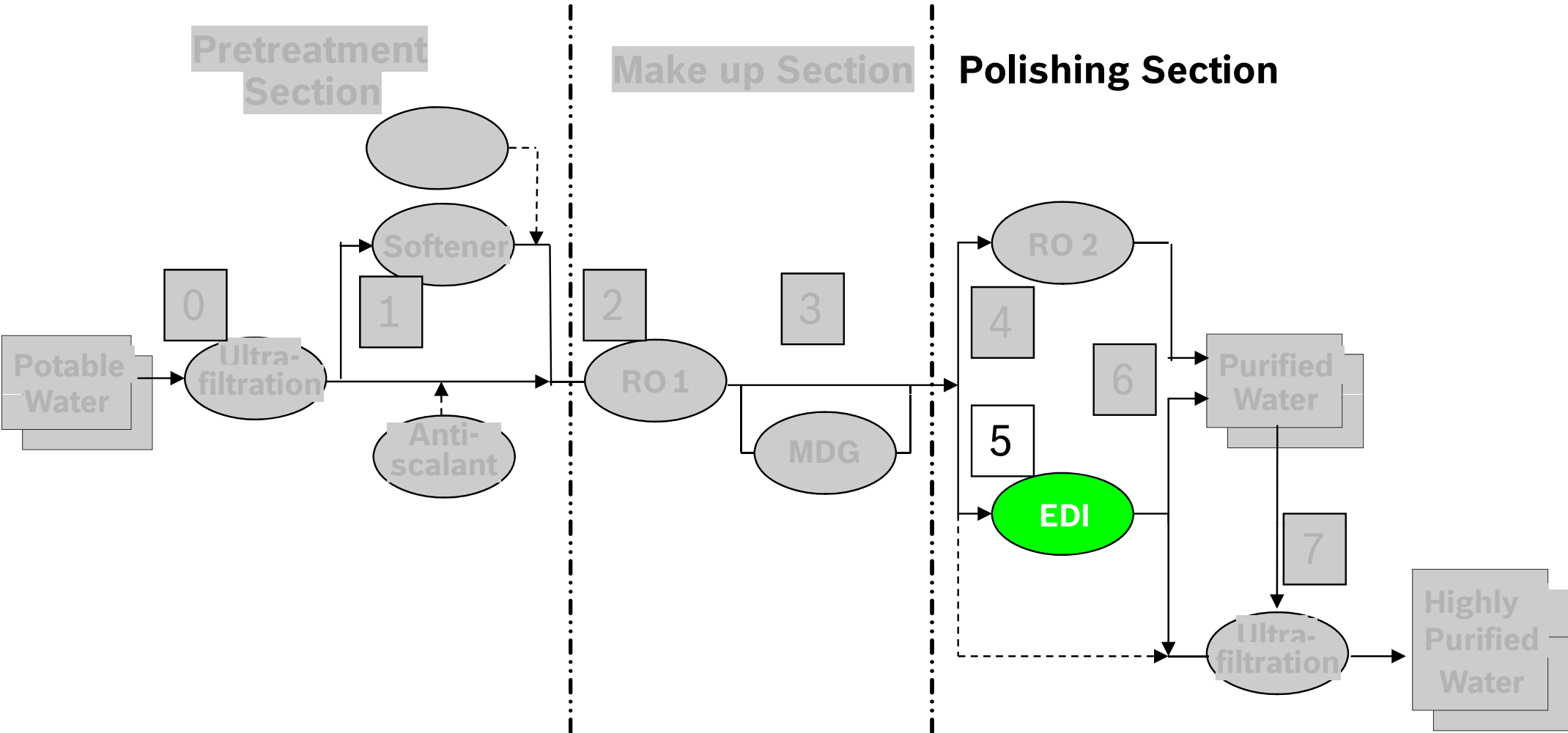
The balance between gas in the gaseous phase and gas in the liquid will be shifted to the side of the gaseous phase by creating a low pressure / Sweep Gas.

This results in a **driving force that moves gases from the water towards the gaseous phase.**



Liquid/Gas  
Contact Surface  
at the Pore

# ELECTRO DE-IONISATION (EDI)



Electrochemical process :  
→ Removal of ions to final level of conductivity

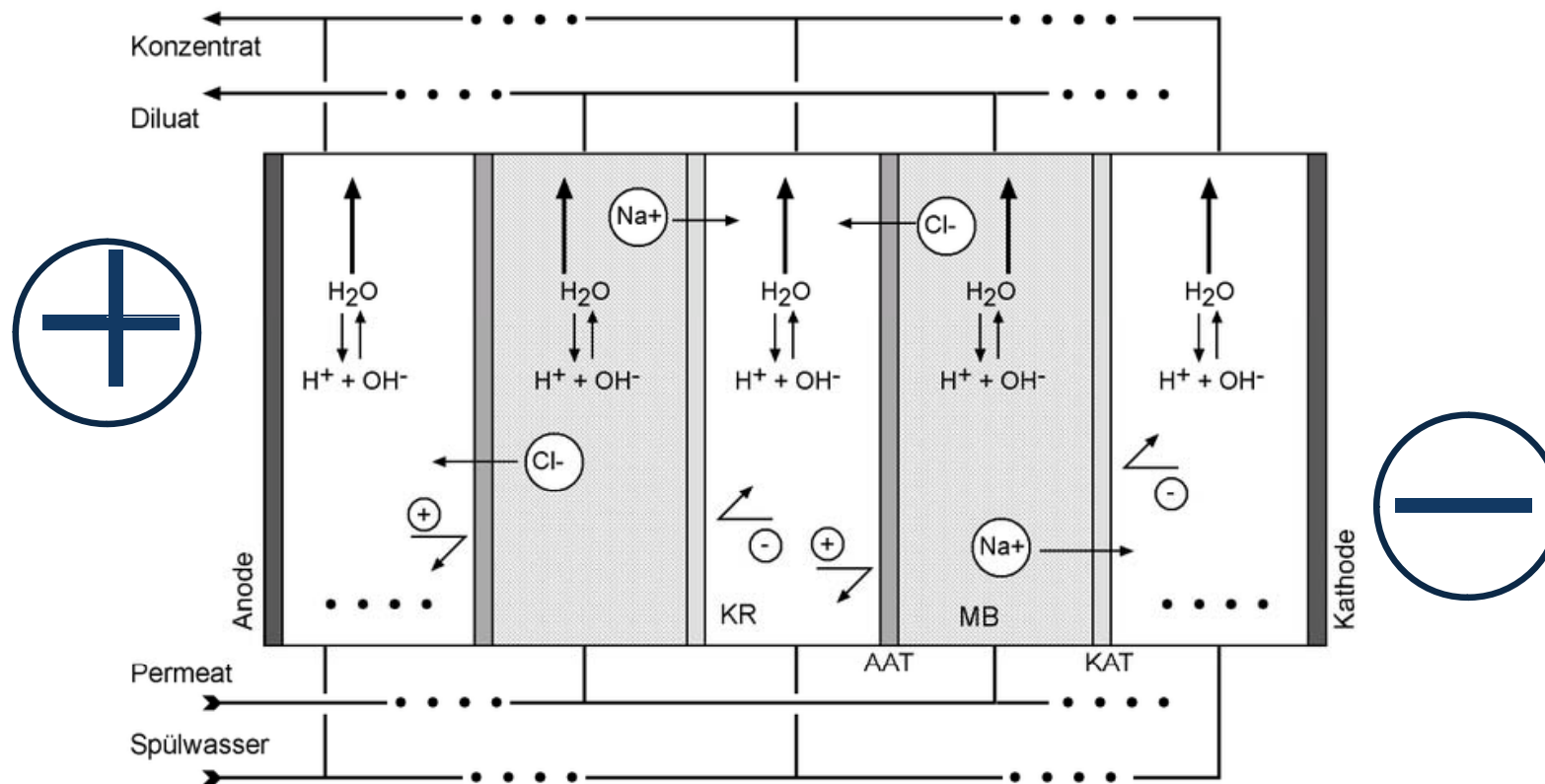


# ELECTRO DE-IONISATION (EDI)



## PW Generation – Electro Deionisation (EDI)

**Electrodeionisation** is an electro-chemical process for the removal of ions. It is a combination of ion-exchange and electrodialysis



# PURIFIED WATER GENERATION - ANIMATION





## Water for Injection Generation

- Main purpose:
  - Treatment of Purified Water (PW) into Water for Injection (WFI) according to USP (United States Pharmacopeia) and Ph Eur (European Pharmacopeia)
  
- Treatment steps:
  - Evaporation and condensing (= Distillation)

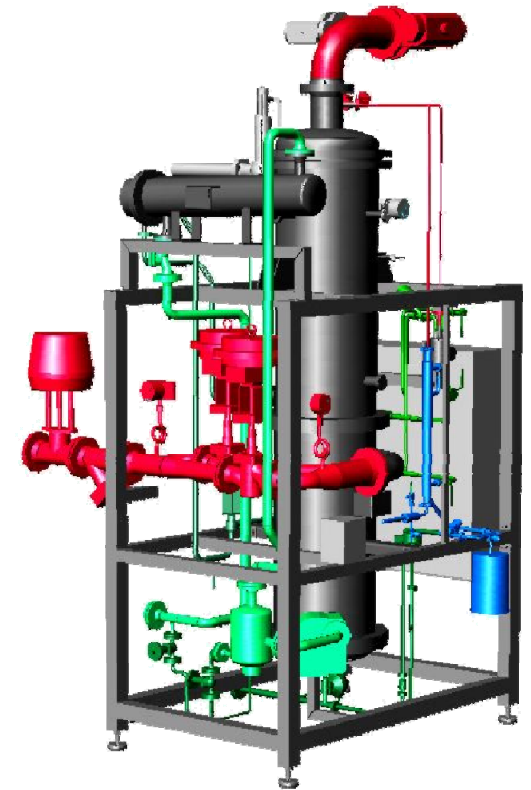


# MULTIEFFECT DISTILLATION UNIT - ANIMATION



## Pure Steam Generation

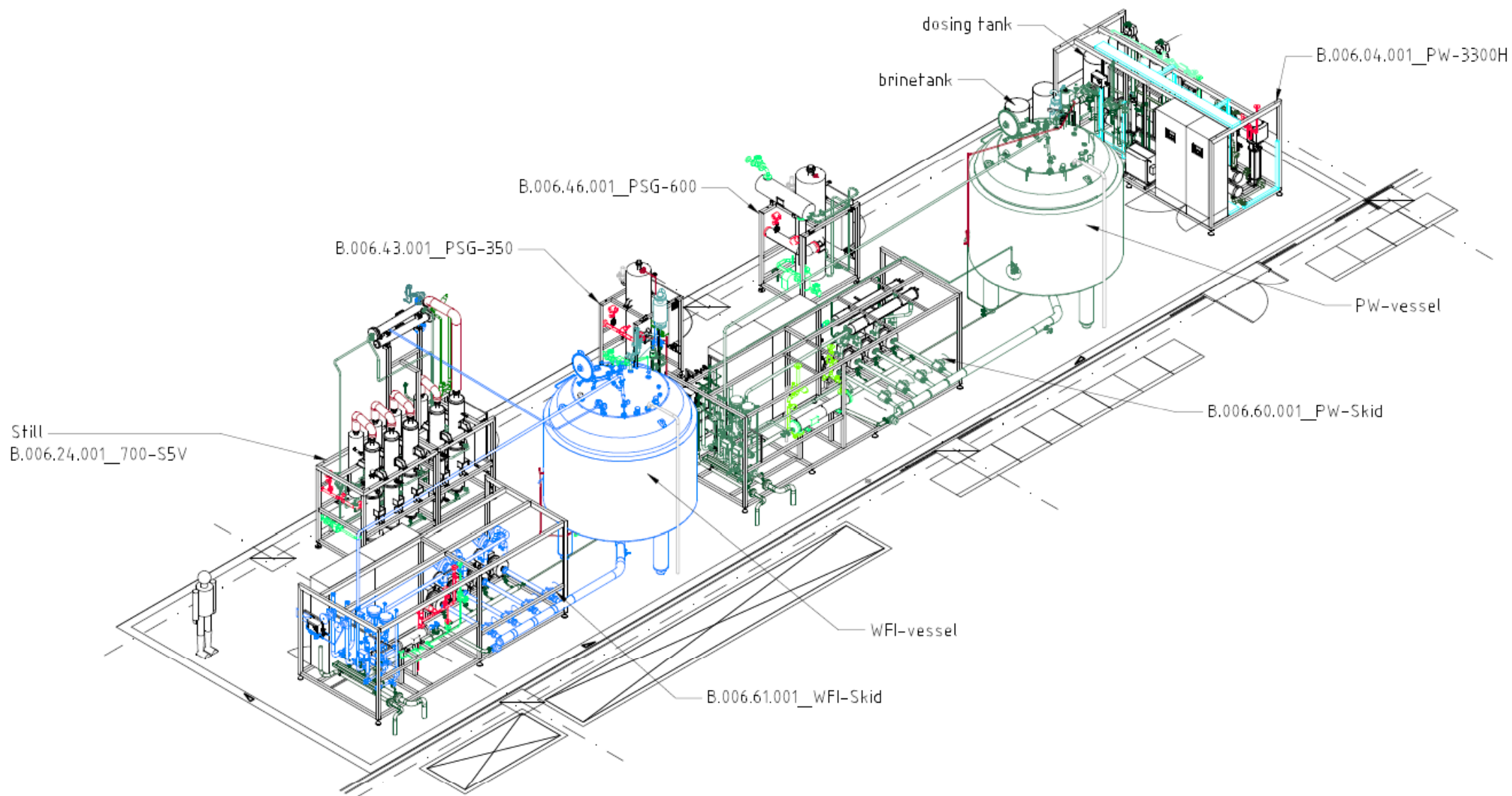
- Main purpose:
  - Treatment of Purified Water (PW) into Pure Steam (PS) according to quality USP (United States Pharmacopeia) and Ph Eur (European Pharmacopeia)
  
- Treatment steps:
  - Degassing (for elimination of non condensable gasses N<sub>2</sub>, O<sub>2</sub>, CO<sub>2</sub>)
  - Evaporation



# PURE STEAM GENERATION - ANIMATION



# PURE MEDIA ROOM - LAYOUT



## Pure Media Systems – Design criteria

- Evaluation of **total consumption** at all points of use (pou)
- **Simultaneous consumption** and interlocking (**pou management**)
- **Generation capacity** as small as possible
- Coverage of **peaks** by storage vessel
- Permanent **circulation** of water ( $V > 1$  m/s in the return pipe)
- Online monitoring of **quality critical parameters** (Flow, Temperature, Pressure, conductivity, TOC)
- **Slope**  $< 1\%$
- No **dead legs** 3d-rule
- **Drainability**
- **Sanitization** concept
  - WFI - superheated water, pure steam
  - PW - hot water, ozone

# PURE MEDIA ROOM - ANIMATION

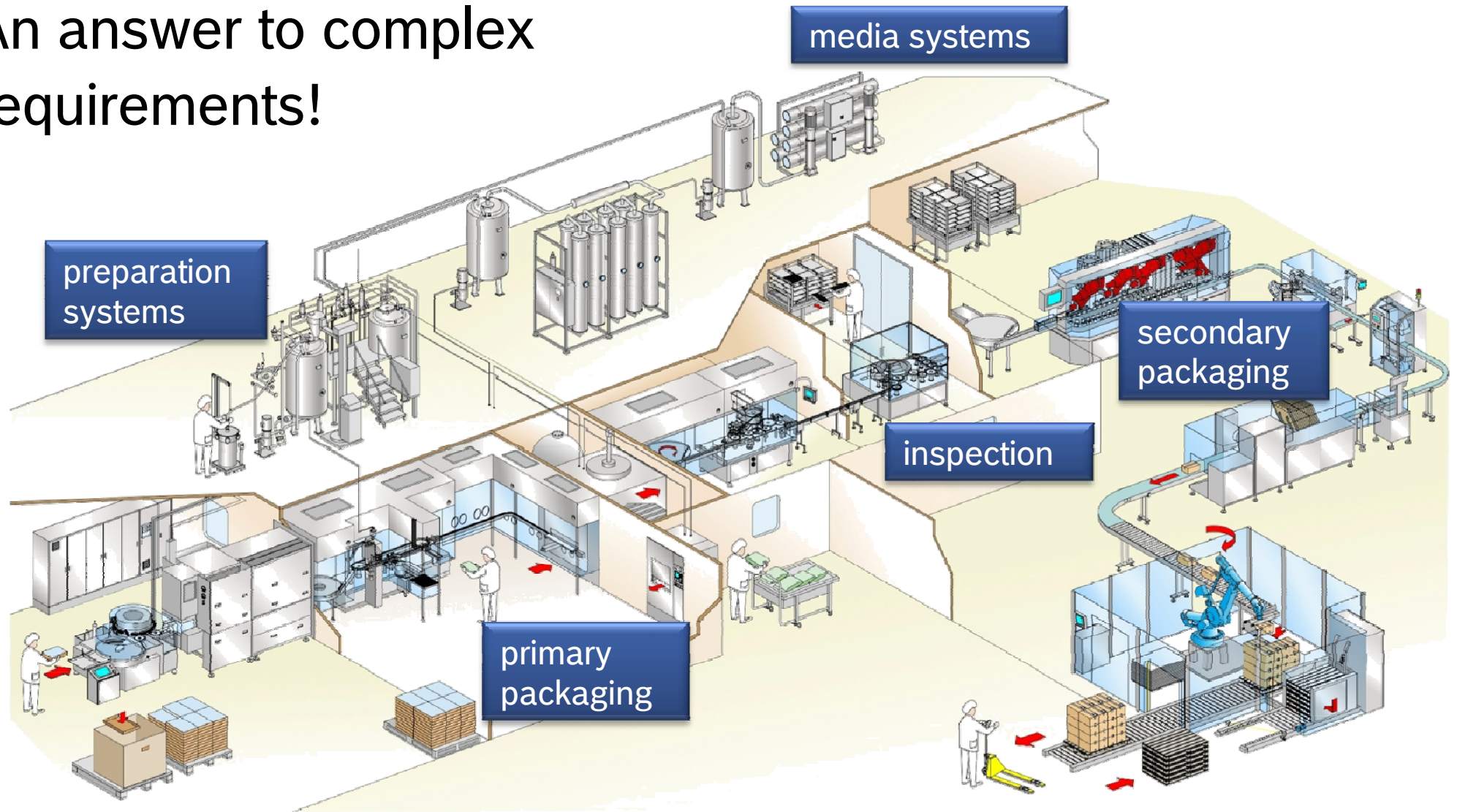


# FAT PURE MEDIA SYSTEM AT BOSCH IN DRESDEN, GERMANY





## BOSCH Integrated Solutions: An answer to complex requirements!



# VACCINES PRODUCTION



## Packaging Technology



# VACCINES PRODUCTION



## Packaging Technology

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Tailor-made solutions  
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