Case History

HAGER+ELSÄSSER

Aventis Pharma Deutschland GmbH Frankfurt

1 Introduction

Aventis Pharma is a globally pharmaceutical company. At their Frankfurt location, the Pharmaceutical Sciences division uses "Purified Water" for various applications in two different buildings.

The ultrapure water plant required for this purpose was designed, delivered and commissioned by Hager + Elsässer in early 1999, including Qualification. Following the first two validation phases (4 weeks), the Purified Water was approved for use on the basis of the positive results obtained. The accompanying system validation was performed from April 1999 to April 2000 and completed successfully.

At the Ultrapure Water Conference in Singapore on 3 and 4 October 2000, the practical experience gained from this innovative ultrapure water plant in the pharmaceutical industry was presented for the first time.[1]

This plant has now been in service for a substantial time. The following is a detailed description of the experience Aventis Pharma has gained from long-term operation and sanitisation of this ultrapure water plant.

Photos

Above: Softeners

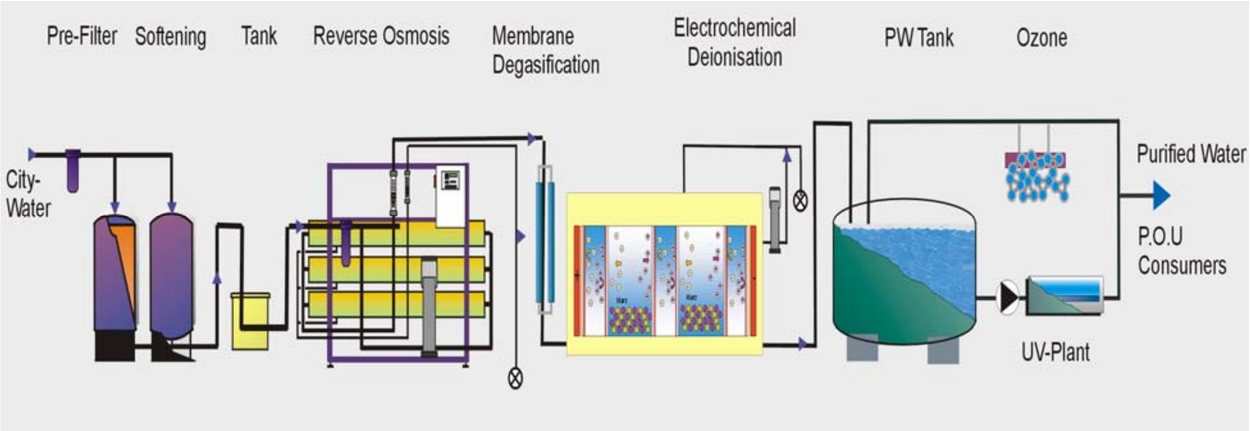
Right: Reverse osmosis unit with feed tank

Far right: Electro-deionisation unit with membrane degasser

1 Authors: Dipl. Ing. (FH) Lars Pfannenschmidt, Aventis Pharma, and Horst Seeger, Hager + Elsässer. The paper is available from Hager + Elsässer .

1.1 Plant design

Fig. 1 shows the process:



Firstly, particles are removed from the feed water in a coarse filter. The water is then softened to protect the reverse osmosis unit, and flows into the RO unit feed tank via a micro-filter.

For water treatment process to produce purified water employs a combination of reverse osmosis (RO) / electrodeionisation (CEDI) is employed in an H+E ROCEDIS unit The reverse osmosis unit is essential to provide the necessary water quality supply quality that is required to feed the electrodeionisation unit Raw (mains or city) water cannot be fed directly to the CEDI unit. The free CO_2 contained in the water is removed in a membrane degasser without the use of chemicals. The water is then finally deionised in the downstream electrodeionisation unit and the Purified Water flows into a stainless steel PW storage tank.

The Purified Water demand varies constantly, depending on the needs of production. When a small volume is consumed and the PW tank is still full, the treatment plant switches into “Recycle Mode”. The Purified Water is then periodically recycled from ROCEDIS to the RO feed tank and circulated in the treatment plant. When production’s demand for Purified Water rises, the plant automatically returns to “standard” operation.

The Purified Water is supplied to the various consumers by one pump and two supply loops.
An electrolytic ozone generator is installed in the return pipe of the loop. Therefore, the PW tank is constantly ozonised, ensuring optimum protection and continuous sanitisation. A UV unit removes the ozone to a value below the 5 ppb detection limit. This UV unit is installed in the inlet to the loops. This combination of ozoniser and UV lamp, the so-called “SANICIRCLE” has been used successfully by Hager + Elsässer literally for decades.
A temperature monitor in the return loop opens a discharge valve if the temperature of the Purified Water temperature in the loop exceeds the set point.

Fully automatic operation of the plant is controlled and monitored via a central switching and control system. An operator panel is provided for operator control. An electronic paperless recorder is used for recording and trending.

The following instruments are installed for continuous on-line monitoring of the Purified Water quality:

- Conductivity (uncompensated)
- Temperature
- Ozone
- TOC (since 11/2001)

Data is sent to a Business Management System for batch documentation and long-term storage. The following water parameters are analysed in the laboratory:

- Colony counts
- Endotoxins
- Chemical / physical parameters

1.2 Additions/Upgrading

In 2000, the PW supply loop was increased in length. The existing system was opened; prefabricated pipe sections were inserted and the new consumers connected. Prefabrication was carried out under extremely clean conditions so that, following a short flushing cycle with ozonised Purified Water, the system was able to be sanitised and put into service after just eight hours. These additions were subjected to re-qualification and validation within the scope of a Change Control procedure.

The removed pipe sections allowed good conclusions to be drawn about the inner loop surface and welds after an operating period of 18 months.

In November 2001, a TOC meter was retrofitted because of the very high cost and error rate in the laboratory for sampling and transportation of the samples and therefore the client requested continuous measurement of TOC.

2 Operating results

2.1 Normal operation

Table 1 below shows the quality requirements for the Purified Water, as well as the values that were normally obtained after an operating period of four years. Further values specified in the pharmacopoeias, such as pH, nitrate content, heavy metals and oxidisable substances, are all within or below the limit values.

Parameter	USP 25 limit	Downstream of ROCEDIS*	Point of use*	Measurement method
Conductivity (25°C)	< 1.3 µS/cm	< 0.1 µS/cm	< 0.7 µS/cm	Online measurement
TOC	< 500 ppb	Not measured	< 10 ppb	Online measurement
Colony count	< 100 CFU/ml	< 10 CFU/ml	< 1 CFU/ml	Membrane filter method
Endotoxins	< 0.25 IU/ml	< 0.25 IU/ml	< 0.25 IU/ml	LAL test

Table 1: Purified water values obtained

The results of the colony count at the sampling points or consumer points in general were below the detection limit of 1CFU/100ml. *A value between 1 and 10 CFU/ml was only found at the sampling point directly downstream of ROCEDIS, because this point is not ozonised.

2.2 Operation and maintenance

The water treatment plant operates automatically. All the Aventis Pharma operators have to do is to make regular inspection rounds. All of the major operating parameters are checked and recorded, the stock of salt for softening and the level of the indicator fluid at the hardness meter is checked and topped up when necessary. Once a week low-pressure washing of the RO membranes is carried out. The pre-filter is cleaned once per month.

This work takes about 30 minutes per day in total.

Hager + Elsässer's Customer Service department performs routine maintenance twice a year, which includes the following work:

- Checking the working condition of all aspects of the water treatment plant.
- Checking treatment efficiency by on-site water analyses and, if necessary, immediately making any adjustments to the plant.
- Carrying out repair work.
- Training of new Aventis Pharma employees.
- Providing a detailed Customer Service Report on the status of the plant.

Under the operating conditions and consumption values prevailing at Aventis Pharma, the following components have to be replaced due to wear:

Component	**Interval**
Vent filter on PW tank	Twice a year
Membranes of loop valves	Up to twice a year, depending on the ozone content. (complete replacement in the loop every 4 years to be on the safe side)
UV lamps	Once a year
Hardness meter, dosing unit	Once a year
RO modules	About every 3 years (up to now one replacement depends on the raw water quality)
Operator panel display	Once a year (no longer necessary thanks to automatic screen saver)

Table 2: Maintenance

TOC and ozone instruments are re-calibrated once per year by an independent calibration service. The temperature and conductivity instruments are recalibrated once a year by Aventis.

The overall state of the plant is checked every two years by a requalification according to Aventis specifications, including a check that the documentation is up to date.

No major repairs have been required throughout the entire period. Due to mechanical defects, a softener tank, the pipe separator and a printed circuit board at the ozoniser and at the storage tank's level measuring system had to be replaced. All major sensitive components, such as electrodeionisation stack, membrane degasification module, ion exchange resin and loop pump, are still fully operative.

2.3 Sanitisation

To ensure consistent water quality, a sanitising interval of once a year has been stipulated for the water generation plant during the validation process. The plant is chemically cleaned to ensure an optimum sanitisation, because successful sanitisation is only possible if any existing deposits or biofilms have been removed from the surfaces.
The plant is sanitised by means of chemicals. 0.2% hydrogen peroxide is mainly used for this purpose, with a reaction time of 60 to 100 minutes.

Sanitisation of the generation plant between the stipulated intervals has not been necessary because microbial growth is prevented by the intermittent recycling operation.

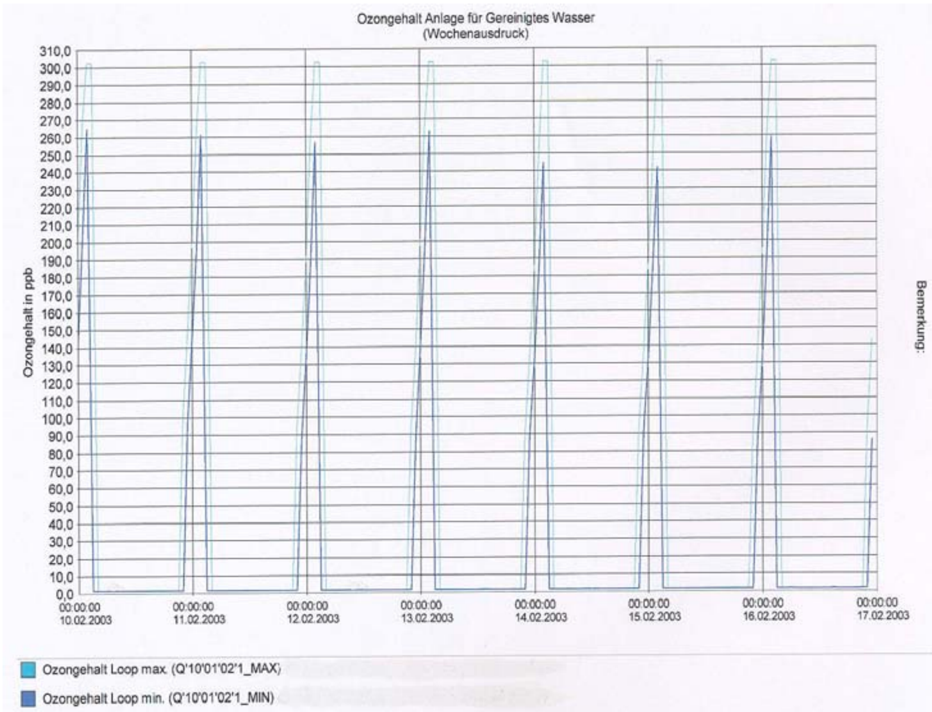
The storage and distribution system is sanitised or kept in a nearly sterile condition by means of ozone. Ozone is a very strong oxidant which attacks the surface of microorganisms and destroys them. The resultant organic matter is decomposed into residual products, mainly carbon dioxide and water.
The ozoniser is installed in the loop's return pipe. The ozone is generated electrolytically directly into the water thereby preventing any contamination from the surroundings.
The ozoniser generates ozone continuously in the water stream by means of a specially developed electrolytic cell. The core of this cell consists of an anode and a cathode, as well as a sold polymer electrolyte membrane which acts as an electrolyte and separator in the cell. The electrolytic process between the anode and cathode generates 2 g/h of high-purity ozone in the water passing through the cell. At the same time, the ozone is dissolved directly into the water.

To ensure continuous ozonation, an ozone concentration of approx. 60 ppb is maintained in the storage tank.

To ensure that water supplied to the consumers is free from ozone, the water in the return loop is irradiated by UV lamps at a wavelength of 254 nm; the ozone is reduced to oxygen below the detection limit and completely removed.

During the non-production periods at night, the UV unit is switched off by a timer for five hours so that ozonised water can circulate through the entire distribution system, thus achieving a sanitisation of the entire loop system (See Graph 1). As a result, the ozone concentration in the loop inlet rises from approx. 60 ppb to approx. 300 ppb. When the UV unit is switched on again in the morning before production re-starts, no ozone can be detected at the end of the return loop after about 20 minutes.

Graph 1

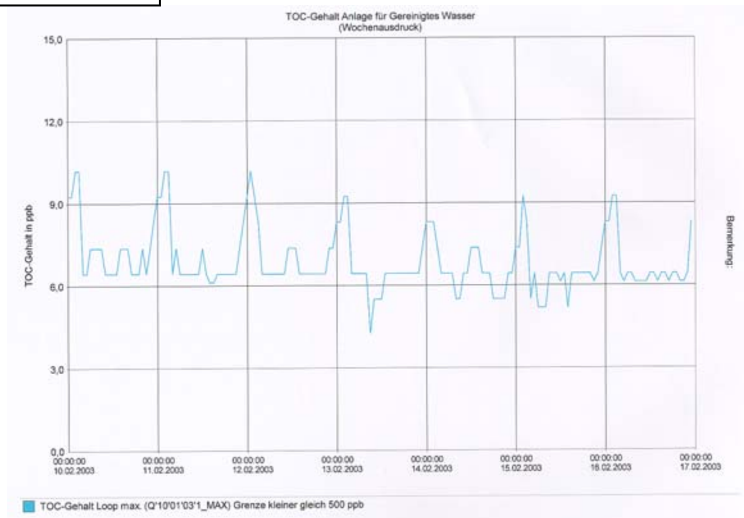


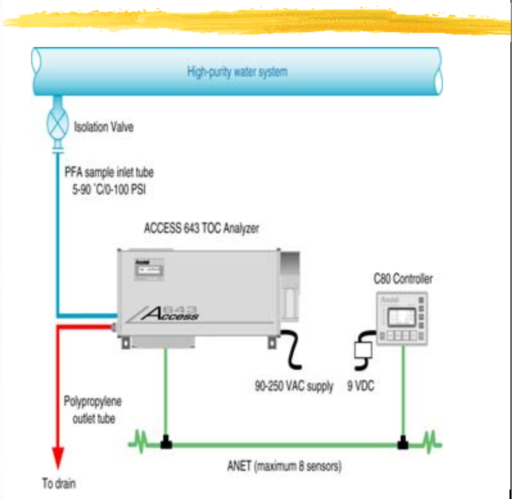
Ozone generator

Graph 2 shows that the TOC content rises slightly during the night-time sanitisation phase. One possibility that cannot be ignored is that the meter (Anatel ACCESS 643) does not measure as precisely at the higher ozone concentration. However, it is more likely that the ozone/UV combination provides a more effective oxidation of the water when the UV unit is on, and that therefore the TOC value is lower than when the UV unit is off.

Graph 2

TOC meter





When the water is circulated for an extended periods without major consumption, the water temperature can rise to about 25-30 °C in the storage and distribution system, because the pump, the UV unit and the environment all transfer heat into the system. The temperature rarely rises to more than 30 °C. However, should this occur, the heated water is cooled via a heat exchanger fed with mains (city) water, which is consumed within the factory anyway. A temperature below 20 °C is normally considered desirable.

3 Conclusions and experience

3.1 Water quality

The Purified Water generated easily conforms to all required specifications, even after four years of continuous operation. The values are far below the requirements of the pharmacopoeias (see also Table 1):

Conductivity (25°C):	0.5 – 0.7 µS/cm	instead of	1.3 µS/cm
TOC:	5 - 10 ppb	instead of	500 ppb
Colony count:	0-1 CFU/ml	instead of	100 CFU/ml

Note: The above values are measured at the Point of Use

The required water volume / flow rate is available at all times.

3.2 Ozonation

The storage and distribution system is sanitised using ozone. Besides the clear advantages offered by this sanitising process, the following special aspects should be considered:

- If the ozone is dosed into the return pipe of the recycle loop and is then fed into the PW tank by a spherical spray nozzle, a relatively high ozone concentration develops in the headspace of the tank. For ventilation, it must be ensured that the aeration filter is largely ozone-resistant. In the case described above, the filter has to be replaced twice a year. In addition, an ozone catalytic converter has to be installed in the vent pipe to prevent ozone from entering into the plant room. On the other hand, the ozone atmosphere in the tank's headspace prevents a biofilm from forming on the tank walls.
- EPDM seals are fitted in the storage and distribution system. Based on the experience gained from operation, the following intervals are proposed for replacement of the valve membranes at the individual points with different ozone concentrations:

  Downstream of ozoniser (approx. 10,000 ppb): replacement twice a year

In continuous sanitisation area (approx. 60 ppb): replacement every two years
In intermittent sanitisation area (approx. 0 – 300 ppb): replacement every four years

When ozone acts on EPDM for too long, it may cause considerable damage to the valve membranes or seals. A typical indication of this is a white coating. The following photos show parts that were attacked and partly or largely destroyed. This effect occurs both in the liquid medium (Fig. 1) and in the gaseous medium (Fig. 2).

Fig. 1 Liquid medium

Fig. 2 Gaseous medium

3.3 Piping system

The recycle loop was increased in length in 2000. The removed pipe sections showed a slightly golden-brown colour which was caused by a coating that can be easily removed by wiping with a wet cloth. This is called a slight rouging (Fig. 3). This colouring is also found at the top of a point of use valve which came into contact with the purified water (Fig. 4), but the colouring has not increased (photo taken in January 2003).

Fig. 3 Rouging

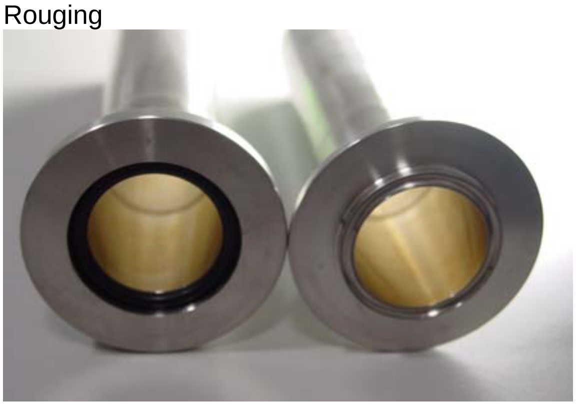


Fig. 4 Rouging

The welds looked new, without coating or colouring, although the distribution system had not been passivated after assembly but only flushed with ozonised purified water (Fig. 5). The welding joints were made using the automatic TIG orbital welding process according to the strict SOPs (standard operating procedures) issued by Hager + Elsässer. Special importance was attached to the absolute absence of oxygen.

Fig. 5   Welds

4 Water costs

Model calculation based on Hager + Elsässer planning data.

4.1 Operating and maintenance costs

Over the three-and-a-half year period evaluated, the costs for maintenance, repair, spares, wearing parts and special chemicals amounted to EUR 24,700.00, i.e. on average EUR 7,000.00 per year.

Approx. 0.5 hours/day are estimated for operator control, monitoring and sampling by Aventis Pharma, corresponding to: EUR 10,600.00 per year.

4.2 Operating costs

The detailed operating costs for supplies and services are:

City water:	28.75 EUR / day
Power generation plant:	6.40 EUR / day
Power distribution plant:	9.60 EUR / day
Compressed air:	0.80 EUR / day
Sodium chloride:	2.25 EUR / day

corresponding to: EUR 10,600.00 per year.

4.3 Purified water costs

With a consumption of 2,400 m³ per year and total costs of EUR 30,600.00 per year, the Purified Water costs are EUR 12.75 per m³ or 1.27 cents per litre.

For sanitisation of the storage and distribution system by means of SANICIRCLE, only electricity costs of EUR 0.08 per hour are incurred. There are no ongoing costs for the water wasted in conventional systems. 13 m³ of purified water are kept free of germs (0.6 cents per m³). If the system were sanitised once a week with hot water (2.5m³ at 85 °C) the costs would be exactly the same.

5 Summary

The ultrapure water plant presented above has now been in operation since 1999 to Aventis Pharma's complete satisfaction. The Purified Water is permanently available, with all necessary documentation for the system maintained throughout.

Little operator control is required, thanks to the continuous mode of operation using the combination of reverse osmosis/electrodeionisation (ROCEDIS) with membrane degassing and continuous/intermittent sanitisation by means of the ozone generator/UV unit (SANICIRCLE) system.

Ozone has proven to be highly effective for sanitisation, even at temperatures of up to 30°C in the storage and distribution system. However, when operating with ozone the filters and membranes, which are subjected to high continuous ozone concentrations, must be replaced at regular intervals.

The removed pipe sections prove that internal passivation of the welds is not needed when the welding work is carried out properly.

The cost of Purified Water production amounts to EUR 12.75 per m³ with an annual output of 2,400m³. The operating and maintenance costs represent 60% of the total costs, and these remain the same even if the output is increased. Therefore, with an annual output of 10,000m³ the costunit cost isd reduced even further to EUR 4.10 per m³.

11/12/2008 Horst Seeger/ Lars Pfannenschmidt

Legende Bild 1:

Stadtwasser	= City water
Vorfilter	= Pre-filter
Enthärtung	= Softener
Umkehrosmose	= Reverse osmosis
Membranentgasung	= Membrane degasifier
Elektrochem. Entsalzung	= Electrochemical deionisation
Ozon	= Ozone
Verbraucher	= Consumer