Supplementary Training Modules on Good Manufacturing Practice

Water for Pharmaceutical Use

Part 1: Introduction and treatment

WHO Technical Report Series No 929, 2005. Annex 3

Water for Pharmaceutical Use

Objective

- Water system requirements
- Water quality specifications
- Application of specific water to processes and dosage forms
- Water purification methods
- Storage and distribution systems
- Commissioning, qualification, operation and maintenance

Water for Pharmaceutical Use

Introduction

- Information on Water for Pharmaceutical Use (WPU)
- Quality of water for APIs, finished products, etc.
- GMP for design, installation, operation of systems
- Supplementary to general GMP guidelines
- See also other guidelines, pharmacopoeia, etc.

Water for Pharmaceutical Use

Additional guidelines

- WHO Guideline for Drinking water quality (WHO)
- Water and steam systems (ISPE)
- Bioprocessing Equipment Standard (ASME – BPE 2000)
- European Pharmacopoeia, United States Pharmacopeia, International Pharmacopoeia
- Inspection of Utilities (PIC/S)

Water for Pharmaceutical Use

Principles

- Like any starting material, production of water should conform to Good Manufacturing Practice (GMP) norms
- Potential for microbial growth
- Systems must be properly validated / qualified
- Water for parenteral use should not be contaminated with pyrogens or endotoxins
- Specifications and periodic testing are required

Water for Pharmaceutical Use

Why purify raw water?

- Although reasonably pure, it is always variable due to seasonal variations, regional variation in water quality
- Must remove impurities and control microbes to avoid contaminating products
- Treatment depends on water's chemistry and contaminants, influenced by, e.g. rainfall, erosion, pollution, dissolution, sedimentation, decomposition

Water for Pharmaceutical Use

Contaminants of water (1)

- There is no pure water in nature, as it can contain up to 90 possible unacceptable contaminants
- Contaminant groups:
  - *Inorganic compounds*
  - *Organic compounds*
  - *Solids*
  - *Gases*
  - *Microorganisms*

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Contaminants of water (2)

Problem minerals

- Calcium, magnesium, copper, aluminium, heavy metals, arsenic, lead, cadmium, nitrates
- Iron, manganese, silicates, carbon dioxide
- Hydrogen sulfide
- Phosphates

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Contaminants of water (3)

Microorganisms – Biofilm formation

- Protozoa
  - *Cryptosporidium*
  - *Giardia*
- Bacteria
  - *Pseudomonas*
  - *Gram negative, non-fermenting bacteria*
  - *Escherichia coli and coliforms*

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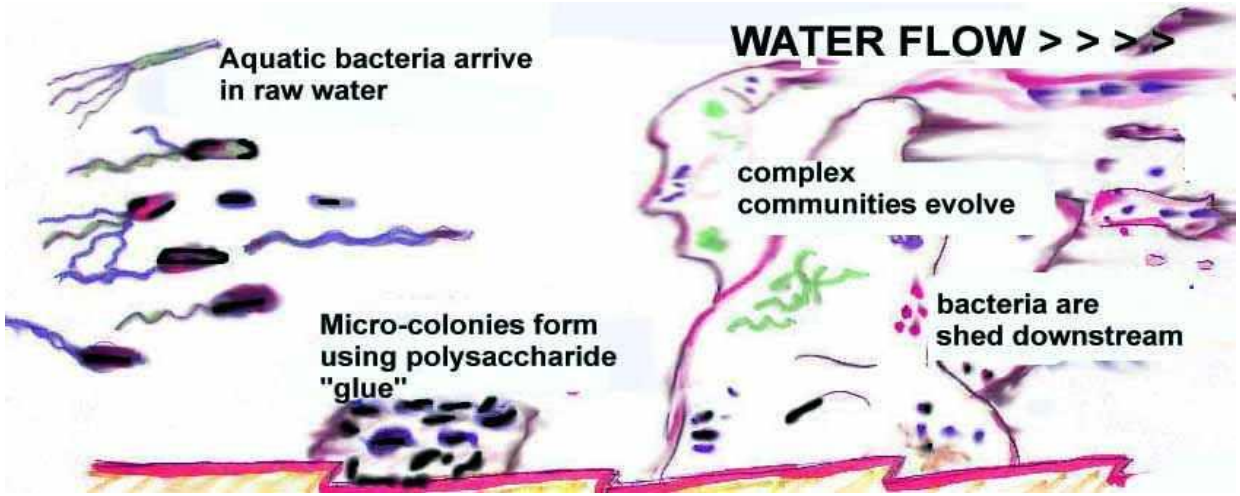
Biofilm formation

1. Free-swimming aquatic bacteria use *polymucosaccharides* to colonize surfaces

2. Complex communities evolve which shed microcolonies and bacteria



Water for Pharmaceutical Use

Background to water requirements and use

- Water is the most widely used substance / raw material
- Used in production, processing, formulation, cleaning, quality control
- Unique chemical properties
  - *Able to dissolve, absorb, adsorb, suspend compounds and contaminants*
- Different grades of water quality available
- See also EMEA "Note for guidance on the quality of water for pharmaceutical use"

Water for Pharmaceutical Use

Background to water requirements and use (2)

- Control quality of water
  - *Production*
  - *Storage and distribution*
- Contaminants, microbial and chemical quality
- Microbial contamination risk and concern
- Water is used on demand
  - *not subjected to testing and batch or lot release before use, therefore has to meet specification "on demand" when used*
  - *Micro test results require incubation periods*

Water for Pharmaceutical Use

Water system requirements

- Design, installation, commissioning, qualification / validation, operation, performance and maintenance to ensure reliable, consistent production of water of required quality
- Operate within design capacity
- Prevent unacceptable microbial, chemical and physical contamination during production, storage and distribution
- Quality Assurance involved in approval of use after installation and maintenance work

Water for Pharmaceutical Use

Water system requirements (2)

- Monitoring of water sources regularly
  - *Chemical and microbiological*
  - *Endotoxin level where relevant*
- Monitoring of system performance, storage and distribution systems
- Records of results, and action taken
- Validated sanitization procedure followed on a routine basis

Water for Pharmaceutical Use

Water quality specifications

Here address *water in bulk* (not for patient administration)

Specifications in pharmacopoeia – relevant to national or international recommendations. Types of water include:

- Drinking water / potable water
- Purified water (PW)
- Highly Purified Water (HPW)
- Water for Injection (WFI)

Water for Pharmaceutical Use

Drinking water / potable water

- Must comply with specification (WHO, ISO and national or regional agencies) – regular testing needed
- Supplied under continuous positive pressure
- Defect free plumbing system to prevent contamination
- Could be from public water supply system or natural sources
- Source water quality influences the treatment required

Water for Pharmaceutical Use

Drinking water:

Natural sources could include springs, wells, rivers and lakes

Treatment includes softening, ion removal, particle reduction, antimicrobial treatment

Water for Pharmaceutical Use

Purified Water (PW)

- Prepared from potable water source
- Meet pharmacopoeia specification for chemical and microbial purity
- Protected from recontamination
- Protected from microbial proliferation

Water for Pharmaceutical Use

Highly Purified Water (HPW)

- Prepared from potable water source
- Specification only in the European Pharmacopoeia
- Same quality standard as WFI including limit for endotoxins, but treatment method considered less reliable than distillation
- Prepared by combination of methods including reverse osmosis (RO), ultrafiltration (UF) and deionization (DI)

Water for Pharmaceutical Use

Water for Injections (WFI)

- Prepared from potable water source
- WFI is not sterile
- WFI is not a final dosage form
- WFI is an intermediate bulk product
- According to *The International and European Pharmacopoeias* – final purification step should be distillation

Water for Pharmaceutical Use

Application of specific water to processes and dosage forms

- Water used for different stages of:
  - *Washing, preparation, synthesis, production, formulation, control*
- Which grade of water is suitable for a particular stage?
- Consider nature and intended use of intermediate or finished product, and stage at which water is used
- Let's look at types of water and indicate their use

Water for Pharmaceutical Use

Complete the table

Use	***Which type of water?***
Preparation of injectable products	?
Final rinse of equipment after cleaning	?
Final rinse of equipment and components that come into contact with injectable products	?
?	HPW
?	Potable water

Water for Pharmaceutical Use

Water purification methods

- Manufacturer to select appropriate method of purification
- Appropriate sequence of purification steps
- Influenced by, e.g.
  - *Water quality specification*
  - *Yield (efficiency) of the system*
  - *Feed water quality*
  - *Reliability and robustness of treatment system*
  - *Supplier support, maintenance and operation costs*

Water for Pharmaceutical Use

Water purification system considerations

- Leaching from contact materials
- Adsorption
- Hygienic and sanitary design
- Corrosion resistance
- Leakage
- Proliferation of microbiological organisms

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Water purification system considerations (2)

- Tolerance to cleaning and sanitizing agents
- Capacity and output capability
- Instruments, sensors, controls, sampling points
- Space needed for installation and structural loading of premises
- Access needed for maintenance
- Regeneration and sanitization

Water for Pharmaceutical Use

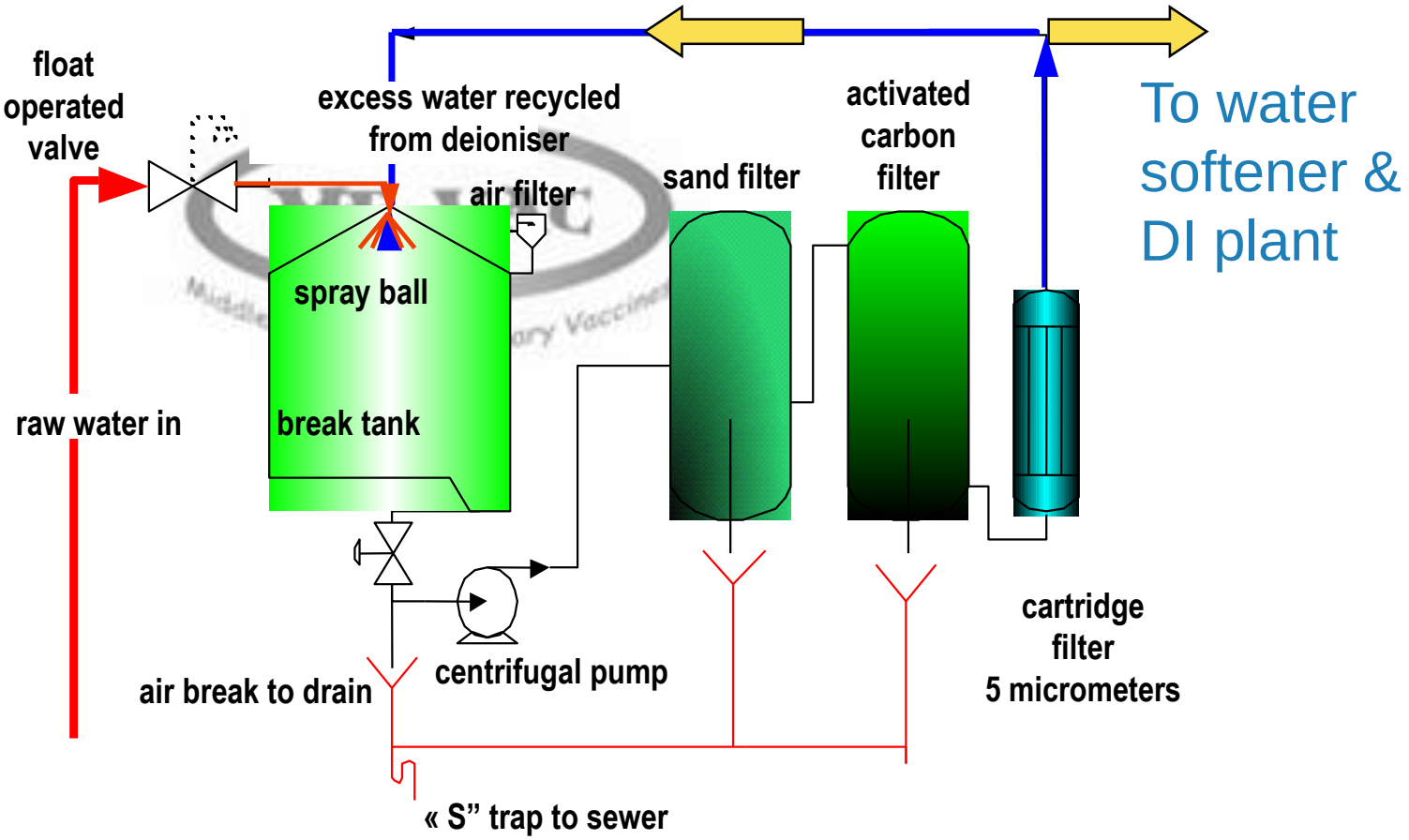
Pre-treatment steps

- Primary filtration and multimedia filter
- Coagulation or flocculation
- Desalination
- Softening

Water for Pharmaceutical Use

Pretreatment – schematic drawing

Water is kept circulating

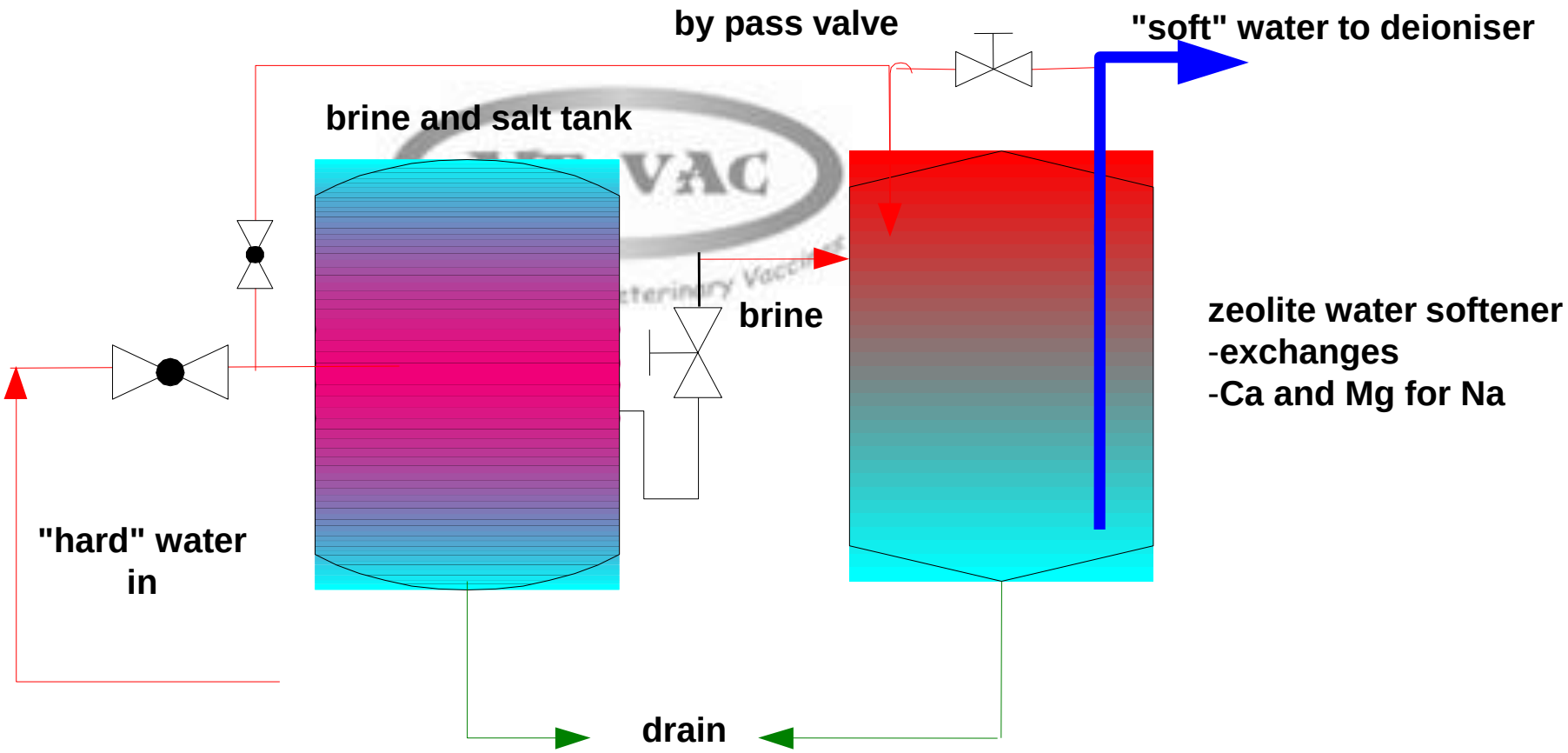


Water for Pharmaceutical Use

Water pre-treatment complex in a pre-treatment room

Water for Pharmaceutical Use

Water Softener – schematic drawing



Water for Pharmaceutical Use

Chlorine removal (Activated-carbon (AC) filtration or bisulphite)

- AC removes chlorine but bacteria can then grow
- AC filtration can remove organic impurities
- Bisulphite leaves sulphate residues but is antimicrobial

Water for Pharmaceutical Use

Production of drinking water

- Derived from raw water (e.g. well, river, reservoir)
- Processes may include:
  - *Filtration, softening*
  - *Disinfection or sanitization*
  - *Iron (ferrous) removal*
  - *Precipitation*
  - *Inorganic / organic reduction*

Water for Pharmaceutical Use

Production of *drinking water (2)*

- When done "in-house" – steps used and system configuration documented, and water quality routinely monitored
- Change control in case of changes to system
- Storage of water:
  - *no degradation, ensure turnover, routine testing*
- "indirect impact system" – qualification not needed

Water for Pharmaceutical Use

Production of drinking water (3)

- System permits draining and sanitization
- Storage tanks:
  - *Closed, with protected vents*
  - *Allows visual inspection, draining and sanitization*
- Care to prevent and control microbiological contamination of sand filters, carbon beds, water softeners
  - *Back-flushing, chemical or thermal sanitization and frequent regeneration, continuous waterflow*

Water for Pharmaceutical Use

Production of drinking water (4)

- Drinking water supplied by tanker – associated problems and risks
- Required vendor assessment
- Authorized certification activities
- Acceptability of delivery vehicle
- As receiving any other starting material

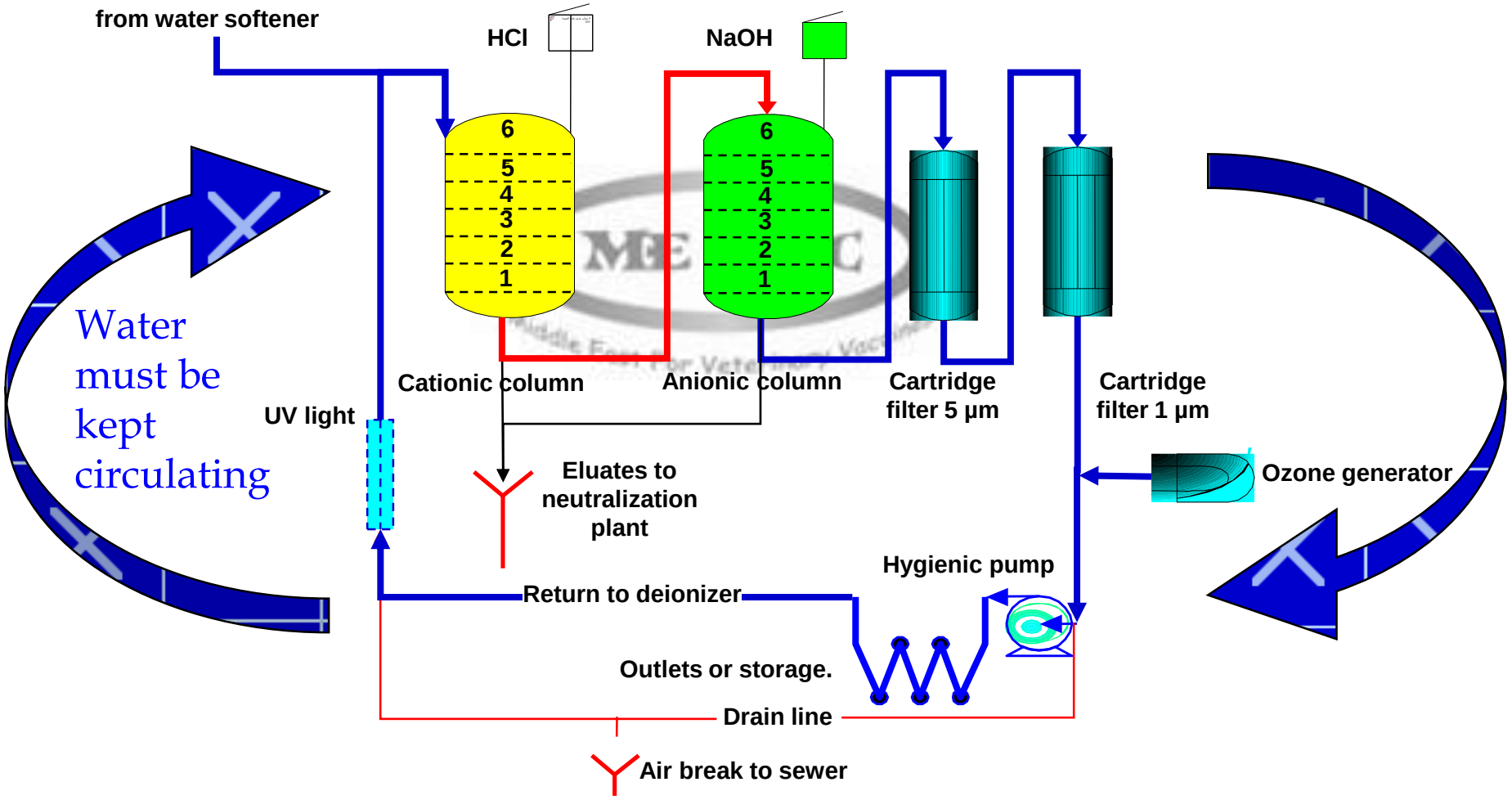
Water for Pharmaceutical Use

Water treatment purification stages downstream of the pre-treatment system may include:

- Filtration
- Disinfection
- Reverse osmosis (RO) or deionization (DI)
- Distillation or ultrafiltration

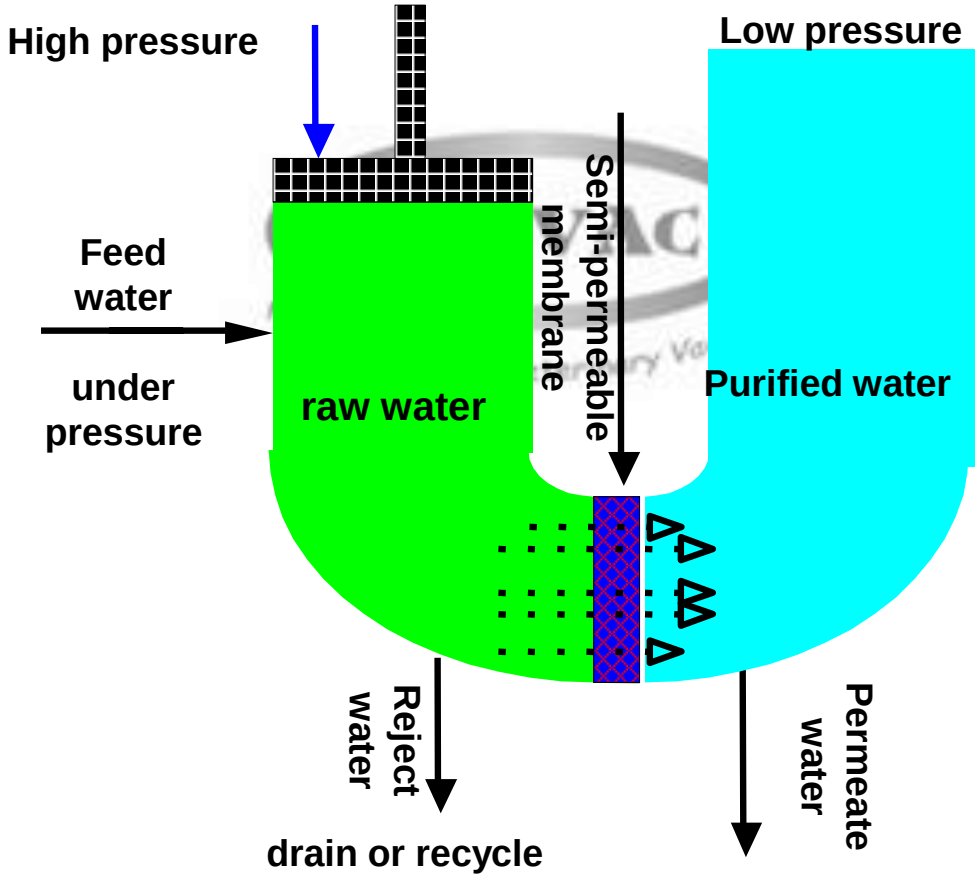
Water for Pharmaceutical Use

Typical deionizer schematic



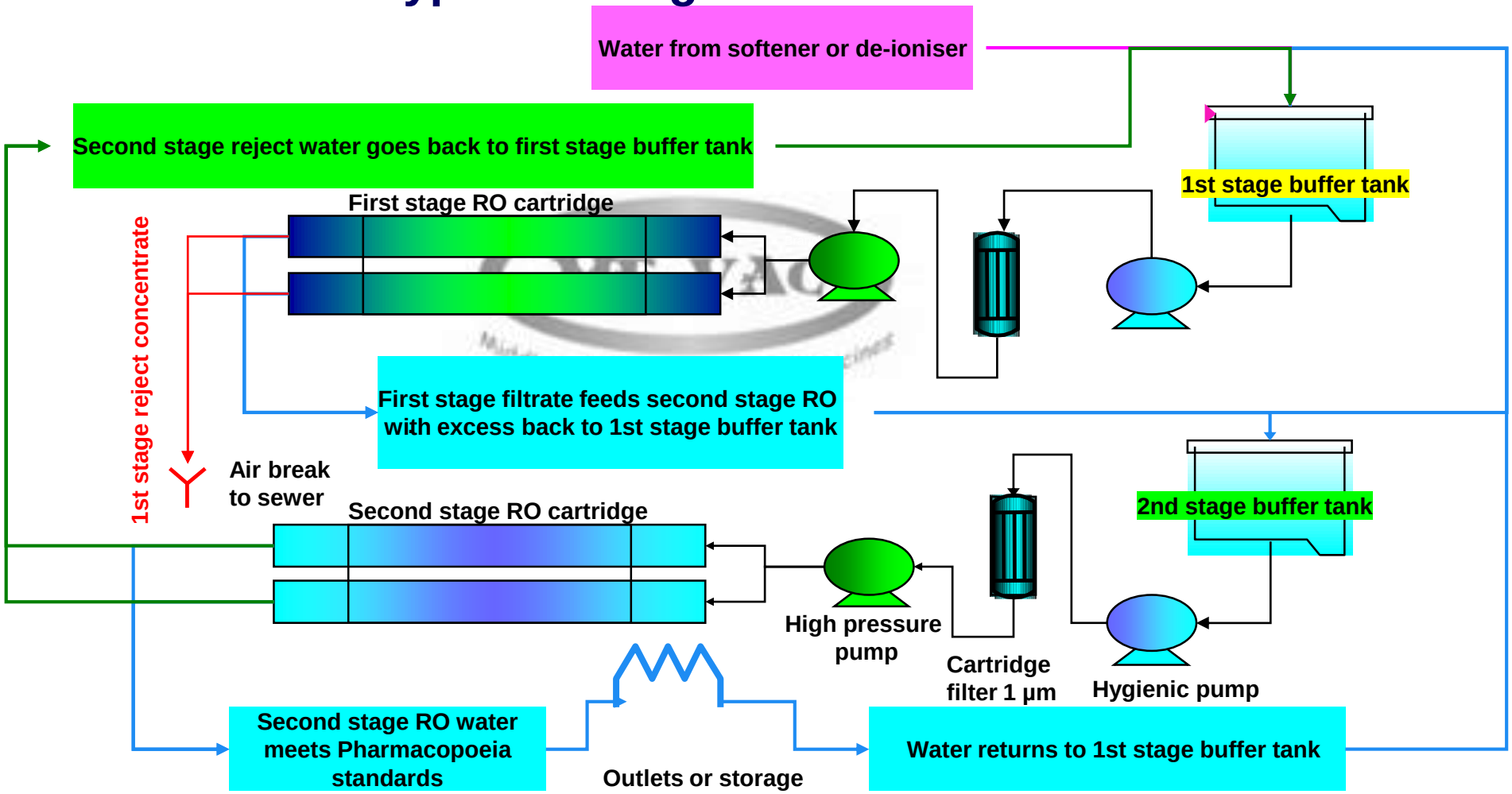
Water for Pharmaceutical Use

Reverse osmosis (RO) theory



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 ultrafiltration units*
  - *Water for Final Rinse*
  - *Water for Injections (if permissible)*

Water for Pharmaceutical Use

Production of Purified Water (PW)

- Use appropriate, qualified methods for production
- Factors to consider:
  - *Feed water quality and required water quality specification*
  - *Sequence of purification stages needed*
  - *Energy consumption, extent of pre-treatment needed*
  - *Yield and efficiency of unit treatment steps*
  - *Location and design of sampling points*
  - *Appropriate instrumentation for measurements*

Water for Pharmaceutical Use

Production of Purified Water (2)

- Measurements:
  - *Flow*
  - *Pressures*
  - *Temperature*
  - *Conductivity*
  - *pH*
  - *Total organic carbon (TOC), etc.*

- Appropriately controlled, monitored, records maintained

Water for Pharmaceutical Use

Production of Purified Water (3)

- Ambient temperature PW systems are susceptible to microbiological contamination – especially when static and periods of low or no demand
- Controls may include:
  - *Maintain flow at all times*
  - *Control temperature in the system (<25 degrees Celsius)*
  - *UV disinfection*
  - *Water treatment components that can be thermally sanitized*
  - *Chemical sanitization (e.g. with ozone)*

Water for Pharmaceutical Use

Production of Highly Purified Water (HPW)

- Use appropriate, qualified methods for production
- Appropriate sequence of techniques
- As for PW
- Processes may include:
  - *Ion exchange*
  - *Ultrafiltration*
  - *Reverse Osmosis*

Water for Pharmaceutical Use

Production of Water for Injections (WFI)

- Pharmacopoeia requires distillation as preferred technique for final purification step
- Factors to consider:
  - *Feed water quality*
  - *Required water quality specification*
  - *Optimum generator sizing (prevent frequent start/stop)*
  - *Blow-down and dump functions*
  - *Cool-down venting (avoid contamination ingress)*