2017 will be the year of the big changes for clean utilities

With the European Pharmacopeia (EP) acceptance of membrane technology for the production of Water for Injection (WFI) this gives pharmaceutical companies, depending on size and configuration of the system, the possibility for yearly savings in the hundreds of thousands of dollars while still producing the same high water quality. This article shows what has been changed within the EP, for what reasons, how it impacts the daily business and what a good system for the generation of cold WFI should look like.

Worldwide different regulations – a constraint for globalized markets

Inside the EP, the requirements for the production of WFI are prescribed in the monograph *Water for Injections (0169)*. Contrary to the United States Pharmacopeia (USP) and the Japanese pharmacopeia (JP) the only accepted process by the EP was the distillation. The USP and the JP since 2003 and 80's respectively have allowed other processes equal to distillation for the production of WFI.

Still most WFI worldwide is produced by distillation even tough it is a very expensive solution due to the high investment and operational costs. Members of multinational pharmaceutical companies have approached WFI production with a global approach and therefore in order to be compliant in their production to all the pharmacopeias have sided traditionally with distillation. Through the changes of the EP starting April 2017, those users of clean utility systems will have more flexibility to choose other membrane system and therefore to realize significant cost savings.

Doubts and Discussions about process safety and a convincing result

It has been a long journey for the new revision of the European WFI-monograph to be accepted. Over the years a lot of concerns and discussions were tabled. Is it possible to guarantee the same safety and comparable quality with membrane systems than with distillation. The biggest doubts were regarding the risk of growth of biofilms in membrane systems and as a result the contamination of water with microorganisms and their decomposition products. In reality, the historical data of systems for the production of Highly Purified Water (HPW) are the proof of concept; that membrane systems fulfill the specifications for WFI continuously and fully. In these HPW systems the Reverse Osmosis (RO) has not been the final barrier as additional process steps such as electro-deionization (EDI) and ultrafiltration (UF) followed the RO. The microbial safety of the system was ensured by different, consecutive and complementary process steps, consequent monitoring, smart operation & sanitization, intelligent construction and selection of high quality components. The semi-conductor industry has far higher regulations regarding water quality than WFI, and even these qualities are produced reliable in very large capacities with multiple-stage cold processes such as RO, EDI and UF.

After a process of evaluation which took years, starting from April 2017 the revised WFI Monograph 0169 will be in force. The amount of written changes inside the monograph isn't that much, but the consequences for the design of future clean utility systems is enormous.

The three main changes inside the Monograph 0169

As a further option next to Distillation the EP allows from April 1st, 2017 the production of WFI "by reverse osmosis, which may be single-pass or double-pass, coupled with other suitable techniques such as deionization and/or ultrafiltration."

Second is an addition, valid for all kind of WFI Systems that: "Correct operation monitoring and maintenance of the system are essential". Whilst the importance of regular GMP-Maintenance was already written down in the current version of the monograph, now also the monitoring of the current and correct operation is an integral part of the operation of every WFI system.

The third change inside the WFI monograph is the newly added, regular monitoring of the organic content (Total Organic Carbon, TOC). Until now, only the control of the microbiology in aerobic bacteria (CFU) and measurement of conductivity was explicitly demanded.

BWT Nederland BV
Coenecoop 1 – 2741PG Waddinxveen
verkoop@bwtnederland.nl • **www.bwtnederland.nl**

Cold WFI production convinces in terms of quality and costs

For manufacturers of medical products and operators of distillation systems the amendment to the WFI monograph means an enormous potential for cost savings at the same or higher product quality and a better ecological balance.

Advantages of WFI production by membrane process:

- Environmentally and economically more efficient
- Higher water quality and better safety margin
- No rouging
- Attractive Investment and Operational costs

Cost Comparison Distillation and Membrane System

As feed water for the WFI production with Multi-Effect (ME) distillation units at least softened water out of a one-level reverse osmosis is needed and therefore regularly Purified Water (PW) is used. Even for the most efficient distillation systems with 6 - 8 Columns the biggest slice of the cake are the costs for heating steam, feed water including pretreatment, cooling water and depreciation. For cold WFI production with OSMOTRON WFI in Europe regular drinking water is sufficient. With the later presented system by BWT, the costs per m^3 are – with at least same product quality – 50 to 70% less.

Cost comparison: 3.5 m³ WFI

	Natural Circulation, 6 Columns, 3.6 m³/h	RO-RO-EDI 3.5 m³/h
€ / m³ WFI incl. Depr	24.39 € / m³ WFI incl. Depr	7.93 € / m³ WFI incl. Depr
Main costs	36% Cooling Water 30% Heating Steam 26% Feed Water (PW)	53% Feed Water (Drinking Water)
Savings per Year	***345,660 € / Year***	

Cost comparison: 10 m³ WFI

	Natural Circulation, 8 Columns, 10 m³/h	RO-RO-EDI 10 m³/h
€ / m³ WFI incl. Depr	12.94 € / m³	5.99 € / m³
Main costs	48% Feed Water (PW) 42% Heating Steam	78% Feed Water (Drinking Water)
Savings per Year	***417,000 € / Year***	

Frame conditions for calculation (typical feed water conditions and operational costs for an example facility in Germany):
(Depr) Depreciation time: 10 years; 300 Operating days per year; 20 operating hours per day; waste water 2 €/m³; energy: 0.2 €/kwh; industrial heating steam, 8 barg 175C: 35 €/t; Cooling water: 3 €/m³; Feed water:

Drinking Water (RO-RO-EDI) 1.50 €/m³, Purified Water (Distillation) 5.70 €/m³

The two examples show the yearly cost savings with cold systems is somewhere between several tens of thousands up to hundreds of thousands of euros.
The responsible use of resources is of economic importance for companies but also and more and more a social challenge. The ISPE broaches the issue of efficient and resource saving construction for the operation of clean utility systems in their sustainability handbook from December 2015 in chapter 15.1. The handbook is in context of the 'Steam and Water Baseline' but gives concrete ideas for sustainable strategies regarding resources for the production of PW, WFI and Pure Steam – for example with waste water recycling, intelligent continuous operation as possible or with smooth capacity control.
At this point it is important how many point of uses need hot WFI. If the WFI is produced with a cold system, then hot WFI is provided by a hot sub-loop where a heat exchanger is used to provide the water at the needed temperature.

Comparison of the WFI qualities

With a cold WFI system made by BWT a water quality with aerobic bacteria < 1/100 CFU/ml and Endotoxins of < 0.005 EU/ml can be expected with a conductivity at the outlet of the generation unit < 0.1µS/cm and a TOC level < 20 ppb.Therefore operators fulfill the current guidelines of EP and USP (< 10 CFU/100ml, < 0.25EU/ml, < 1.1µS/cm @ 20°C, < 500ppb TOC) in every area significantly. With these parameters WFI via membrane systems provide a better water quality with margin of safety

BWT Nederland BV
Coenecoop 1 – 2741 PG Waddinxveen
verkoop@bwtnederland.nl • **www.bwtnederland.nl**

between action limit and alert limits at the storage and distribution until the point of uses.

Design of a good WFI generation system

Many pharmaceutical companies want to know, how a valid, reliable and safe system for the cold production of WFI should look like.
BWT Pharma and Biotech has delivered for the past 25 years the OSMOTRON, the standard for the production of PW and fro the last 10 years with the option for the production of HPW. All the needed process steps from softening and reverse osmosis, electro-deionization and ultrafiltration are mounted on one compact skid. Based on the experiences of more than 1,000 units sold worldwide, the OSMOTRON WFI has been created.

Ideal safety for classic systems

From a microbial point of view, the two most risky points of every classic clean utility system is the pretreatment and

the tank. But both are reliable controllable with the right expertise and technology.
The actions for best safety at the softener are continuous operation, selection of the right sanitization method and cycle, monitoring and use of the best available technology, e.g. multi-port block valves. Operation during regeneration and sanitization is possible and additional safety is achieved by alternating position of the softening vessels between worker and polisher. Through the compact and intelligent design of the multi-port block valves, pipework is optimized and dead legs minimized.

Picture 1:

BU: Common Single Valve Nest

Picture 2:

BU: Advanced control of the softener with multi-port block valves

The risk of microbial growth in cold tanks due to stagnant water can be safely prevented by continuous sanitization with in-situ generated ozone and concentrations of 20 ppb.

Customers, seeking the most cost-efficient and safest solution of cold WFI Production, BWT offers the OSMOTRON WFI with triple safety by three membrane barriers.

This System goes without the Softener. The hardness in the water is kept in solution by adding anti-scalant and is rejected at the two-staged reverse osmosis. This solution is environmentally friendly and more sustainable as the salt, which is necessary for the regeneration of softeners is not required. Through the space saving design all components fit onto one frame, the system is user and maintenance friendly and saves money. After the first and second membrane stage electro-deionization is used for final polishing by SEPTRON Biosafe with has an integrated UF as the third and final membrane barrier with a 5 log reduction (>99.999%) of all endotoxins, germs and particles.
For the reverse osmosis stage, FDA compliant Full-Fit Membranes are used. This is an improvement on other standard modules where chevron seals are used between the membrane elements that cause areas of stagnant water. For Full-fit Modules a full circulation flow is realized which helps prevent biofilm on the membrane. For the use in the pharmaceutical regulated industry the Full-Fit Membranes for the RO are a convincing solution.
BWT developed dedicated for the requests of the pharmaceutical industry the SEPTRON Biosafe Modules for Electro-deionization with high quality housings made of 316L Stainless Steel and a spiral wounding ion-exchange design. In comparison to conventional plate & frame EDI

modules the SEPTRON Biosafe is deadleg free and has excellent hot water sanitization performance. With the directly integrated ultrafiltration (UF) the unique SEPTRON Biosafe EDI modules provide the best efficiency with simultaneously the best WFI quality Picture 3:

BU: EDI module with spiral wound design, housing made of 316 L Stainless steel and integrated UF – a lot of advantages compared to standard plate & frame EDI modules.

Conclusion

Starting in April 2017, pharmaceutical companies will have a new opportunity for the production of WFI which promise higher quality at lower costs. With the right partner and a smart, high quality system like the OSMOTRON WFI by BWT there is already today the right system available with; triple safety barriers , integrated SEPTRON Biosafe EDI , standard fully hot water sanitizable and with capacities of 0.5 to 17.5 m3 WFI per hour on a compact single-skid.