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Installation of a new Highly Purified Water plant during on-going company operations

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This article describes how hameln pharmaceuticals implemented a new pharmaceutical water treatment facility without significantly disrupting current production. Purified water is the primary raw material for a company specialising in the manufacture of preparations for parenteral use, so it was essential to minimise the time during which the water was unavailable.

In diesem Beitrag wird beschrieben, wie das Pharmaunternehmen hameln pharmaceuticals gmbh eine neue Pharmawasseraufbereitungsanlage nach umfangreicher Qualifizierung (DQ, IQ, OQ) in Betrieb genommen hat, ohne dabei die laufende Produktion in größerem Umfang zu stören.
In drei Phasen verläuft parallel zur Montage und ständigen Kontrolle der Betriebsparameter die Qualifizierung und Validierung der Anlage sowie des Aufbereitungsprozesses. Dabei wird vor allem auf eine ausführliche chemische und mikrobiologische Analyse Wert gelegt, um den Qualitätsanforderungen der Arzneibücher zu genügen.

Erst wenn alle Akzeptanzkriterien der Validierungsanweisung erfüllt werden und die Wasseraufbereitungsanlage somit in der Lage ist, dauerhaft und reproduzierbar HPW zu erzeugen, ist die Qualifizierung erfolgreich abgeschlossen.

Key words: Highly Purified Water, water treatment plant, reverse osmosis, electro-deionisation, ultrafiltration, installation

Introduction

In 2002, the European Pharmacopoeia (EP) introduced the water quality "Highly Purified Water" (HPW), which has the same quality requirements as Water for Injections (WFI), but is not restricted to manufacture by means of distillation.

If contact with the product is indirect, for example, for washing of primary packaging material, HPW can now be used. Accordingly, it may be used for cleaning equipment and rinsing containers if there is a final depyrogenisation stage.[1] This will enable us to produce WFI, the manufacture of which is associated with high energy costs, on a smaller, more economical scale. Taking this into account, hameln pharmaceuticals decided to invest in a new HPW treatment plant (made by Letzner).

Construction of the HPW plant

Figure 1 shows a flow-chart of the new HPW plant now being used successfully at hameln pharmaceuticals.

The pharmaceutical water treatment starts with municipal water. This first undergoes filtration to remove most of the impurities (filter grade 30µm). It then passes through a UV burner to reduce the viable count (low pressure mercury lamp, wave length 254nm) and enters the softening plant.

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Water softening

Following filtration and UV treatment, the water passes through pure cation exchangers that serve primarily to exchange calcium and magnesium ions in the water for sodium ions, thus reducing the hardness of the water (to ~ 0.018mmol Ca^{2+}/l). The anions in the feed water are not removed. As the total ionic concentration is increased (a Ca^{2+}/Mg^{2+} ion is exchanged for two Na^{+} ions), conductivity is raised by approximately 10–20%.

The exchange is carried out on ion-exchange resins with a polystyrol base, formed into small "pearls" (particle size 0.3–1.5mm).[2] These pearls have a large surface area and as a result offer an excellent opportunity for micro-organisms to adhere. The level of bacterial growth on the ion-exchange resins must be monitored constantly to enable sanitisation of the ion-exchange columns to be initiated in good time.

Dosage of sodium hydroxide solution

Sodium hydroxide solution (30%) is added to the softened water to remove the carbon dioxide. As a result, the pH value is raised to ≥8.5, thus displacing the carbonate–bicarbonate equilibrium (see below) to the right. The carbon dioxide released is converted into carbonate. This is unable to pass through the membranes in the subsequent reverse osmosis (RO) process and is eliminated with the flow of concentrate.[3]

Carbonate-bicarbonate equilibrium:
$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+ \leftrightarrow CO_3^{2-} + 2H^+$

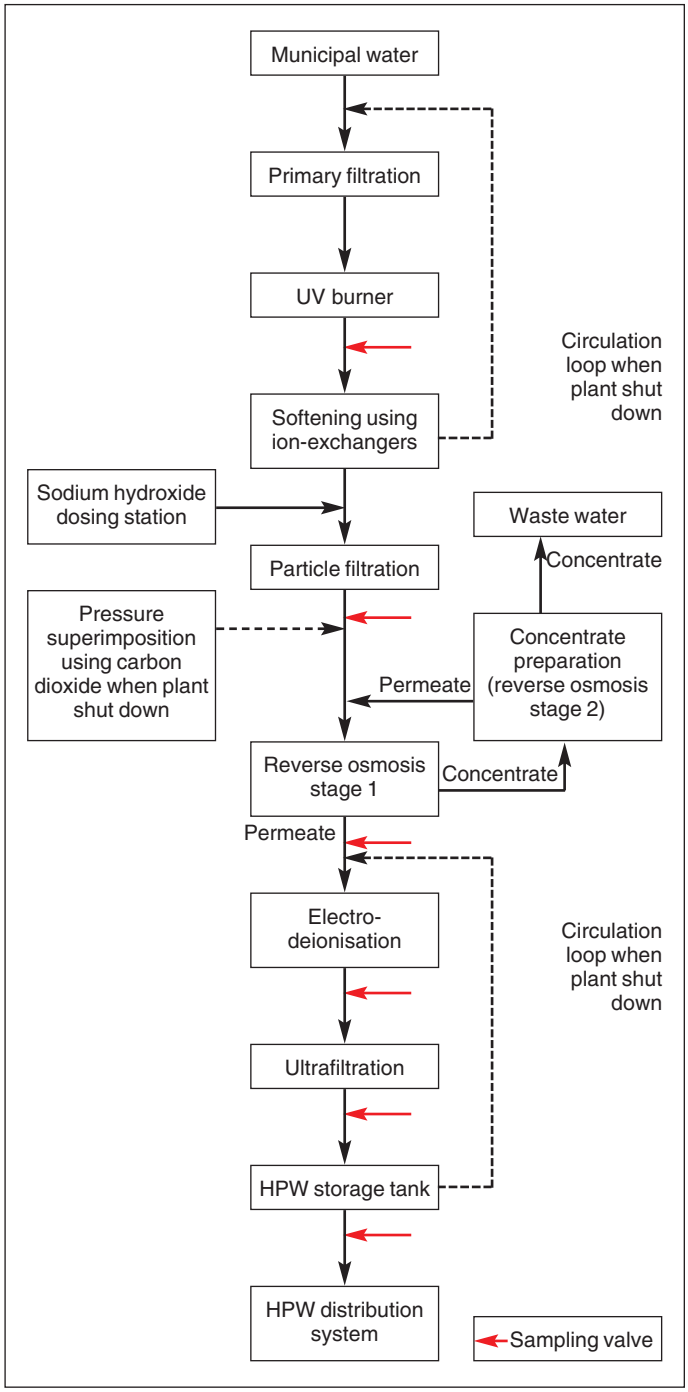

Figure 1. Highly Purified Water plant (schematic).

Reverse osmosis

The water then passes through a first-stage RO process. The concentrate thus produced could be disposed of, but this would generate large quantities of waste water, resulting in a low output and high waste disposal costs. To avoid this, the concentrate undergoes a further RO stage where the concentration is even more intense (**Figure 1**). The concentrate that results from this second-stage RO is now waste water, but the permeate is returned to pass through the first stage of RO in a way that economises resources.

The permeate from these RO stages finally undergoes electro-deionisation (EDI) and ultrafiltration, which give the finished conditioned water a pharmacopoeia quality of HPW.

Pressure superposition with carbon dioxide

When the water plant is not in production (standby phase), the RO equipment is rinsed with HPW and then superposed with carbon dioxide. The carbon dioxide produces a decrease in the pH value. The low pH value creates unfavourable conditions for micro-organisms. The correct water quality is thus maintained at all times.[4,5]

Electro-deionisation

Through a combination of electrodialysis, membrane technology and deionisation, the EDI module produces ultrapure water up to 18.2MΩ^{-1}cm^{-1} (0.0549µS/cm). The feed water is directed over ion-exchange resins (mixed bed). There the anion exchangers exchange their hydroxide ions (OH^-) for anions in the feed water, and the cation exchangers their hydrogen ions (H^+) for cations in the feed water.[6]

The ions are then separated using two types of ion-selective membrane, consisting of the same material as the ion-exchange resins. One membrane is passable only by cations, the other only by anions. None of the membranes is permeable to water. As a result of the DC field placed on the electrodes (5–10 volts/cell), the cations and anions migrate over the surfaces of the resin pearls, according to their charge, in the direction of the anode (anions) or cathode (cations), and then pass through the membrane permeable to them. Through an alternating superposed layer of anion- or cation-permeable ion-exchange membranes, parallel flow channels are formed, which in an alternating process direct water with high ion concentration (concentrate) and low ion concentration (dilute product). Through convergence of these channels it is possible to draw off a dilute product and a concentrate flow.[2,6]

Ultrafiltration

To produce the required HPW quality, the Purified Water produced by the EDI system is subsequently treated in two parallel connected hollow-fibre ultrafiltration modules. These do not contain membranes with a defined pore size but act as a molecular screen and are able to eliminate both bacteria and endotoxins. This process ensures that HPW free of pyrogens is constantly produced.[7] Smaller molecules such as water and ionic impurities can pass through the membrane. As salts cannot be retained, the conductivity remains virtually unchanged.[2]

Plant capacity

Water balances have shown that the amount of Purified Water needed by hameln pharmaceuticals is 3m^3/hr. There are also individual peak requirements, which may increase demand to up to 10m^3/hr in the short term. For cost and technical reasons, and primarily because of micro-biological concerns, it is impractical to maintain Purified Water production capacity at the peak level and thus to operate a plant that is possibly too large and as a consequence underutilised. It is preferable for the plant to operate continuously at a level of up to 5m^3/hr. Larger quantities can be withdrawn by using a storage tank that contains up to 15,000 litres.

The old Purified Water plant could produce 8m^3/hr, but

the storage tank contained only 4m^3. This system was unable to manage peak water requirements of up to 10m^3/hr. At other times, the plant worked for only 0.5–1 hours and was then in standby mode for many hours. This led to considerable wastage of water because the water circulating in the plant during standby phase was disposed of before the plant started the production phase. Furthermore, there is an increased carbon dioxide requirement for pressure superposition during standby mode. The decision was therefore made in favour of a smaller production capability based on the average amount of Purified Water required and a higher storage capacity to manage the peak requirements.

As nowadays the focus is on flexibility, this compact plant offers the opportunity to increase production capacity rapidly and at any time – by exchanging individual components for larger ones and even adding on a further plant.

Installing the HPW plant while the company was still operating

The HPW plant described was intended to replace its predecessor, a water facility that had produced Purified Water. For this purpose the new plant was installed in stages – in three sections.

Phase 1 (checking phase): assembly of the plant

The new HPW plant was delivered as individual structural components, which in view of the size of the overall plant could be assembled only in the room in which it was intended to be used. Installation (IQ) and Operational Qualification (OQ) were carried out by the manufacturer so that the new water treatment plant could finally be put into operation (**Figure 2**).

In order to continue water production, the old and new water treatment plants were operated in parallel. The new HPW plant takes up approximately 12m^2; the former plant needed an area of about 13–14m^2, but without a storage tank.

Purified Water from the former plant continued to be used. The water from the new HPW plant was rejected until it was established that the new plant was ready to deliver water of the required quality (HPW) in a continuous, reliable and reproducible way. The first phase established the fitness for purpose of the plant in relation to feeding Hameln municipal water. (Duration and acceptance criteria are described in "Practice example" below.)

Phase 2 (transition phase): main installation process

The new HPW plant was connected to the existing Purified Water storage tank and the distribution system for the HPW (**Figure 3**). The water from the new plant was also used for production after an intensive trial operation. (Duration and acceptance criteria are described in "Practice example" below.)

The existing plant could now be dismantled and the new storage tank installed. This contains 15,000 litres of HPW, is 7 metres long and requires a surface area of approximately 12m^2. Because of its size, the storage tank could not be delivered in one piece but had to be installed in individual sections *in situ*.

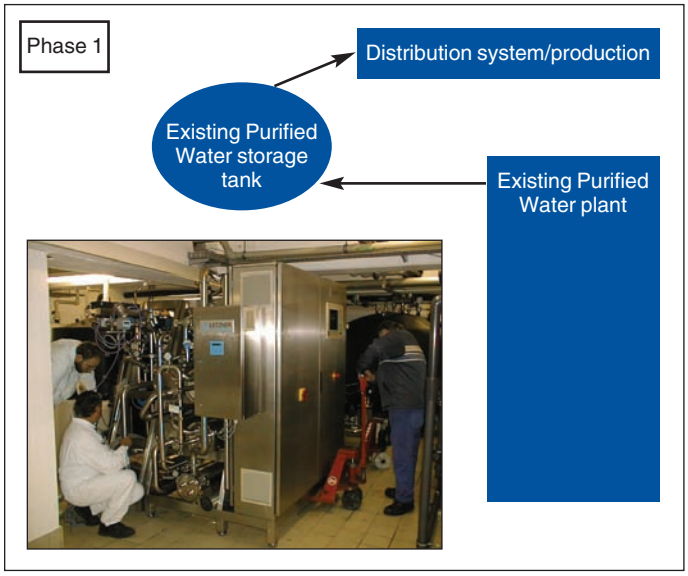

Figure 2. Phase 1: assembly of the new HPW plant.

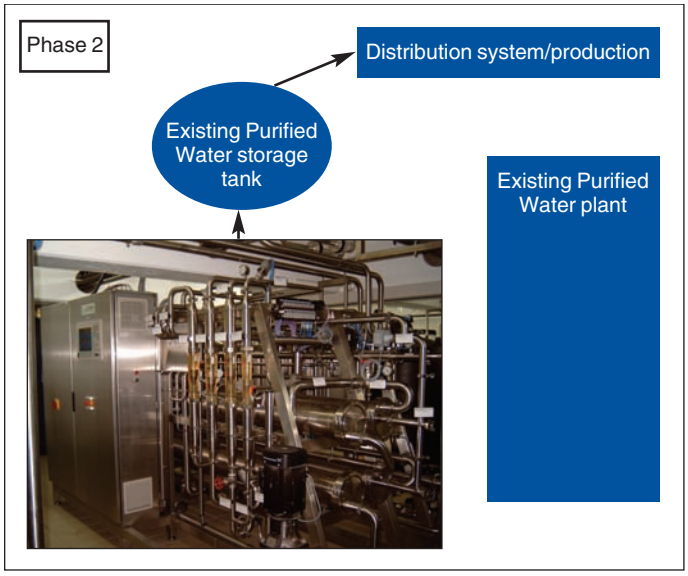

Figure 3. Phase 2: connection of the new HPW plant to the old Purified Water storage tank.

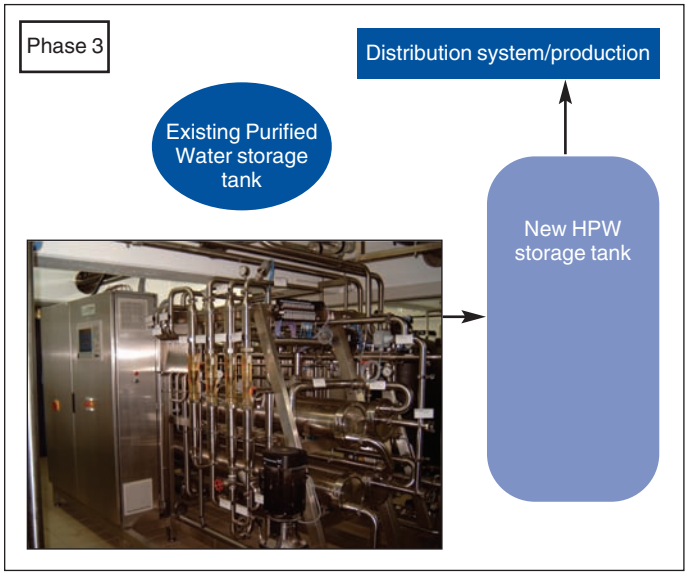

Figure 4. Phase 3: operation of the new HPW plant with the new storage tank.

To guarantee high water purity, the tank's welding seams underwent precision smoothing on the inside.

A loop was attached behind the tank, which transports the HPW for production or allows it to circulate if there is no current demand for ultrapurified water. Consequently, at no point is the water still, which is an important prerequisite for ensuring high microbiological quality.

After completion of the installation works and the IQ and OQ of tank and loop, these were thoroughly sanitised and ready to be put into operation.

The time for connecting the new HPW plant to the new tank had to be agreed precisely with production planning. Water was available for production after only 4 days.

Phase 3 (final phase): operation of the HPW plant with the new storage tank

The new HPW plant could now be operated in conjunction with the new storage tank (**Figure 4**). The installation work had been completed. Sanitisation (80°C) of the ultrafiltration, EDI, RO and softening components was carried out. During this phase the focus was on the analytical and microbiological assays to guarantee the quality of the water produced, even during possible seasonal variations (especially the quality of the municipal water).

Operational data: operational monitoring on a daily basis

During the course of all three phases, all parameters that could be recorded at the plant were documented daily and analysed on a regular basis. These included, for example, all flow and rejection readings, and also measurement of pressure, temperature, pH value, conductivity (online) and desired output at several points during water treatment.

The following describes some of the more fundamental points.

Primary and particle filtration

To monitor the condition of the filter, the pressure drop between feed water and permeate was determined. A pressure drop of greater than 1 bar is a sign that the filters have become clogged and must be replaced.

Monitoring of conductivity

The conductivity was measured at 20°C (EP). After softening, the conductivity was higher (~630µS/cm) than in the feed municipal water (~530µS/cm). This was due to exchange of the multivalent ions for sodium ions, whereby a calcium or magnesium ion was exchanged for two sodium ions, thus increasing the overall ionic concentration.

The RO process reduced the conductivity to ~4µS/cm and EDI produced a further reduction to ~0.06µS/cm, thus complying with the value required by the US Pharmacopeia and EP for HPW of <1.1µS/cm.

Monitoring of pH value

The dosing of sodium hydroxide solution to remove carbon dioxide increased the pH value from ~7.4 (before NaOH dosing) to ~9.2. At this pH, carbon dioxide was present as sodium carbonate and could be separated by RO.

After RO the pH value was still ~9. A reduction to the range required (pH 5–7) was achieved by ion exchange in EDI.

The measuring equipment was calibrated on a regular basis as part of the maintenance programme.

Monitoring of the filling level

The filling level of the saline water tank for regenerating the ion-exchange columns, the sodium hydroxide holding tank for removal of carbon dioxide and the CO_2 cylinder for pressure superposition if the plant shuts down must be monitored and/or filled up on a regular basis.

Reverse osmosis

The quantity of permeate was monitored: clogging of the membranes due to scaling and fouling can be recognised by a reduction in the amount of permeate because, if the pressure remains the same, the same amount of water is no longer able to reach the permeate surface.

The pressure drop across the membrane should also be monitored. A pressure drop between the feed and the permeate of greater than 1 bar is a sign that the membranes are clogged and must be cleaned.

Monitoring of conductivity (<20µS/cm) and of pH value (<9.5) of the water related to temperature should also be carried out in order to maintain the water quality needed for trouble-free use of the EDI.

Electro-deionisation

The percentage distribution of the feed (permeate from RO) to the three flow channels (feed, concentrate, electrode flushing) has to be controlled regularly.

The conductivity (<1.1µS/cm) and pH value (5–7) related to temperature must be monitored as well as the current conductivity and voltage.[8]

Ultrafiltration

To facilitate continuous operation of the water treatment plant after successful completion of installation and qualification, along with the regular cleaning, maintenance and repair work, it is also essential to continue monitoring the flow of permeate and concentrate.[5,7]

Qualification

To demonstrate the suitability of the plant for producing HPW, standard equipment qualification (Design Qualification, IQ and OQ) procedures were conducted, followed by Performance Qualification (PQ) studies.

Practice example – PQ of the HPW plant

Following the installation, continuous qualification and validation of the plant and the process was carried out (in three phases). For this purpose, water samples were taken at regular intervals and subjected to chemical and microbiological analyses.

Phase 1: The chemical and microbiological quality of the

water was checked each working day for a minimum of 2 weeks according to **Tables 1** and **2**.

During these investigations the following were noted:

- After the softening process there was an increase in the total viable count, which was attributed to the large surface area of the ion-exchange resins. They offer an ideal opportunity for micro-organisms to adhere, resulting in higher water contamination. During the water treatment process, the total viable count was, however, reduced again to the quantity set by the pharmacopoeias. It was primarily the EDI electric field that was shown to make a considerable contribution to minimising bacterial growth (**Figure 5**).
- The conductivity of the water samples tested in the laboratory was higher than the values measured online at the plant. This was probably attributable to a higher carbon dioxide content in the sample, diffused into the sample itself from the ambient air when taking the sample, or during conductometric measurements. The requirements of the pharmacopoeias were, however, maintained.

Phase 2: In addition to the sites where samples were tested in Phase 1, the water was analysed, on a daily basis, for chemical and microbiological quality after the existing storage tank, as well as in the distribution system leading to production (**Tables 1** and **2**). Here, at least Purified Water quality must be maintained.

The requirements for water after ultrafiltration (in fact HPW) had to be reduced to the level of Purified Water (100CFU/ml) with regard to viable count as there had been a rise in the total viable count in the ultrafiltration phase. It was not possible to carry out hot water sanitisation at this point as the heat exchanger required for this was in the new loop and this was only to be connected with the tank in Phase 3.

However, as the pharmacopoeia quality "Purified Water" had been maintained at all times, this did not cause any further problems for current production. Before planning this new HPW plant, Purified Water had always been used.

As the acceptance criteria had been successfully maintained, it was possible to limit the sampling to a certain extent:

- For the municipal water feed and the individual conditioning stages (up to EDI), it was possible in the meantime to

Table 1. Microbiological analysis of water samples, taking into account the requirements of the pharmacopoeias for Purified Water (PW) and Highly Purified Water (HPW).[9,10] CFU = colony-forming units; EU = endotoxin units

Location of sample	Microbiological parameter
Municipal water	Total viable count (to be registered) Endotoxin content (to be registered) Absence of *Escherichia coli* and *Pseudomonas aeruginosa*
After decontamination with UV burner	Total viable count (to be registered) Endotoxin content (to be registered)
Softened water after softening plant	Total viable count (to be registered)
After reverse osmosis (PW)	Total viable count (PW ≤100CFU/ml)
After electro-deionisation (PW)	Total viable count (PW ≤100CFU/ml) Endotoxin content (to be registered)
After ultrafiltration (HPW)	Total viable count (HPW ≤10CFU/100ml) Endotoxin content (HPW ≤0.25EU/ml)
Existing storage tank (Phase 2)	Total viable count (PW ≤100CFU/ml) Endotoxin content (≤0.25 EU/ml)
Distribution system (Phase 2)	Total viable count (PW ≤100CFU/ml) Endotoxin content (≤0.25EU/ml)
New HPW storage tank (Phase 3)	Total viable count (HPW ≤10CFU/100ml) Endotoxin content (HPW ≤0.25EU/ml)
Distribution system (Phase 3)	Total viable count (HPW ≤10CFU/100ml) Endotoxin content (HPW ≤0.25EU/ml)

Table 2. Chemical analysis of water samples, taking into account the requirements of the European Pharmacopoeia (EP) and the US Pharmacopeia (USP) for Purified Water and Highly Purified Water (HPW)[9,10]

	HPW EP 5.0	Purified Water EP 5.0	Purified Water USP 28
Valid for sampling location	After ultra-filtration, (Phase 3: new HPW storage tank, distribution system)	After EDI (Phase 2: old storage tank, distribution system)	After EDI (Phase 2: old storage tank, distribution system
General assessment	Clear, colourless, odourless, tasteless	Clear, colourless, odourless, tasteless	–
pH value	5.0–7.0	5.0–7.0	5.0–7.0
Conductivity	At 20°C ≤1.1µS/cm	At 20°C ≤4.3µS/cm	At 20°C ≤1.1µS/cm
Total organic carbon	≤0.5ppm	≤0.5ppm	≤0.5ppm
Nitrate	≤0.2ppm	≤0.2ppm	–
Heavy metals as Pb	≤0.1ppm	≤0.1ppm	–
Ammonium	≤0.2ppm	≤0.2ppm	≤0.3ppm
Calcium/ magnesium	Complies Limited testing	Complies Limited testing	Complies Limited testing
Carbon dioxide	Complies Limited testing	Complies Limited testing	Complies Limited testing
Chloride	≤0.5ppm	≤0.5ppm	≤0.5ppm
Sulphate	Complies Limited testing	Complies Limited testing	Complies Limited testing
Oxidisable substances	Complies Limited testing	Complies Limited testing	Complies Limited testing

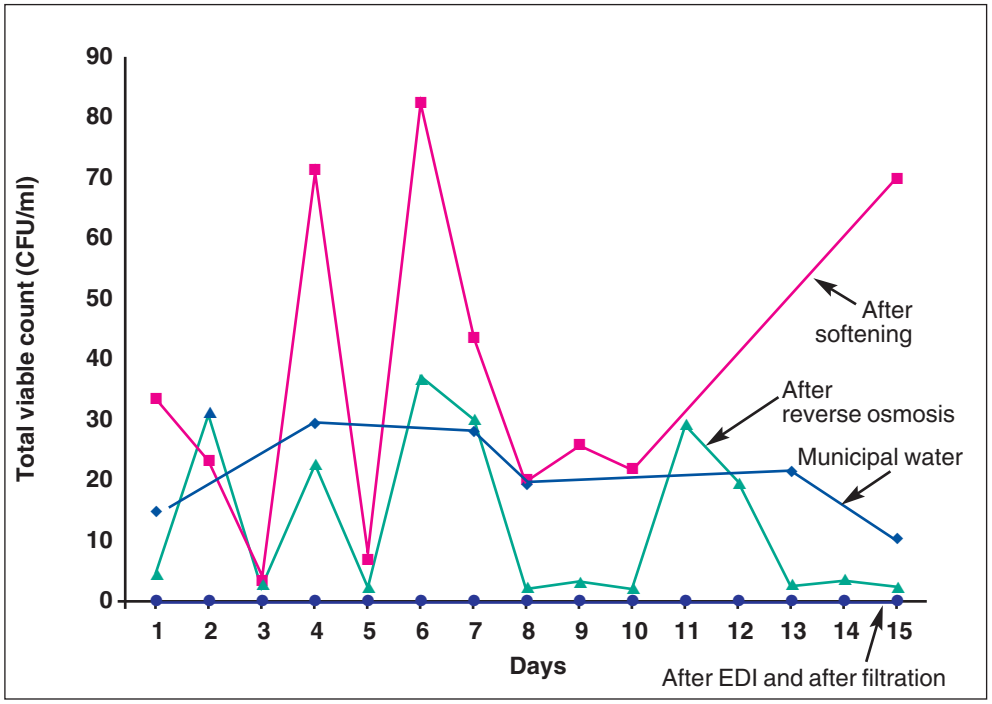

Figure 5. Total viable counts in the HPW plant.

reduce microbiological sampling to once per week, as this sector had demonstrated its full operational capability in Phase 1 and focus was now on HPW (after ultrafiltration) and its storage and distribution until it reached the production department.

- For the chemical analysis, after 2 weeks of intensive full analysis as part of Phase 2, daily sample testing was limited to the most important criteria of conductivity and pH value. Full chemical analysis in accordance with Table 2 was carried out on a weekly basis.

Phase 3: After sanitisation of the new HPW storage tank and the loop, the plant was connected to the tank and via the loop to the distribution system for production. All the components in the plant then underwent hot water sanitisation (80°C).

Just as in Phase 1, all the samples were analysed rigorously on a daily basis for a minimum of 2 weeks (**Tables 1** and **2**). The emphasis was on the water leaving the new storage tank. The water must be of HPW quality at the outlet of the tank.

Once the acceptance criteria had been successfully maintained, sampling was reduced (weekly analysis). Daily sampling and testing for total viable count, endotoxin content, conductivity and pH value were carried out from then on only for samples after ultrafiltration, after the tank and in the distribution system.

These parameters were analysed and monitored precisely for 1 year. Only then was the PQ successfully completed.

Conclusion of PQ

The results of the microbiological and chemical analysis complied with requirements set down in the validation plan. The water treatment plant is thus able to produce reproducible HWP long-term and has therefore been successfully qualified.

Summary

A new HPW treatment plant was successfully assembled, installed and put into operation as three separate structural components without any great disruption to current production. The requirements of the pharmacopoeias concerning the microbiological and chemical quality of the water were maintained, and thus all the acceptance criteria for the validation protocol were fulfilled.

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