PharmaWaterSystems
ENVIROFALK

# Cold WFI

## by membrane processes

# The production of Water for Injection using the membrane process

An amendment to the European Pharmacopoeia, in force since 1 April 2017, has had a significant impact on the manufacture of Water for Injection (WFI). While up to that point only a distillation process was permitted for the generation of WFI, now a membrane-based process can also be used. In this way, Europe is mirroring America, Japan and other areas for whose markets cold manufacture has been approved for some considerable time.

## Advantages of cold production

For companies that produce for the European market and are thus subject to the specifications of the European Pharmacopoeia, this may result in major financial and organisational advantages. This is because Purified Water is usually used as feed water for distillative production. Purified Water (PW) is produced separately via a reverse osmosis plant and is also subject to strict regulations.
The Purified Water produced is also first fed into a storage tank and from there distributed to the consumers via a ring main. The situation is identical for the WFI produced.

In the cold production of WFI, on the other hand, drinking water is used as feed water and WFI is produced by a single manufacturing process, with the result that significant cost savings are possible.
This results in investment, operating and monitoring costs for two monitoring costs for two different production processes, as well as for their storage and distribution systems.

## A combination of reverse osmosis, electrodeionisation and ultrafiltration

For cold manufacture, the essential stages of preparation that have emerged are a combination of reverse osmosis, electrodeionisation and ultra-filtration. Reverse osmosis acts as a barrier for ions, organic contamination and microorganisms. In the subsequent electrodeionisation stage, the remaining ions that were able to pass through the osmotic membrane are removed. Ultra-filtration is integrated as a final safety stage, making sure that no endotoxins or microorganisms get into the storage tank and from there to the distributed product.


## Our patent for absolute safety

Ultrafiltration represents an important process step in cold WFI generation, which we have focused on in particular: EnviroFALK PharmaWaterSystems uses very robust ceramic modules that can be continuously exposed to ozone.

We have patented this process as it ensures a robust and reliable manufacturing process as well as extended patient protection. In addition to the possibility of hot water sanitization of the entire production, ozonization of the ultrafiltration is another important measure to ensure continuous killing of microorganisms. Another positive side effect:
the ozone can be fed back via the plant circulation downstream of the water pretreatment softening process and ensures a continuous reduction of microorganisms here as well.

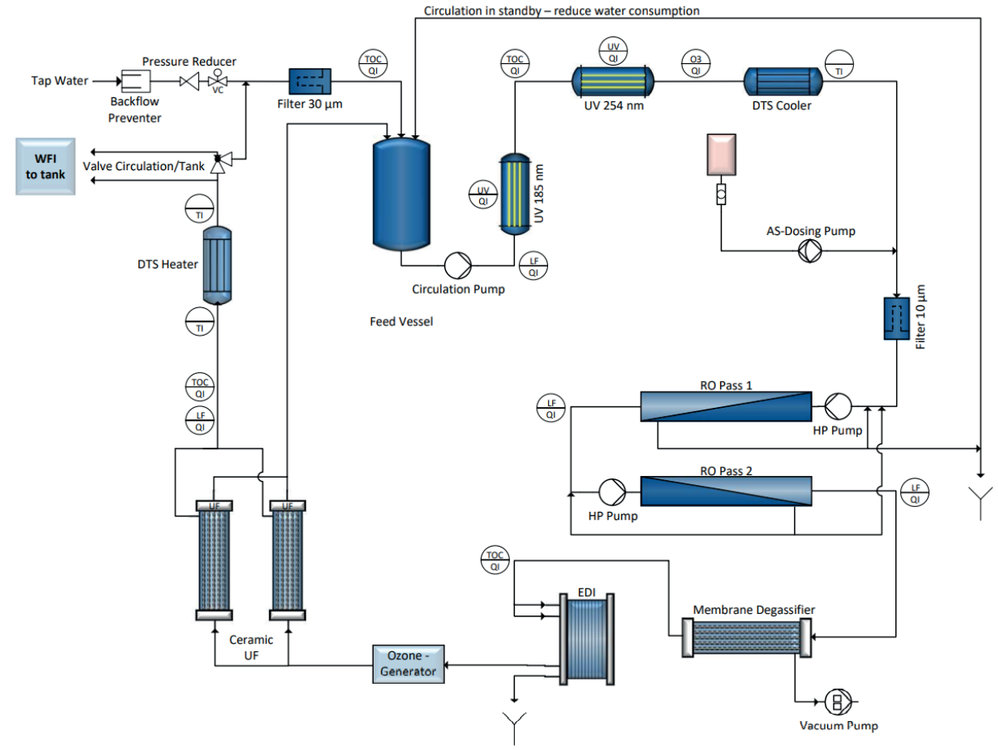
# Cold WFI production using M-WFI

The processes used in pre-treatment are chosen depending on the composition of the feed water, which can differ widely depending on the source. For this reason, the feed water quality must be assessed individually for every plant and the suitable components required for water preparation will be determined and integrated in the plant.

As a cold process, in comparison to hot distillation, is nevertheless more vulnerable to microbial growth, therefore further important measures are vital to ensuring no such growth in the plant.

**EnviroFALK PharmaWaterSystems relies on the following components and design characteristics in the M-WFI plant:**

- UV systems for reduction of microorganisms and TOC in feed water
- Pharma double softener or dosing of antiscalant
- Plant construction in Hygienic Design: 316L, detachable connections according to DIN 11864-3 aseptic connections
- Accomplish the requirements of the EMA as well as all current guidelines (ISPE, GMP and qualification standards)
- Biofilm and control strategy via intelligent alarm concept
- One- or two-stage reverse osmosis membrane system with downstream electrodeionization and ultrafiltration
- Fully automatic sanitizing and stand-by concepts (>80°C, hot water or chemical sanitization)
- Patent: ozonizable ceramic ultrafiltration with cut-off 5,000 Dalton (ozonization possible up to pretreatment). Alternative: Hollow fiber ultrafiltration 6,000 Dalton
- Extensive process monitoring: several online TOC measurements (including of the feed water), conductivity, temperature, pressure and flow measurements at various points in the plant ensure absolute safety
- Optional: online germ count monitoring




Block diagram M-WFI

# Storage and distribution system for cold WFI

The safe storage and distribution of cold-generated WFI is the biggest challenge and requires a consistent hygienic design. The generated WFI is distributed from the storage tank to the consumers via a hygienic pump. Various measurement sensors ensure fully automatic and safe operation. Hygienic diaphragm valves are used for shut-off and withdrawal.

## Preventing microbial growth

Compared to hot production, cold storage and distribution of the water is a viable option for cold WFI for energy reasons.

To prevent microbial growth, cold systems must be provided with measures to kill microorganisms and prevent their multiplication. Various methods may be used to this end. One possible method is to ozonise the tank continuously and distribution system, including the pipe non-continuously.

Alternatively or in combination with ozonization regular hot-water sanitization can be carried out at >80°C or a pressurised hot water sanitization at >121°C. Even a sterilisation with pure steam is possible.

Where discontinuous processes such as hot water sanitization are used, however, an additional, continuous process to kill microorganisms must be added by installing a UV system in the plant and keeping the circulating water at a temperature <20°C.

It also makes sense to install ultrafiltration. As in the production plant, this reliably traps microorganisms and endotoxins and can easily be installed in a bypass to the storage tank in the loop.

## Cold WFI distribution C-WFI

The components of the WFI distribution include the hygienic pump(s) and DTS heat exchangers for heating and/or cooling the water. Depending on the application, individual sanitization concepts are developed together with the customer. Depending on the respective risk analysis, further components such as ozone generators and UV systems will be used. For ozone-sensitive applications, an additional ultrafiltration unit can alternatively be added to reduce endotoxins and microorganisms.

Specific material and process requirements, such as electropolishing of the stainless steel or subloop systems with cold and hot taps as well as various withdrawal management systems, can be flexibly planned and integrated. As the WFI is usually stored and distributed cold in a cold manufacturing process, extensive monitoring and reliable sanitization measures are crucial.


WFI distribution with C-WFI

## Comprehensive and individual service & maintenance concepts according to risk-based GMP lifecycle management

Our service promise encompasses not only advice, project planning and operational implementation, but also the reliable system maintenance, as well as a comprehensive service tailored to each and every customer. We offer flexible, comprehensive and modular service agreements designed to meet your needs perfectly. We offer the widest possible range of support, consultation, service and maintenance to ensure the best possible support for your lifecycle management of every aspect of your water treatment systems. Preventative maintenance is a key element in the lifecycle management of a water treatment system and thus a key point in our service agreements.

# M-WFI
# technical data at a glance

| | |
|---|---|
| **Material** | stainless steel 1.4404 or 1.4435, roughness <0.8 µm (optional <0.6 µm and e-polished) |
| **Process technology** | pre-treatment, 2-stage reverse osmosis, EDI, UF |
| **Achievable output** | 50 - 20,000 l/h |
| **Total yield** | approx. 70 - 80%, at concentrate level approx. 85 - 90% |
| **Ultrafiltration module type** | ceramic, optional hollow fibre |
| **Ultrafiltration cut-off** | 5,000 Dalton (hollow fibre 6,000 Dalton) |
| **Ultrafiltration** | optional fully automatic and logged verification of the integrity of the UF modules during operation |
| **Sanitization of entire system** | discontinuous with hot water, continuous with UV radiation |
| **Sanitization of ultrafiltration** | ozone (own patent), hot water (optional steam sterilization) |
| **Connections** | Aseptic-Clamp to DIN 11864-3 A |
| **Valves** | membrane valves (optional T-valves) |
| **Inline/online process monitoring** | TOC and conductivity (also for drinking water), flow rate, temperature and pressure (optional microbial count) |
| **Control and visualization** | Plant control via Simatic S7 PLC, Operation and visualization via Siemens TIA Portal (19“ touch panel) |
| **Computer validation** | according to GAMP 5 |

# C-WFI
# technical data at a glance

| | |
|---|---|
| **Material of storage tank** | stainless steel 1.4404 or 1.4435, roughness <0.8 µm (optional <0.6 µm and e-polished) |
| **Volume of storage tank** | 100 - 50,000 l |
| **Level of pressure resistance** | -0,49/0,49 bar or -1/3 bar |
| **Pump(s) in distribution system** | 100 - 60,000 l/h, optional redundant design |
| **Sanitization of storage and distribution system** | discontinuous using hot water, storage tank continuously with ozone (loop discontinuously) |
| **Separating out of endotoxins and microorganisms** | optional via UF in bypass to tank |
| **Point of use management** | various concepts available |
| **Point of use cooling/ heating** | automated via sup-loop with heater or cooler |
| **Material distribution system** | stainless steel 1.4404 or 1.4435, roughness < 0.8 µm (optional < 0.6 and e-polished) |
| **Connections** | Aseptic-Clamp to DIN 11864-3 A |
| **Valves** | membrane valves (optional T-valves) |
| **Inline/online process monitoring** | fill level, TOC, conductivity, flow rate, temperature and pressure (optional microbial count) |
| **Control and visualization** | Plant control via Simatic S7 PLC, Operation and visualization via Siemens TIA Portal (19“ touch panel) |
| **Computer validation** | according to GAMP 5 |

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