PHARMACEUTICAL WATER (PW AND WFI) IN STABLE QUALITY

A CRUCIAL MATERIAL FOR VACCINE PRODUCTION

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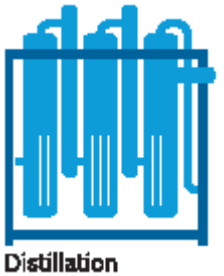
Water for Pharmaceutical Use

The use of Pharmaceutical water in vaccine production

- Purified water (PW)
  - Oral liquid dosage forms
  - Solid dosage forms
  - Feed water for WFI and PS generation



- Water for injection (WFI)
  - For injectables

REGULATORY ASPECTS OF WATER FOR PHARMACEUTICAL USE

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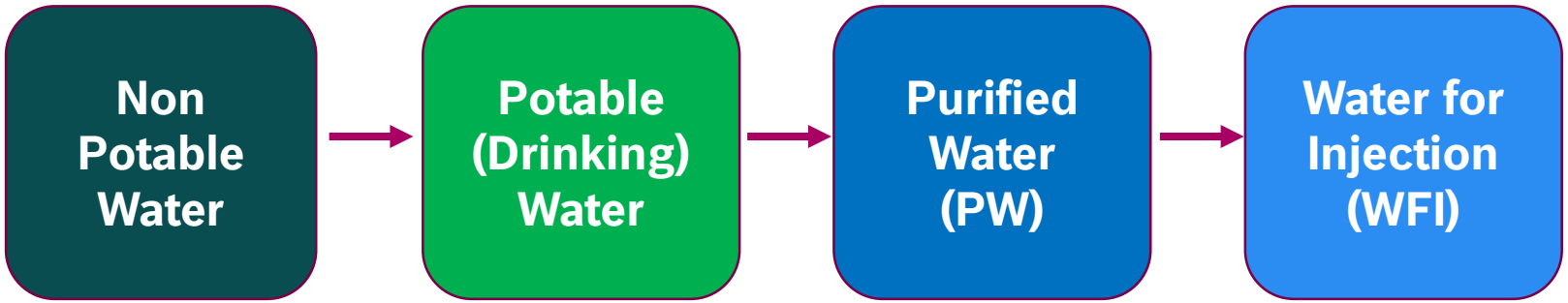
Water for Pharmaceutical Use
International Regulations and Guidelines

Water quality and analytical methods	European Pharmacopeia EP US Pharmacopeia USP Japanese Pharmacopeia JP
EMA (European Medicines Agency)	Note for Guidance on Quality of Water for Pharmaceutical Use“
FDA (U.S. Food and Drug Administration)	Guide to Inspection of high purity water systems 21 CFR 210/211, 21 CFR Part 11, 21 CFR 177
European Commission (EG)	Guide to Good Manufacturing Practice
PIC/S (Pharmaceutical Inspection Convention)	Guide to Good Manufacturing Practice for Medicinal Products
GAMP-Forum	GAMP 5.0 Guide for Validation of Automated Systems
ISPE (Intern. Society for Pharmaceutical Eng.)	BASELINE Pharmaceutical Engineering Guide Volume 4 Water and Steam Systems

Water for Pharmaceutical Use
Regulated Water Qualities



National regulations	National regulations WHO	Pharmacopoeias	Pharmacopoeias

Water for Pharmaceutical Use
Basic Criteria & Principles

- Like any starting material, **production of water for pharmaceutical use** should conform to **Good Manufacturing Practice (GMP)** norms
- **Criteria and generation methods** defined by **National Pharmacopeias** (EP/USP/JP/WHO/...)
- **Main Target** is avoiding of potential of **microbial growth**
- Systems must be properly **validated / qualified**
- Water for parenteral use should not be contaminated with **pyrogene or endotoxins**
- Specifications and **periodic testing** are required

Water for Pharmaceutical Use

Requirements for Water for Pharmaceutical Use

Purified Water (PW)	Ph.Eur	USP
TOC	≤0,5mg/l	500 ppb
Conductivity	≤4.3 µS/cm at 20°C	≤1.3 µS/cm at 25°C*
Nitrates	≤0.2 ppm	---
Heavy metals	≤ 0.1 ppm	---
Aerobic bacteria	< 100 CFU/ml	< 100 CFU/ml
Endotoxins	<0.25 EU/ml (only for bulk water for dialysis)	---

Water for Injection (WFI)	Ph.Eur.	USP
TOC	≤0,5mg/l	500 ppb
Conductivity	≤1.1 µS/cm at 20°C	≤1.3 µS/cm at 25°C*
Nitrates	≤0.2 ppm	---
Heavy metals	≤ 0.1 ppm	---
Aerobic bacteria	< 10 CFU/100ml	< 10 CFU/100ml
Endotoxins	<0.25 IU/ml	<0.25 EU/ml

Water for Pharmaceutical Use

Requirements for Water for Pharmaceutical Use

❑ Requirements for feed water

All Pharmacopoeias recommend **potable (drinking) water quality** as feed water based on the requirements of national legislations or the specifications of WHO

❑ Requirements for generation methods

Purified Water (PW)

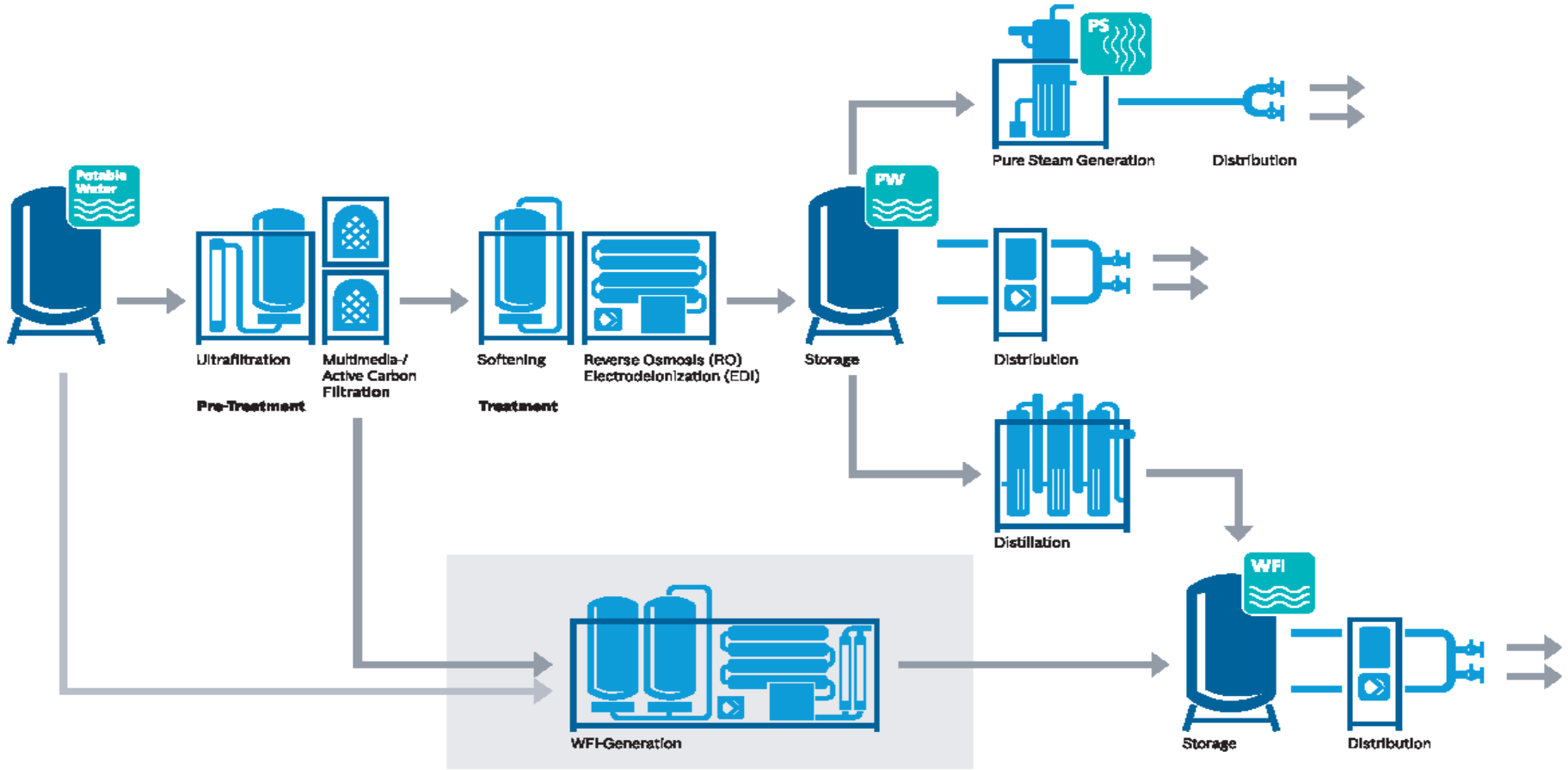
Normally the Pharmacopoeias like EP, USP, WHO permit production by **distillation, reverse osmosis, de-ionization, filtration, or equivalent means**.

Water for Injection (WFI)

USP/JP permits "**distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals or microorganisms**"

EP and WHO permit **distillation with droplet separation only**, but EP permit since from 2017 membrane based processes (RO + UF) (direct influence to PIC and ICH)

Water for Pharmaceutical Use
BOSCH Solutions



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PRETREATMENT OF FEED WATER

FILTRATION & DIVERSE TECHNOLOGIES

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Pretreatment

Feed water is not always drinking water quality

- According to WHO, ISO and national or regional agencies the drinking water must comply with **regulated specifications** and need **regular testing**.
- But the reality shows that the potable water could be from **public water supply system** or **natural sources,** natural sources could include springs, wells, rivers and lakes
- Although reasonably pure, it is always **variable** due to **seasonal variations**, regional variation in water quality is influenced by, e.g. **rainfall, erosion, pollution, dissolution, sedimentation, decomposition**
- Must remove **impurities and control microbes** to avoid contaminating products

Pretreatment
Contaminants of source water

- Inorganic compounds
- Organic compounds
- Solids
- Gases
- Microorganisms
- Minerals
  - Calcium, magnesium, copper, aluminum, heavy metals, arsenic, lead, cadmium, nitrates
  - Iron, manganese, silicates, carbon dioxide
  - Hydrogen sulfide
  - Phosphates

Pretreatment
Information required for Design

- **Detailed water analysis** to determinate water impurities and contaminants
- **TSS** (Total Suspended Solids) or **Turbidity** to determinate suspended solids
- **SDI** (silt density index) to fouling potential of suspended solids

Pretreatment

Pretreatment Systems offered by BOSCH

Untreated water substances	Iron and manganese	Calcium and magnesium (hardness components)	Barium and strontium	Suspended solids > 50 µm	Colloids	Solute silicon dioxide (SiO_2)	Carbonic acid (CO_2)	Chlorine and ozone	Organic impurities (TOC)	Germs (CFU)
Alternative pretreatment										
Reversible flow filter	■	–	–	■■	–	–	–	–	–	–
Multi-layer filtration	■■	–	–	■■	■	–	–	–	–	–
Precoat filtration	■■	–	–	■■■	■■	–	–	–	–	–
Microfiltration	■	–	–	■■	–	–	–	–	–	–
Ultrafiltration	■■■	–	–	■■■	■■■	–	–	–	■	■■■
Water softening	■	■■■	■■■	■	–	■	–	■	–	–
Acid dosage (HCl, H_2SO_4 or CO_2)	–	■■	–	–	–	–	–	–	–	–
Anti-scalant dosage	■	■■	■■	–	–	■	–	–	–	–
Active carbon filtration	–	–	–	■	–	–	–	■■■	■■	–
Sulphite dosage ($NaHSO_3$, Na_2SO_3)	–	–	–	–	–	–	–	■■■	–	–
UV radiation	–	–	–	–	–	–	–	■■	■	■■
Brine dosage (NaOH)	–	–	–	–	–	■■	■■■	–	■	–
Membrane degasification	–	–	–	–	–	–	■■■	–	■	–

Pretreatment
Membrane Filtrations

Microfiltration
> 0,1 µm

- Turbidity
- Particles
- Plankton
- Algae

Ultrafiltration
0,1 - 0,01 µm

- Colloids
- Bacteria
- Viruses
- Macro-molecules
- Iron & Manganese

Pretreatment

Membrane Filtrations – the benefits clearly outweigh

Characteristics

- No addition of chemicals during the process
- Robust, simple and safe to operate and manage
- Thermal and chemical sanitization possible
- Relatively low energy consumption
- Filter systems can be adapted to the different requirements and water qualities
- The quality of the treated water remains the same regardless of the degree of contamination of the original water

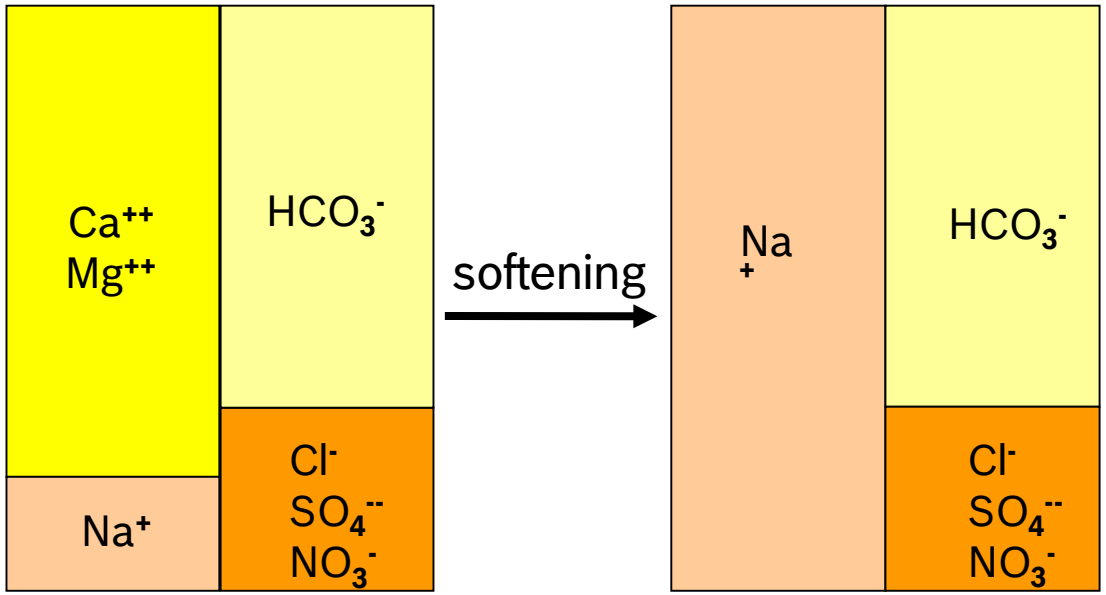
SOFTENING OF FEED WATER

SALT-BASED WATER SOFTENER (ION-EXCHANGE)

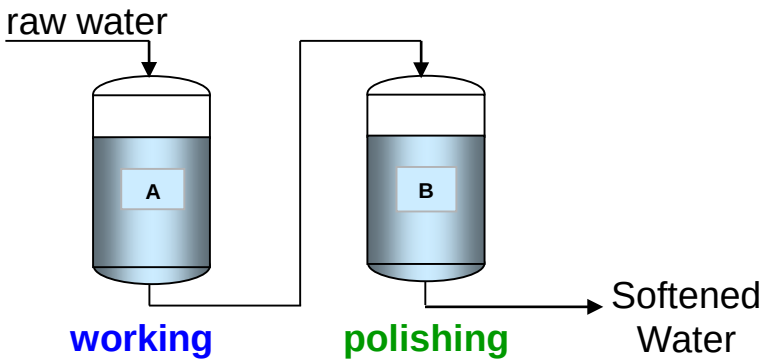
BOSCH

Generation of Purified Water (PW)
Softening - Salt-based Water Softener (Ion-Exchange)

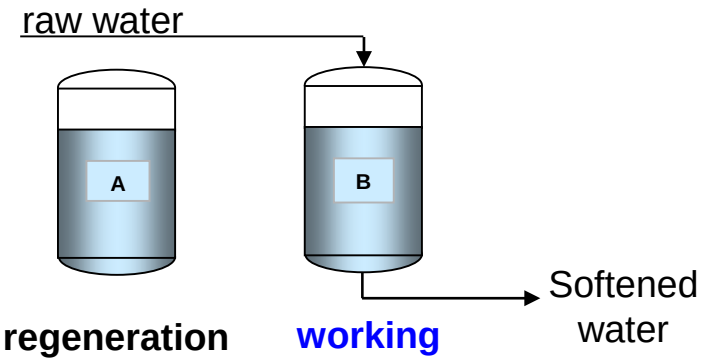
Salt-based Water Softener removes **water hardness** builders such as **calcium ions (Ca2+) and magnesium ions (Mg2+)** as well as metals like **divalent iron (Fe^{++})** and replaces them by **sodium ions**.



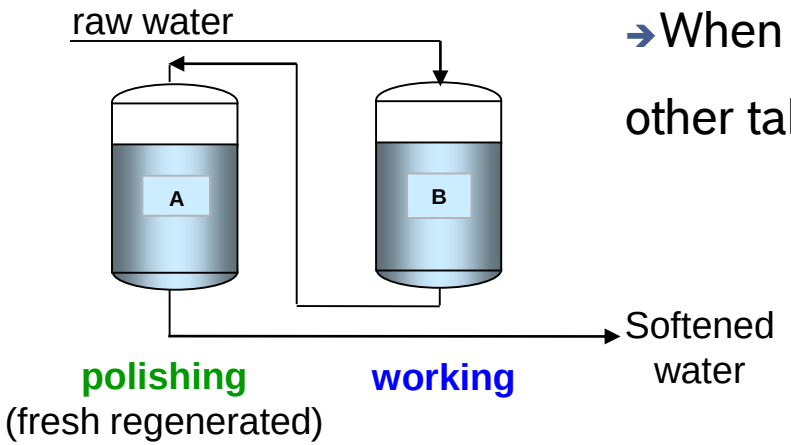
Generation of Purified Water (PW)
Softening – Various operation conditions



➔Both filters in operation



➔When one filter is regenerating, the other takes over the full capacity



Generation of Purified Water (PW)
Softening Operation Steps

Generation of Purified Water (PW)
Softening

Characteristics & Advantages

- Reliable and permanent protection of the downstream RO and EDI against precipitation
- Minimized risk of microbiological contamination due to serial operation (continuous flow)
- Polisher minimizes the risk of hardness breakthrough
- Robust, simple and safe to operate and manage
- Chemical and thermal Sanitization possible
- Sanitization during regular operation possible

PURIFIED WATER GENERATION

REVERSE OSMOSIS & EDI TECHNOLOGY

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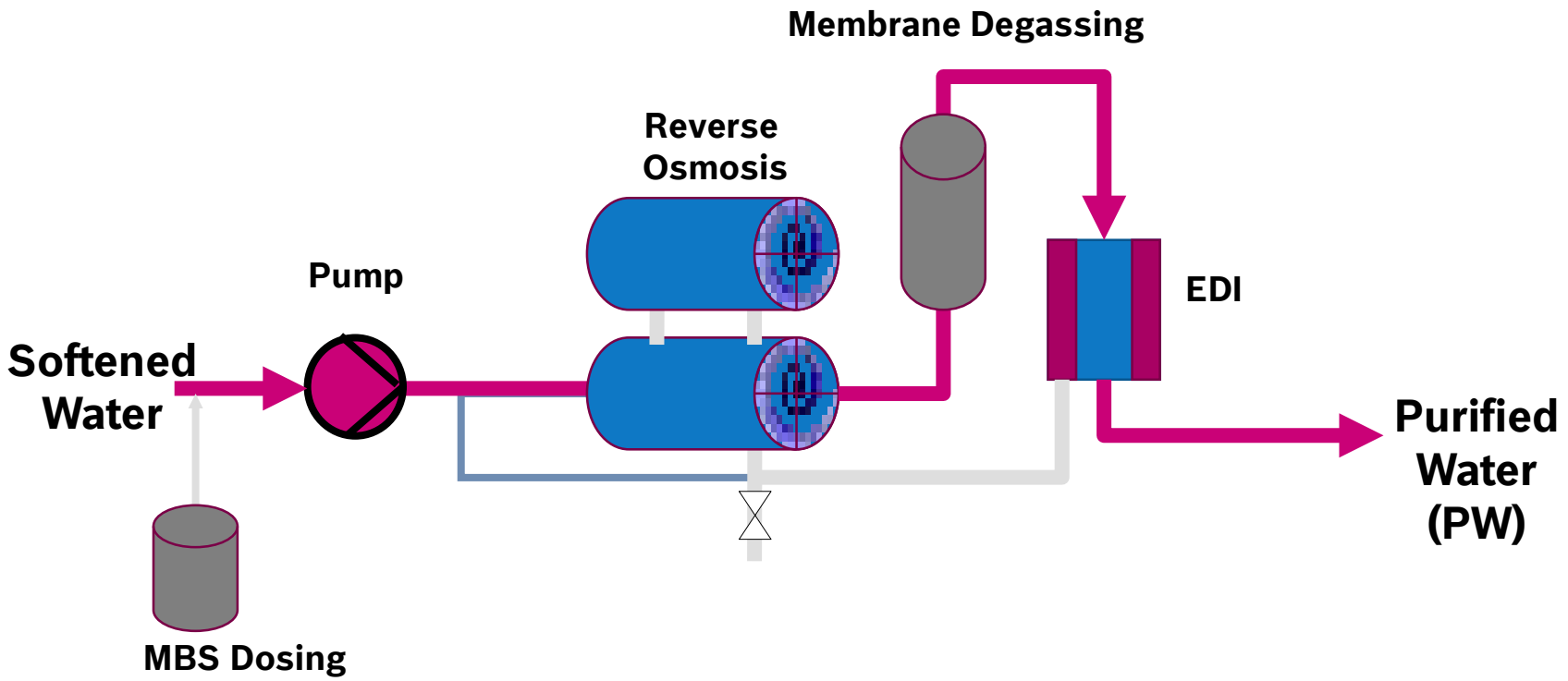
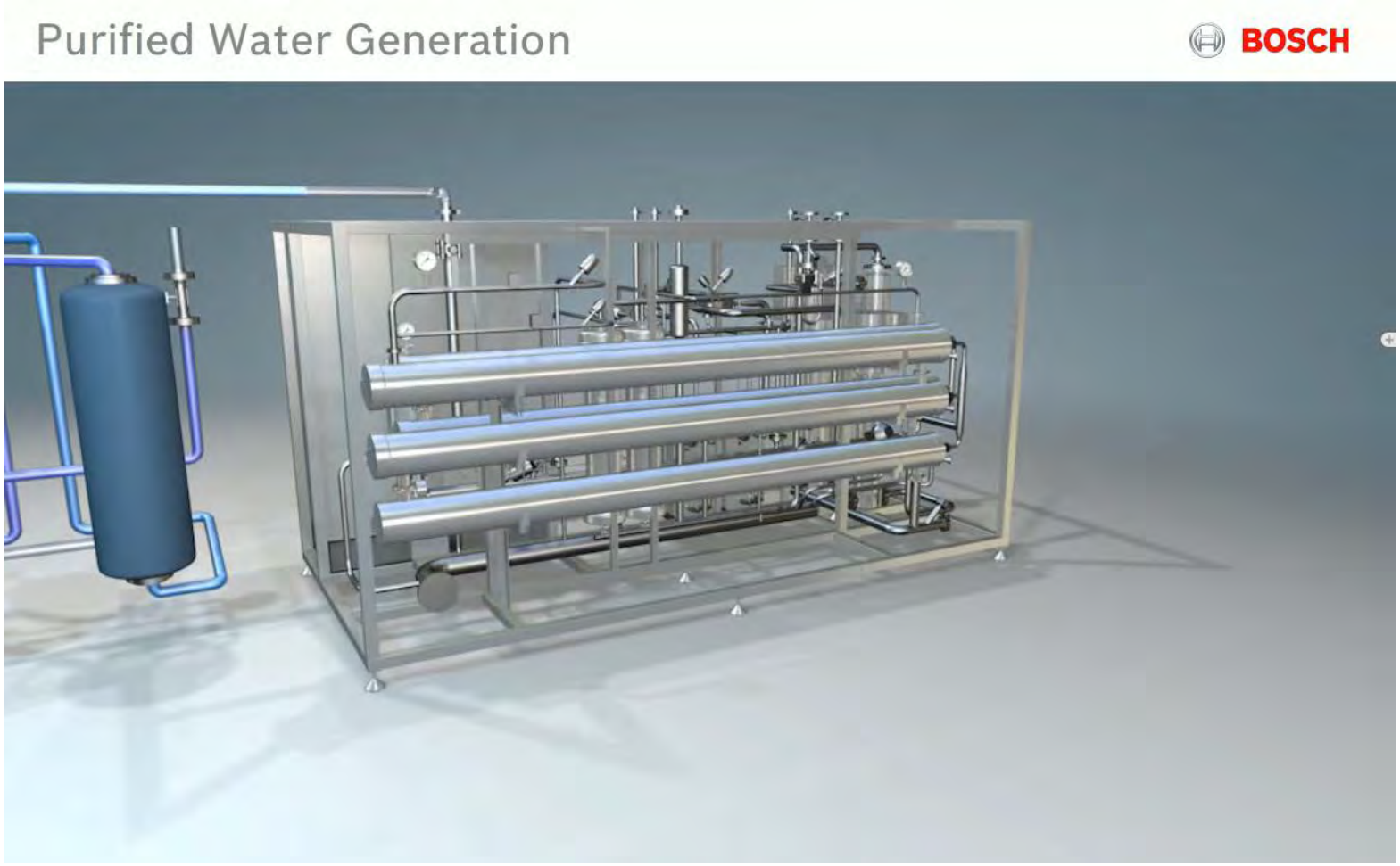
Generation of Purified Water (PW)
Purified Water Generation

- Design of the Reverse Osmosis with Electrodeionisation (EDI)



Generation of Purified Water (PW)
Reverse Osmosis

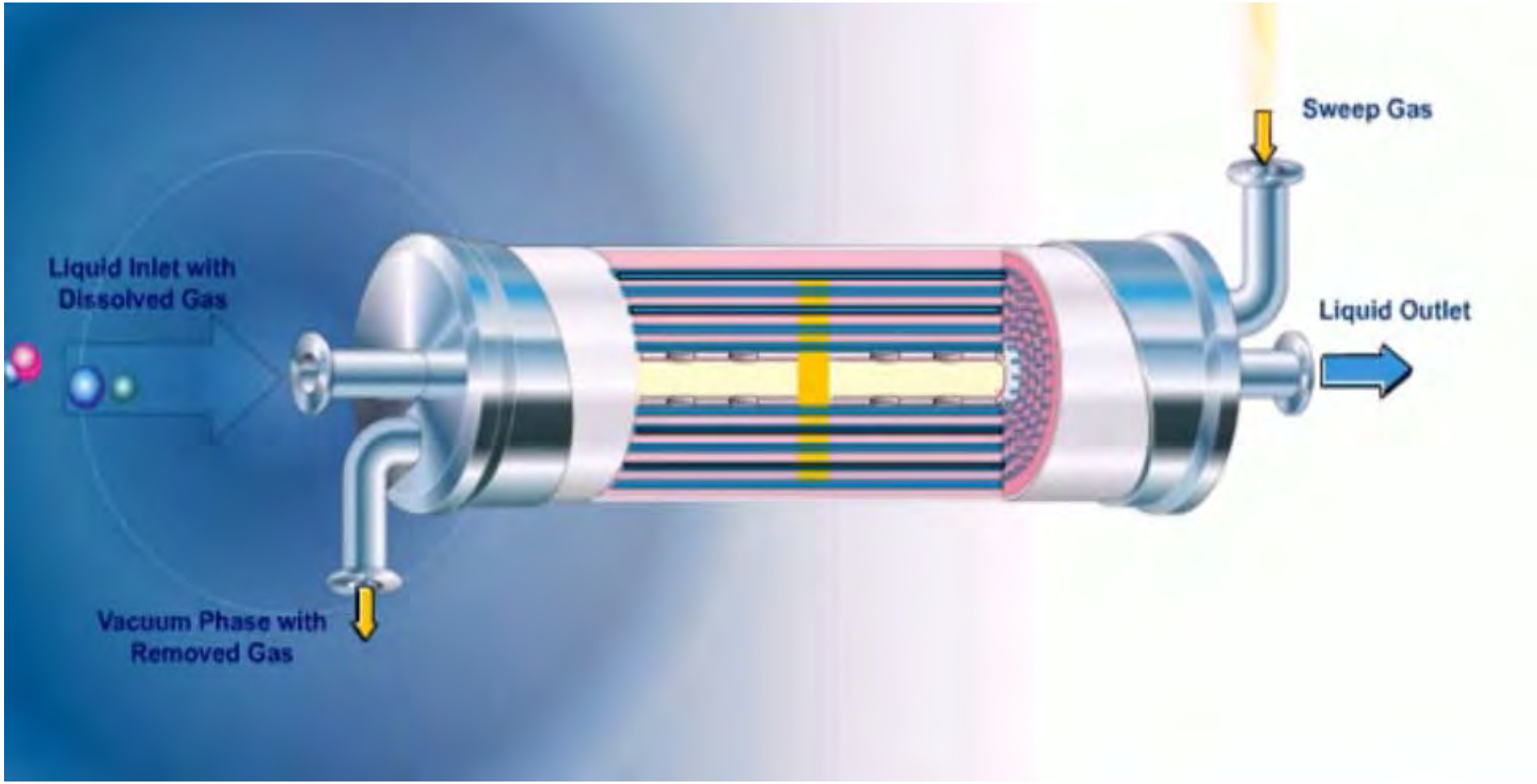


Generation of Purified Water (PW)
Reverse Osmosis

Characteristics & Advantages

- Water ingredients (salt ions, particles, colloids, Bacteria, endotoxins) are held back
- Removal of Salt ions approx. 98-99%
- Removal of Organics > 90%
- Minimised risk of microbiological contamination due to serial operation (continuous flow)
- Robust, simple and safe to operate and manage
- Chemical and Thermal Sanitization possible
- Lifetime of modules approx. 3 up to 5 years

Generation of Purified Water (PW)
Membrane Degasification (CO2 Reduction)



Generation of Purified Water (PW)
Membrane Degasification

Characteristics & Advantages

- Chemical-free CO2-removal
- No risk of bacterial contamination
- Robust, simple and safe to operate and manage
- Chemical and Thermal Sanitization possible
- Lifetime of modules up to 5 years

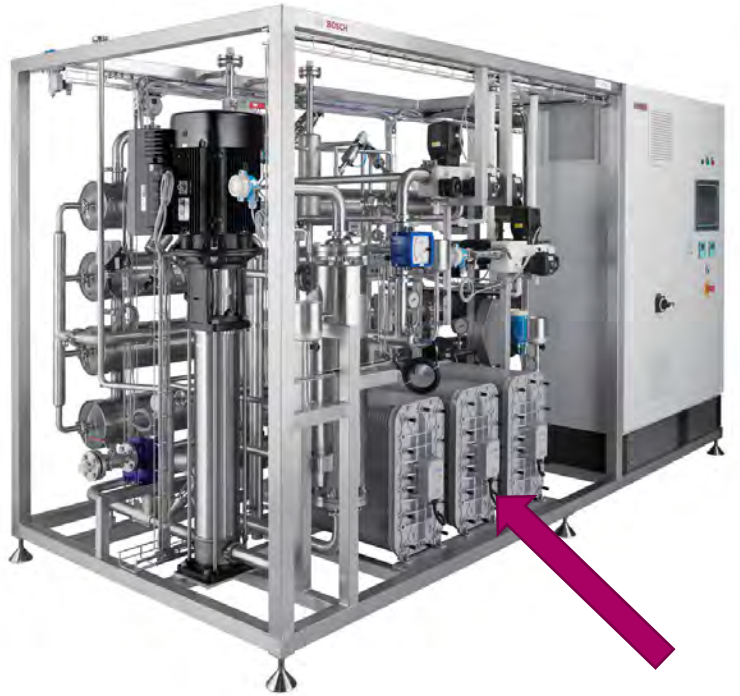
Generation of Purified Water (PW)
Electro-Deionization (EDI)

This process separates electrically charged water components (ions, ionizable particles) from a feed stream into a product stream (dilute) and a concentrate stream using the driving forces of an electrical DC-field.

Generation of Purified Water (PW)
Electro Deionization (EDI)

Characteristics & Advantages

- Removal of ions and ionizable particles
- Chemical free, combination of Membrane- and Ion Exchanger technology
- Minimised risk of microbiological contamination due to serial operation (continuous flow)
- Robust, simple and safe to operate and manage
- Chemical and Thermal Sanitization possible
- Lifetime of modules up to 5 years



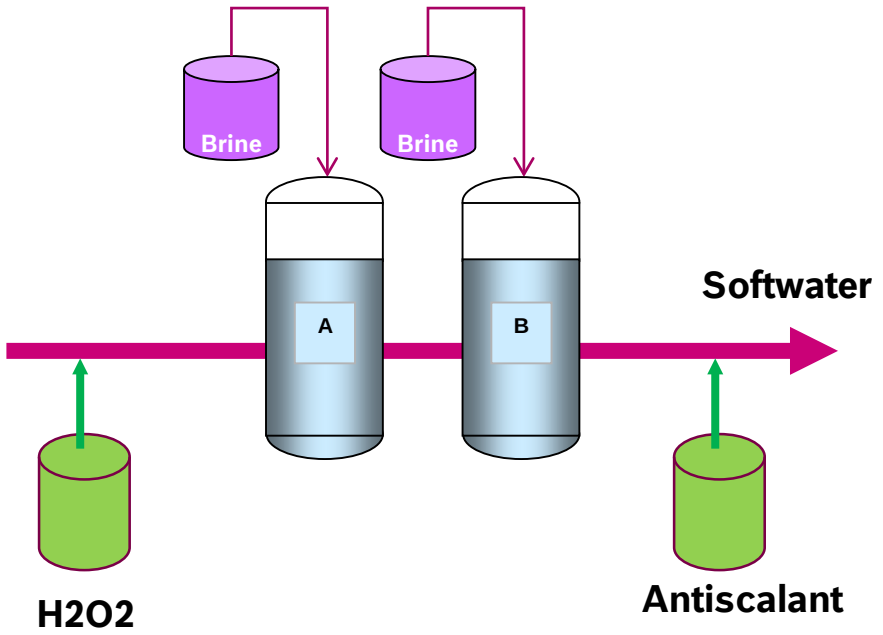
Water for Pharmaceutical Use
Sanitization of Purified Water Generation System

- The microbiological control (number of germs) of water treatment systems is mainly achieved by sanitization
- Depending on the method, sanitization should reduce viable organisms by 50 to 99.9%
- The systems are either chemically or thermally sanitized

Configurations	Softening	RO + EDI
C (Chemical)	C	C
H (thermal)	H	H
C/H (chemical / thermal)	C	H

Sanitization	Medium	Conditions
Chemical	Hydrogen peroxide (H_2O_2)	2000 – 10000 ppm > 1h
Thermal	Hot water	80°C – 85°C > 1h (4h total) Heating and cooling rate 2°C/min

Generation of Purified Water (PW)
Softening– Chemical Sanitization



- disinfection of the system
(Concentration 2000 – 10000 ppm)
Antiscalant - hardness stabilizer / Scaling inhibitor

Generation of Purified Water (PW)
Softening– Hot Sanitization

- Highest Sanitization effect with hot water (85°C)
- Fully Automatic Sanitization
- No chemicals used in process

Generation of Purified Water (PW)
Reverse Osmosis with Electrodeionisation (EDI)

PWGU Typ	400	1 100	2 000	3 300	6 600	9 900	13 300	16 500
Performance from	220	550	1 250	2 500	4 500	7 500	10 500	11 500
Up to l/h PW	550	1 250	2 500	4 500	7 500	11 500	14 500	20 000

PURE STEAM & WFI GENERATION

NATURAL CIRCULATION TECHNOLOGY

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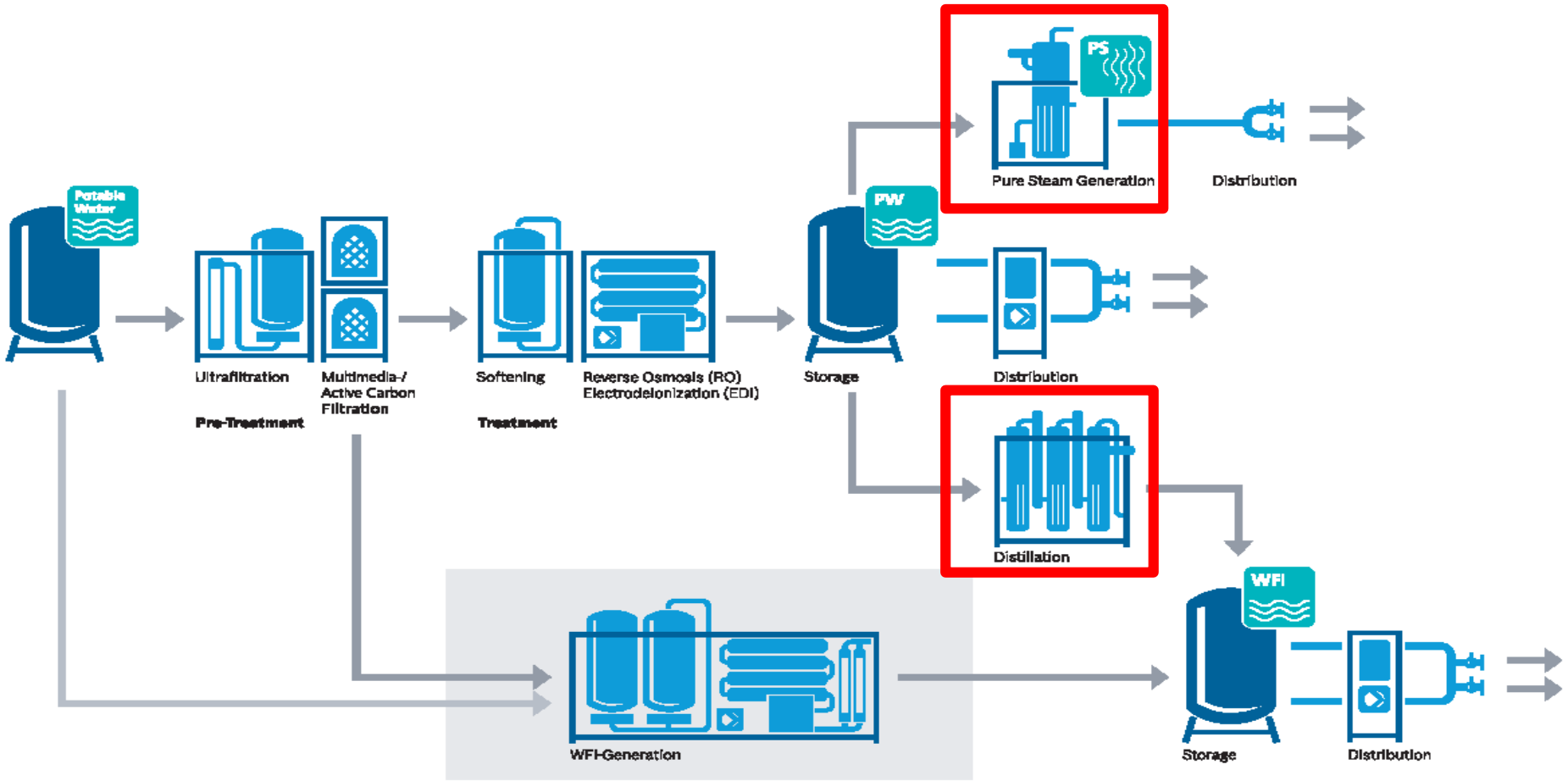
Water for Pharmaceutical Use
BOSCH Solutions

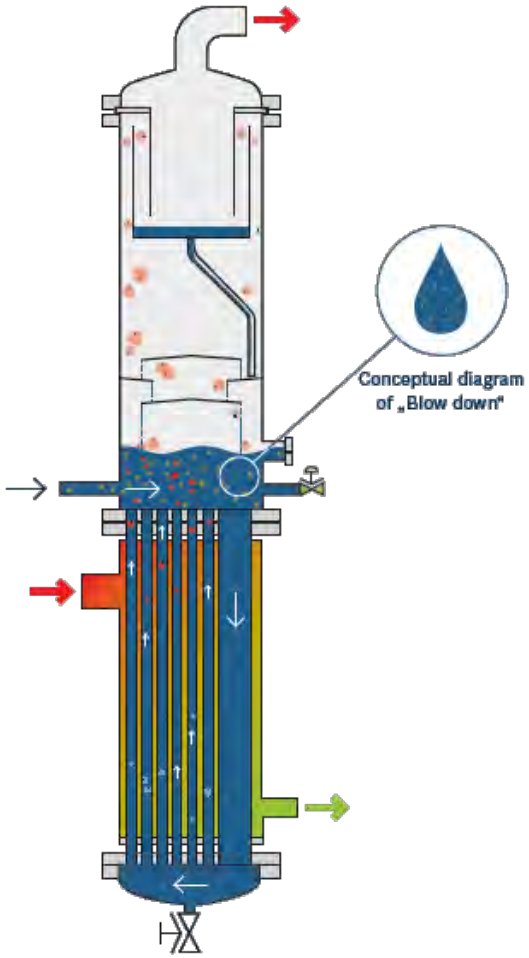


Water for Injection (WFI) and Pure Steam (PS)

WFI and PS generation

Characteristics

- PSG and Still work by the principle of the natural circulation evaporator
- Segregation of endotoxins and pyrogene during transition to the pure steam phase
- Continuous separation of droplets
- Special shell-and-tube heat exchanger to avoid cross contamination
- Single or Multistage Distillation

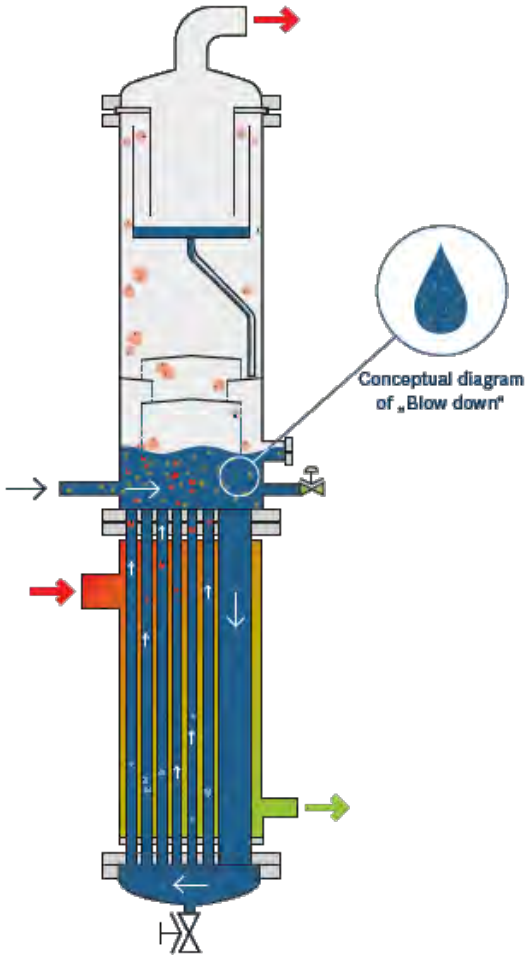


Water for Injection (WFI) and Pure Steam (PS)
Pure Steam Generation (natural circulation evaporator)

Water for Injection (WFI) and Pure Steam (PS)
Advantages of natural circulation process

Characteristics

- Maximal performance by optimized design
- High Efficiency, less than 4% blow down
- Reducing of consumption of utilities
- Low mechanical stress and maximum leakage protection on heat exchanger
- Optimized droplet separator
- Robust, simple and safe to operate and manage



Water for Injection (WFI) and Pure Steam (PS)

WFI Generation (Distillation Process)

Water for Injection (WFI) and Pure Steam (PS)

WFI and PS generation

PSG

WFI Still

Multiple-Effect Distillation Unit		501	1101	1501	2201	3301	5001	6001	8001	10001	12001
Output l/h of WFI	Heating steam pressure										
	4 bar(g)	350	750	950	1600	2000	3 000	3 600	5 200	6 000	7 200
	6 bar(g)	450	950	1 250	1 900	2 800	4 000	5 000	7 000	8 200	9 600
	8 bar(g)	500	1100	1 500	2 200	3 300	5 000	6 000	8 000	10 000	12 000

MWFI – COLD WFI PRODUCTION

RO + EDI + UF

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Cold Generation of Water for Injection (WFI)
Regulatory requirements – background information

- **REGULATORY CHANGE** of the water for injection **(WFI) MONOGRAPH*** (0169) of the European Pharmacopeia (Ph. Eur.)
- From 2017 water for injection may be produced by a "…purification process **equivalent to distillation** such as **REVERSE OSMOSIS**, **COUPLED** with **APPROPRIATE TECHNIQUES**. …"
- **Until now** PH. Eur. required **DISTILLATION** as the **SOLE PROCESS** for the generation of WFI
- Purified water (**PW**) which has been treated (e.g. by ultrafiltration) to achieve the **same quality** as WFI was **HPW** acc. to Ph. Eur.

Cold Generation of Water for Injection (WFI)
Regulatory requirements – different design

- **COLD MEMBRANE** based processes bear the **RISK** of water **CONTAMINATION** and the development of **BIOFILM**
- Therefore, Ph.Eur. set **SPECIFIC REQUIREMENTS** for membrane based WFI generation

1. Specific **TREATMENT STEPS** of feed water (= potable water) to achieve WFI quality

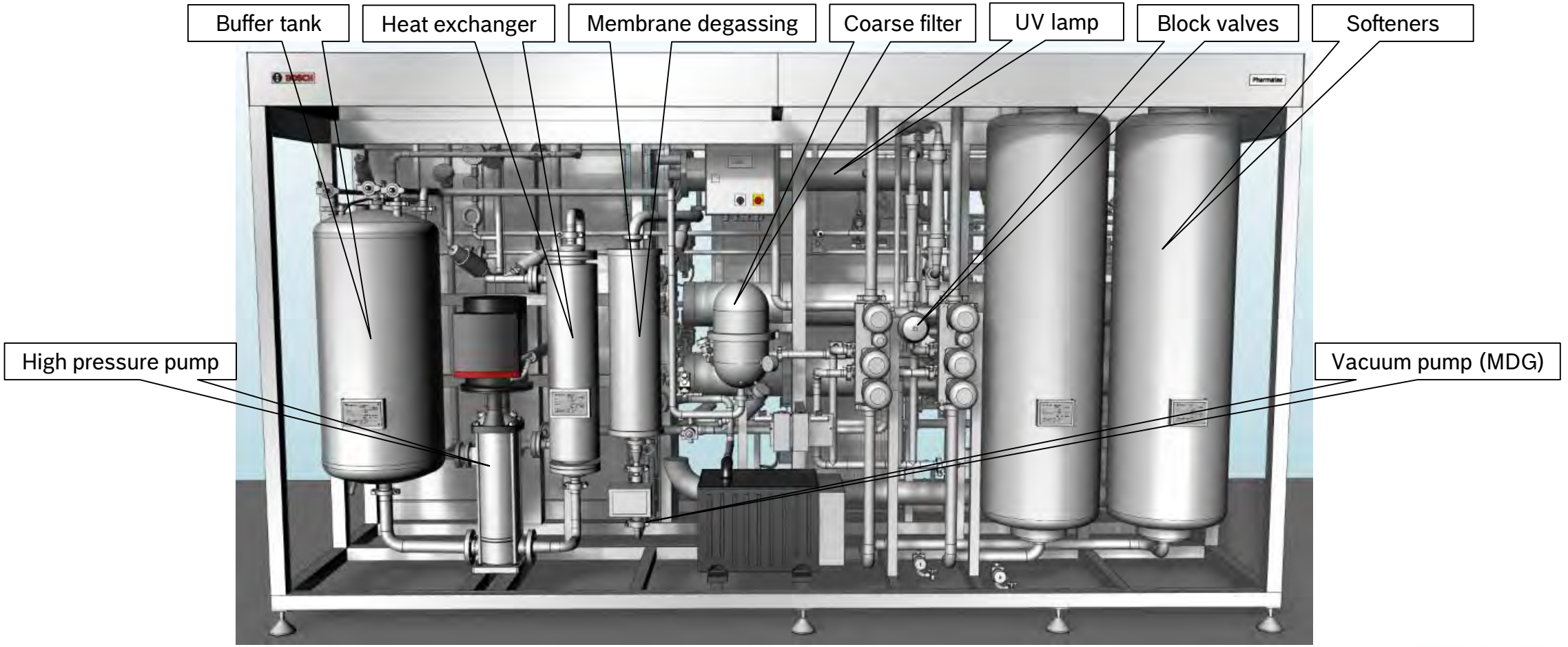
2. Use of **HIGH QUALITY MATERIALS** and **sub-assemblies** which allow routine **HOT SANITIZATION** of the entire system and additionally the possibility of **CHEMICAL SANITIZATION**

3. **MONITORING** of the **water quality** throughout the generation process (not only at the end)

4. **STORAGE AND DISTRIBUTION** of WFI needs to fulfil certain **sanitization** requirements

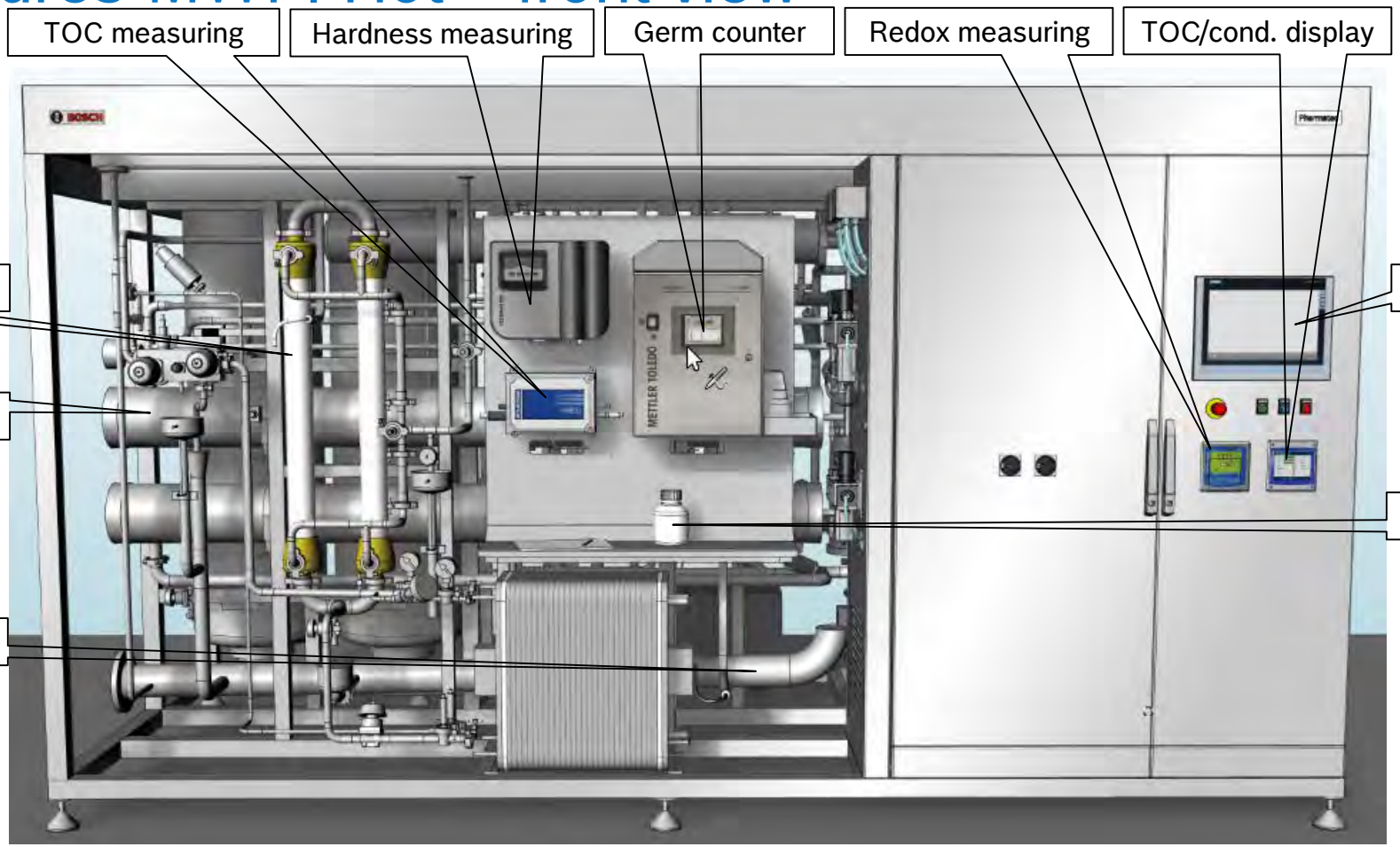
Cold Generation of Water for Injection (WFI)

Main features MWFI – Hot – back view



Cold Generation of Water for Injection (WFI)

Main features MWFI Hot – front view



Cold Generation of Water for Injection (WFI)
Microbiological control – sanitization and UV

- Ph.Eur. requires **hot water** sanitization of the treatment system incl. **storage + distribution**
  - Softeners
  - RO
  - EDI
  - UF
- Additional **chemical sanitization** needs to be available
- **RO water** has to be treated by **UV** light for **TOC reduction**

Cold Generation of Water for Injection (WFI)
Microbiological control – process monitoring

- Microbiological **risks**
  - Water **contamination**
  - Developing of **biofilm**
- Ph.Eur requires
  - Online **TOC** measuring
  - Online **conductivity** measuring
  - Rapid **biological methods**
    - SOP's (standard operating procedures)
    - Automatic **germ counter**
  - Statistical **data analysis**

Cold Generation of Water for Injection (WFI)
MWFI

Characteristics & Advantages

- According to the new regulatory requirements
- Thermal (periodical) and UV (permanent) Sanitization
- Minimised risk of microbiological contamination due to double sanitization
- Conductivity, TOC and online germ counter for trends
- Permanent sanitization of softener
- Robust, simple and safe to operate and manage

STORAGE & DISTRIBUTION OF WATER FOR PHARMACEUTICAL USE

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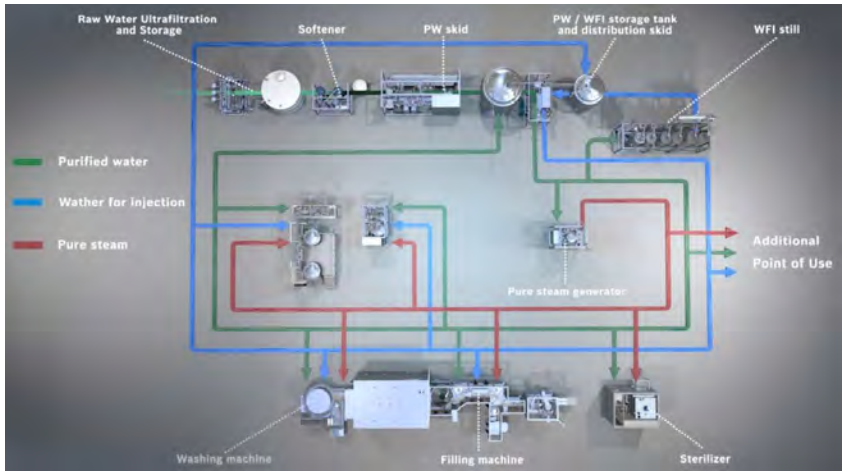
Storage & Distribution
Advantages of S&D Systems

Characteristics

- Continuous recirculation system with turbulent flow (turbulent flow (Re>10000) in the return line)
- Eliminate piping dead-legs (≤ “6 D”; suggestion ≤ “3 D”) and use zero dead-leg outlet valves
- Establish standard operating procedures (SOP) for frequent draining, flushing, sampling and sanitizing
- Smooth, clean surface for wetted parts
- Positive system pressure to avoid external contamination
- Robust, simple and safe to operate and manage



Water for Pharmaceutical Use
Design criteria for a state of the art pure media system

- Evaluation of total consumption at all points of use (POU)
- Simultaneous consumption and interlocking (POUs - points of use 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 min 1%
- No dead legs 3d-rule
- Complete drainability
- Sanitization concept

Water for Pharmaceutical Use

Storage conditions for water for pharmaceutical use

TYPE OF STORAGE	CONDITIONS	WATER QUALITY	OZONE CONCENTRATION	ADVANTAGES
Cold storage	4° - 10°C	PW	N/A	• Low operating costs • accepted • easily controllable
Hot storage	75 - 80°C	WFI	N/A	• High operating costs • “no chemicals” • high safety • accepted • easily controllable
Cold storage with ozone	4° - 10°C	PW	0,02 - 0,05 ppm Continuously	• Higher investment costs (Ozone generator + sensors + UV light) • high safety • accepted • easily controllable

Water for Pharmaceutical Use
Types of Sanitization

TYPE OF SANITIZATION	CONDITIONS	PERIOD	WATER QUALITY	FREQUENCY
Ozonisation	>90 min >20 ppb	8h total	PW	Weekly (1-2 times)
Hot water sanitization	> 85 °C > 90 min	7-8 h total (long heating process)	PW	Periodically as required / opening of system
High pressure hot water sanitization	> 121 °C > 60 min	7-8 h total (long heating process)	WFI	Periodically as required / opening of system
Sanitization with steam	> 122 °C > 20 min	7-8 h total (long heating process)	WFI	Periodically as required / opening of system

Storage & Distribution
Distribution skid

Characteristics

- Compact skid- mounted system
- Variable speed-drive pumps
- Heat exchanger for cooling / heating
- Hot water sanitization, Ozone sanitization and steam sterilization available
- Measurement of quality relevant parameters (Flow, Conductivity, Temperature and TOC [optional])
- Robust, simple and safe to operate and manage

S&D	4.500	10.000	20.000	30.000
Performance up to l/h	4.500	10.000	20.000	30.000

Storage & Distribution

Storage and Distribution of PW and WFI

Characteristics

- Control system for complete storage and distribution
- Tanks in 316 L in different dimensions
- Points of use (cold and hot)
- Additional skid for cold PoU by hot distribution system
- PoU in 3 automation levels
  - Manual
  - Automatic with panel with push buttons
  - Automatic with control panel
- Installation of loop at site
- Supervision of loop installation by local company

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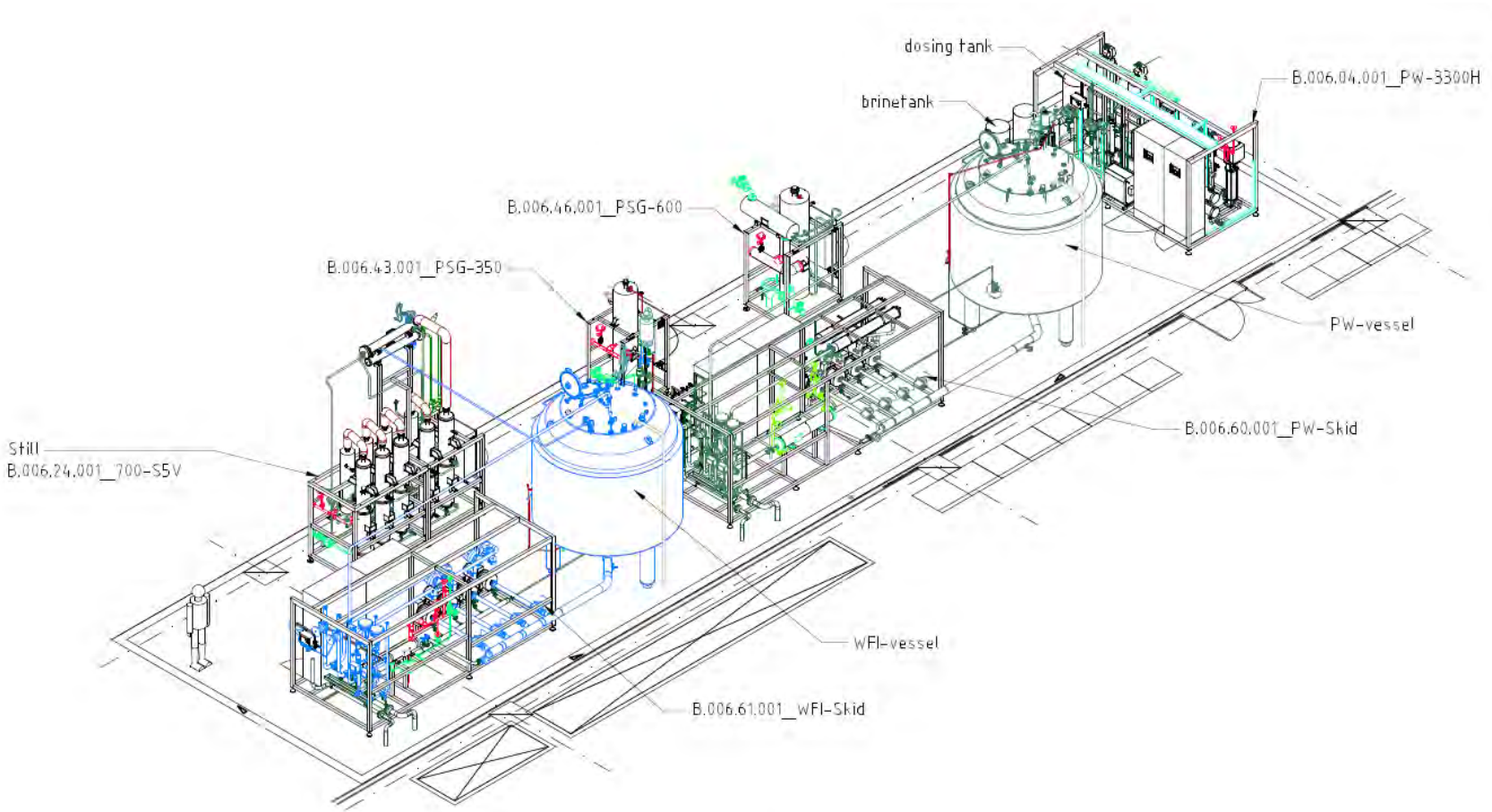
Water for Pharmaceutical Use

Sample layout of a complete pure media system



Storage & Distribution

Storage and Distribution of PW and WFI

video

Water for Pharmaceutical Use

Summary - Pre-conditions for good quality of pharma water production

- State of the art design of water generation equipment
- Appropriate pre-treatment technologies (=> feed water analysis)
- State of the art design of storage and distribution system
- Close pure media system and process monitoring
- Regular maintenance and routine sanitization
- Skilled operating and maintenance personnel